Breast cancer and common malignancies in older adults

Dr Nicolò Matteo Luca Battisti MD
Breast Cancer Research Division, The Institute of Cancer Research
Breast Unit, The Royal Marsden NHS Foundation Trust
London

A thesis submitted to the Institute of Cancer Research – University of London in accordance with the requirements for degree of Doctor of Medicine (Research) - MD(Res)

July 2022

Word count: 39,827

DECLARATION

The work presented in this thesis comprises of original work undertaken by me from October 2019. I confirm that I am the sole author and that none of the subject matter has been submitted previously as a higher degree.

OVERVIEW

Cancer is increasingly a disease of older adults. However, they are heterogeneous and life expectancy and tolerance to stressors may vary greatly among within this age group. Comorbidities, functional impairments, malnutrition, polypharmacy, cognitive impairment, psychological distress and lack of social support, may substantially impact on the wellbeing of older adults, on anticancer treatment benefits and toxicities and on clinical decision-making. Treatment decisions should not be guided by chronological age alone. Geriatric assessments can provide a more comprehensive understanding of functional and physiological age in older individuals with cancer to better assess treatment risks and benefits, engage in shared decision-making and provide more personalised care.

This thesis describes the impact of age and comorbidities on different aspects of the management of breast cancer and other common malignancies in five research projects. The first project evaluated the patterns of systemic therapy use in older adults with early breast cancer enrolled in the Bridging The Age Gap study and its effect on recurrence and survival outcomes. Since treatment effects on quality of life may be more relevant in the context of more limited life expectancy and reduced survival benefits, the second study investigated the impact of chemotherapy on this specific outcome in adults with early breast cancer at high risk of recurrence enrolled in the same trial. The radiotherapy use patterns and its effect on quality of life were evaluated in a third project including the same trial population. As cardiovascular disease is critical in determining fitness, the fourth study investigated the prevalence of this comorbidity in individuals with curable malignancies retrieved from a national cancer registry dataset linked to cardiovascular disease databases. Finally, the fifth project assessed the cardiac toxicity risk and the performance of a cardiotoxicity prediction tool in older and younger patients with early breast cancer receiving trastuzumab.

ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to several people who in many different ways supported me while working on this research and on this thesis and certainly are helping me becoming a better clinician and researcher.

I am greatly indebted to Dr Alistair Ring not only for being my primary supervisor and for providing ongoing input and insight on this research, but crucially for the constant mentoring, the innumerable opportunities of professional growth since I joined The Royal Marsden and for being a constant source of inspiration on what a clinician and an investigator should be.

Also, I am greatly indebted to Professor Stephen Johnston, who has also been supervising this work, for welcoming me in the Breast Unit at The Royal Marsden, for giving me constant direction and purpose to further develop my career and for providing invaluable insight and ongoing advice to accomplish my aspirations.

I am extremely grateful to Dr Sophie McGrath, who is my associate supervisor, for the continuous support on my work on these research projects and on my clinical work in the hospital.

I would also like to offer my special thanks to Dr Mark Allen for the constant mentoring, for the words of wisdom on my clinical and research work and for making me feel at home also in the UK.

I would also like to thank Dr Susannah Stanway for the enthusiasm and the constant support during the last six years.

Furthermore, I am honoured to have had the opportunity to work alongside so many additional talented clinicians and investigators during these two years of work. I have learnt a lot from each one of them.

I would like to express my sincere gratitude to Professor Lynda Wyld, Chief Investigator of The Bridging The Age Gap study, for allowing me to work on the trial dataset, for providing ongoing insight and words of wisdom on this research and for setting with this trial one of the most compelling examples of what research in geriatric oncology should be. Also, I am deeply grateful to Esther Hebert and Mike Bradburn (Clinical Trials Research Unit, University of Sheffield) for the support on conducting the statistical analyses and Dr Jenna Morgan and Dr Matthew Hatton for their contribution to this research.

I am deeply grateful also to Dr David Adlam, Chief Investigator of the Virtual Cardio-Oncology Research Initiative, for giving me the opportunity to work on this research and the constant and insightful input on the study findings and their interpretation. Moreover, I would like to thank Catherine Welch and Michael Sweeting (University of Leicester) for the support on conducting the statistical analyses and on interpreting our findings. I would like to express my sincere gratitude also to Professor Michael Peake and Dr Mark de Belder for their expert comments and contribution to formulate the research questions and the interpretation of these results.

I would like to offer my special thanks to Dr Alex Lyon (The Royal Brompton Cardio-Oncology Service) for his insightful comments and suggestions on the research project included in the last chapter of this thesis. I am also grateful to Dr Maria Sol Andres, Professor Stuart Rosen and Dr Tharshini Ramalingam for their assistance at every stage of this project and for their expertise and contribution.

Moreover, I would like to extend my sincere thanks to the Cridlan Ross Smith Charitable Trust for supporting my work. I am greatly indebted to Professor Ian Smith for the mentoring and for the unwavering support since the very first time I met him at a Breast Unit research meeting at The Royal Marsden.

I would like to express my sincere gratitude to Professor Nandita deSouza and Professor Nicola Valeri for welcoming me at The Institute of Cancer Research and for the support and valuable input on pursuing a higher degree.

I am also greatly indebted to Dr Martine Extermann for the ongoing mentoring and support since my time at the Moffitt Cancer Center and for being a constant source of inspiration for my work in the field of geriatric oncology.

I am also grateful to the International Society of Geriatric Oncology for giving me the opportunity to advocate for older adults living with and beyond cancer at global level and to the entire geriatric oncology community for being a continuous source of inspiration and belonging.
I would also like to acknowledge the financial support provided by National Institute for Health Research, Cancer Research UK and the British Heart Foundation; without their support these projects would never have started.

I am also indebted to the patients that have participated and have been included in these research projects.

Finally, I would like to express my very profound gratitude to my mother Anna and my partner Hugo for providing me with unfailing support and continuous encouragement throughout these long years of study, clinical work and research. This accomplishment would not have been possible without them.

TABLE OF CONTENTS

TABLE OF ABBREVIATIONS

ACE	Angiotensin-converting enzyme
ACheW	Adjuvant chemotherapy in elderly women with breast cancer
ADL	Activities of daily living
aPG-SGA	Abridged Patient Generated Subjective Global Assessment
ASCO	American Society of Clinical Oncology
BCS	Breast-conserving surgery
BCSS	Breast cancer-specific survival
BMI	Body mass index
CA	Cancer Alliance
CALGB	Cancer and Leukemia Group B
CARG	Cancer and Aging Research Group
CCI	Charlson comorbidity index
CGA	Comprehensive geriatric assessment
CHF	Congestive heart failure
CI	Confidence interval
CMF	Cyclophosphamide, Methotrexate and Fluorouracil
CRASH	Chemotherapy Risk Assessment Scale for High-Age Patients
CTCAE	Common Terminology Criteria for Adverse Events
CVD	Cardiovascular disease
DLBCL	Diffuse large B cell lymphoma
EBC	Early breast cancer
EBCTCG	Early Breast Cancer Trialists' Collaborative Group
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D-5L	5-level Euroqol-5D
ER	Oestrogen receptor
ESMO	European Society for Medical Oncology
FASG 08	French Adjuvant Study Group 08
GLS	Global longitudinal strain
HEDIS	Healthcare Effectiveness Data and Information Set

HER2	Human epidermal growth factor receptor 2
HES	Hospital Episode Statistics
HFA	Heart Failure Association
HR	Hazard ratio
IADL	Instrumental activities of daily living
ICD	International Statistical Classification of Diseases and Related Health Problems
ICE	Ibandronate with or without Capecitabine in Elderly Patients
ICOS	International Cardio-Oncology Society
IMD	Index of Multiple Deprivation
IQR	Interquartile range
LVEF	Left ventricular ejection fraction
MINAP	Myocardial Ischaemia National Audit Project
MMSE	Mini Mental State Examination
MNA	Mini-Nutritional Assessment
MUGA	Multiple-gated acquisition
NACSA	National Adult Cardiac Surgery Audit
NAPCI	National Adult Percutaneous Coronary Intervention
NCCN	National Comprehensive Cancer Network
NCRAS	National Cancer Registration and Analysis Service
NCRD	National Cancer Registration Dataset
NHFA	National Heart Failure Audit
NHS	National Health Service
NICOR	National Institute for Cardiovascular Outcomes Researcher
NPI	Nottingham Prognostic Index
NPV	Negative predictive value
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
OADR	Old-age dependency ratio
OS	Overall survival
PIM	Potentially inappropriate medication
PMRT	Post-mastectomy radiotherapy
POADR	Prospective old-age dependency ratio

PPV	Positive predictive value
PR	Progesterone receptor
PS	Performance Status
QLQ	Quality of Life Questionnaires
QoL	Quality of life
RCT	Randomised clinical trials
ROC	Receiver-operating characteristic
RR	Relative risk
RTDS	National Radiotherapy Dataset
SACT	Systemic anticancer therapy
SCF	Supraclavicular fossa
SD	Standard deviation
SEER	Surveillance, Epidemiology, and End Results
SIOG	International Society of Geriatric Oncology
STOPP	Screening Tool of Older Person's Prescriptions
VAS	Visual analogue scale
VICORI	Virtual Cardio-Oncology Research Institute
WHO	World Health Organization

AIMS

We aimed to investigate the impact of age and comorbidities on different aspects of the management of breast cancer and other common malignancies. We hypothesized that a comprehensive evaluation of older patients with cancer alongside tumour-related factors would better inform patients and identify those likely to benefit from and tolerate standard therapeutic approaches.

The overarching aims of the five projects were:

1. To describe the age- and risk-stratified patterns of receipt of adjuvant systemic therapy in older patients with early breast cancer (EBC) enrolled in the Bridging the Age Gap study in order to determine which patients might benefit from treatment.

2. To investigate the impact of curative chemotherapy on the quality of life (QoL) of older patients with EBC enrolled in the Bridging the Age Gap study in order to help inform treatment decisions.

3. To describe the age- and risk-stratified patterns of receipt of adjuvant radiotherapy following breast conserving surgery or mastectomy and its impact on QoL in older patients with EBC enrolled in the Bridging the Age Gap study. This would help to identify those at risk of over- or under-treatment and those suitable for de-escalation strategies.

4. To determine the prevalence of pre-existing cardiovascular disease in patients with a new diagnosis of potentially curable cancer on the UK National Cancer Registration and Analysis Service and the National Institute for Cardiovascular Outcomes Researcher datasets. By examining a key component of fitness for treatment, this would provide

context to where over or under-treatment of older patients of cancer may occur.

5. To evaluate the risk of cardiotoxicity in older versus younger patients with human epidermal growth factor receptor 2 (HER2)-positive EBC receiving trastuzumab and validating the performance of a cardiovascular risk prediction tool. This would potentially enable prediction of adverse cardiovascular outcomes in older patients with HER2-positive breast cancer.

CHAPTER 1. BACKGROUND

1.1. DEFINITION OF OLDER ADULTS

Older age refers to ages nearing or surpassing the life expectancy of human beings. Nonetheless, old age is not a definite biological state, as the chronological age denoted as old varies among different cultural settings and historical periods.

In most high-income countries, the age of retirement is set within the range of 60 to 65 years. This is also generally considered to mark the transition from middle to old age. Also, chronological age is frequently a requirement to become eligible for senior social programmes, such as Medicare in the United States.[1] Nevertheless, in different geographical areas old age can begin as early as the mid-40s or as late as the 70s. Old age cannot be universally defined because it is context-sensitive. For example, the United Nations considers old age to be 60 years or older.[2] On the other hand, a 2001 joint report by the United States National Institute on Aging and the World Health Organization (WHO) Regional Office for Africa set the beginning of older age in the Sub-Saharan Africa at 50 years.[3] These thresholds reflects differences in demographic trends, life expectancy and conceptions about old age in different geographical areas. These are critical considerations to define older age appropriately.

Historically, the geriatric oncology field has defined older adults as those aged 65 years and older based on epidemiological data linked to Medicare eligibility in the United States.[4] While international consensus[5, 6] and some recent clinical trials[7] have retained this definition, other studies have adopted different age cut-offs, such as 70 years.[8-10] In the context of the current demographic trends, an age cut-off of 70 years is reasonable and widely accepted in the geriatric oncology field. Nonetheless, in a population of individuals diagnosed with specific cancers, defining older age should also pragmatically take into consideration also their age-specific incidence. For

example, while an age cut-off of 70 years may be appropriate to define older adults in the breast cancer patient population, in different tumour cohorts a lower age cut-off may be more relevant to understand treatment patterns and for service provision purposes.

However, older persons are increasingly diverse with respect to sociodemographic and health status. Importantly, it is necessary to approach this definition comprehensively, understanding all domains of health and looking beyond one's chronological age to predict prognosis, morbidity, and mortality. A comprehensive assessment of older persons' medical, mental health and social dimensions facilitates informed decision-making and care planning.

1.2. BURDEN OF CANCER IN OLDER ADULTS

Age is the most relevant risk factor for the development of cancer, with a median age at diagnosis of 66 years in the overall population[11] and older adults having nearly 10 times the risk of developing cancer compared with their younger counterparts.[12] In the United States, 10,288,440 individuals aged ≥65 years were living with cancer in 2018, corresponding to 19.9% of the general population.[11] In 2018, in England there were 680,050 women and 678,460 men living with a cancer diagnosis aged ≥65 years.[13] In the same year, the prevalence of cancer was 11.1% in individuals aged 65-74 years compared with 16.1% in those aged 75-84 years, 15.9% in those aged ≥85 and 4.1% in those aged 45-64 years and 1.2% in those aged <45 years. As a result, the care of older patients constitutes an important part of the everyday practice for oncologists.

1.2.1. Incidence

Data from the Surveillance, Epidemiology, and End Results (SEER) database suggest that 55.3% of cancer incidence affects individuals aged 65 years and older.[11] Similarly, in the United Kingdom this age group accounts overall for 65.4% of cancer cases diagnosed in 2015-2017.[14]

In the United Kingdom, cancer incidence rates rise steeply from around the age of 55-59 years, with the highest rates observed in adults aged 85-89 years for females and males.[14] Based on National Cancer Registration and Analysis Service (NCRAS) data, in 2015-2017 in women the overall annual incidence of cancer gradually increased from 73.5/100,000 at the age of 25-29 years to 576.2/100,000 in those aged 50-54 years and 1,289.7/100,000 in those aged 65-69 years, with a peak at 2,233.1/100,000 at the age of 85-89 years.[14] During the same period, in men the annual incidence of cancer ranged from 46.6/100,000 at the age of 25-29 years to 381.7/100,000 in those aged 50-54 years and 1,740.7/100,000 in those aged 65-69 years, with a peak at 3,448.4/100,000 at the age of 85-89 years. Similar trends are observed within the SEER database, with the annual incidence of cancer in 2018

ranging from 106.1/100,000 in individuals aged less than 50 years to 815.0/100,000 in those aged 50-64 years and 1,989.4/100,000 in those aged ≥65 years for both sexes in the United States.[11]

1.2.2. Mortality

SEER data also document that 70% of cancer mortality involves adults aged 65 years and older.[11] In the United Kingdom this age group was affected by 80.1% of cancer-related mortality in 2016-2018.[14]

Cancer-related mortality rates are also strongly influenced by age. In the United Kingdom, age-specific mortality rises steadily from around age 45-49 and even more steeply around age 70-74.[14] NCRAS data shows that in 2015-2017 in women the overall annual age-specific mortality for cancer gradually increased from 6.3/100,000 at the age of 25-29 years to 120.9/100,000 in those aged 50-54 years and 467.4/100,000 in those aged 65-69 years, with a peak at 1,977.2/100,000 above the age of 90 years.[14] During the same period, in men the age-specific mortality for cancer of cancer ranged from 5.5/100,000 at the age of 25-29 years to 116.0/100,000 in those aged 50-54 years and 635.0/100,000 in those aged 65-69 years, with a peak at 3,843.1/100,000 above the age of 90 years. Likewise, in 2018 SEER data shows that the age-adjusted mortality rates for all cancers in the United States ranged from 13.6/100,000 in adults aged less than 50 years to 222.4/100,000 in those aged 50-64 years and 1,059.2/100,000 in those aged ≥65 years for both sexes.[11]

1.2.3. Survival

Older adults also experience worse survival outcomes compared with younger individuals. Whilst survival generally decreases with increasing age and is lowest for those aged 80-99 years, this is likely to reflect the higher prevalence of competing mortality risks in older individuals, along with differences in tumour characteristics (such as stage at presentation) and management influenced by the availability and ability to tolerate the most effective

anticancer therapeutic approaches.[15] The SEER dataset shows that in 2013 the relative survival rate for all cancers (i.e., cancer survival in the absence of other causes of death) at 5 years was 76.2% for individuals aged <50 years, 68.1% for those aged 50-64 years and 61.4% for those aged ≥65 years.[11]

1.2.4. Cancer distribution

The distribution of the most common malignancies varies considerably across age groups, with particular differences seen in younger versus older individuals. In adults aged ≥55 years, the three most common malignancies are breast, lung and colorectal cancer in women and breast, lung and colorectal cancer in men.[16] Specifically, based on NCRAS data,[16] in 2017 in England breast cancer was the most common cancer in women across various age groups (15-44 years: 35%; 45-54 years: 50%; 55-64 years: 37%; 65-74 years: 28%; ≥75 years: 21%). However, the second most frequently diagnosed malignancy was lung cancer in women aged 55-64 years (16%), 65-74 years (16%) and ≥75 years (11%) melanoma in those aged 45-54 years (6%) and cervical cancer in those aged 15-44 years (11%). Colorectal cancer was the third most common tumour diagnosed in women aged 45-54 years (6%), 55-64 years (9%), 65-74 years (10%) and ≥75 years (14%), while in those aged 15-44 years this was melanoma (10%).

In men, in 2017 prostate cancer was the most common cancer in various age groups (45-54 years: 16%; 55-64 years: 29%; 65-74 years: 33%; ≥75 years: 24%), while in those aged 15-44 years this was testicular carcinoma (20.5%).[16] Lung cancer was the second most frequent tumour in men aged 55-64 years (11%), 65-74 years (14%) and ≥75 years (16%), while in those aged 45-54 years this was colorectal cancer (11%) and in those aged 15-44 years this was melanoma (10%). The third most common malignancy diagnosed in men was colorectal cancer in those aged 15-44 years (9%), 55-64 years (13%), 65-74 years (12%) and ≥75 years (14%), while in those aged 45-54 years this was head and neck cancer (9%).

1.3. ONGOING DEMOGRAPHIC CHANGES

1.3.1. Global and regional trends in population ageing

The general population continues to experience a sustained change in its age structure driven by increasing life expectancy and decreasing levels of fertility.[17] Therefore, both proportion and the number of older persons in the total population are growing rapidly. Globally, there were 727 million individuals aged 65 years and older in 2020.[18] Most older individuals live in Eastern and South-Eastern Asia (260 million) and Europe and North America (over 200 million).

Over the next three decades, the number of older individuals worldwide is projected to more than double, reaching over 1.5 billion in 2050.[2] Globally, the proportion of the population aged 65 years and older is projected to increase from 9.3% in 2020 to approximately 16.0% in 2050. This increase in size of the older population will be observed in all geographical areas between 2020 and 2050. However, the largest increase is projected to occur in Eastern and South-Eastern Asia, where the number of older adults will increase by 312 million. The number of older individuals is expected to grow fastest in Northern Africa and Western Asia from 29 million in 2019 to 96 million in 2050 (+226%). Sub-Saharan Africa will have the second fastest rise (+218%), with an expected growth from 32 million in 2019 to 101 million in 2050. On the contrary, the projected increase will be relatively smaller in Australia and New Zealand (+84%) and Europe and North America (+48%), where the population is already significantly older compared with other geographical areas. While Eastern and South-Eastern Asia have the largest share of the global older population (37%) and this is projected to remain so in 2050, the second largest proportion lives in Europe and North America (28.5%).[2] Nonetheless, this is expected to shrink to 19.1% in 2050 in the context of the ageing of the general population elsewhere.

Along with the key role of fertility decline, the improvements in survival into older ages associated with better treatment of cardiovascular and cerebrovascular disease and communicable conditions and public health

measures have also contributed significantly to the population ageing.[19-21] This process involves not only improvements in life expectancy at birth, but also the even more rapid improvements in life expectancy at older ages. Between 1990-1995 and 2015-2020, at global level life expectancy at birth has increased by 7.7 years (12%) and is expected to increase by an additional 4.5 years (6%) between 2015-2020 and 2045-2050. Sub-Saharan Africa has experienced the largest increase (11.4 years) between 1990-1995 and 2015-2020.

Life expectancy at age 65 corresponds to the average number of additional years of life that a 65-year-old person would live if subjected to the age-specific mortality risks of a given period throughout the remaining lifetime. Globally, an individual aged 65 years in 2015-2020 is expected to live, on average, an additional 17 years.[2] By 2045-2050, the life expectancy will have increased to 19 years. Life expectancy at 65 years is currently highest in Australia and New Zealand at 17.5 years and it is projected to increase further to 23.9 years in 2050. This specific trend is projected to occur in all countries. although women currently outlive men by 4.8 years, this global gender gap is expected to narrow over the next three decades.

Globally, women tend to live longer than men. In 2015-2020, women's life expectancy at birth exceeded that of men by 4.8 years.[2] This gap was largest in Latin America and the Caribbean (6.5 years), Europe and Northern America (6.1 years) and Eastern and South-Eastern Asia (5.3 years). Life expectancy at 65 years was also longer for women (18 years) compared with men (16 years) in 2015-2020, with the largest gap in Eastern and South-Eastern Asia (3.4 years), Europe and Northern America (3.1 years) and Latin America and the Caribbean (2.8 years). Therefore, in 2050 women will represent 54% of the population aged 65 years and older worldwide.

1.3.2. Additional indicators of population ageing

While the proportion of older individuals is frequently used as a measure of the ageing of the general population, additional indicators have been

developed to account for the diversity of capacities and dependencies across ages and increased life expectancy. The ageing of the general population can be defined conventionally based on chronological age (years since birth), with a fixed threshold of old age at age 65, or based on prospective age (remaining years of life), with a dynamic threshold of older age progressively rising with increasing life expectancy.[22]

The old-age dependency ratio (OADR) corresponds to the number of individuals aged 65 years and older per 100 persons of working age (aged 20 to 64 years). In the context of the increasing longevity and declining fertility of the general population, the proportion of the older age group is increasing whilst the share of younger age is declining. Since 1990s, the OADR has steadily increased globally, with 16 individuals aged 65 years and older per 100 persons aged 20-64 years in 2019.[2] In 2050, the global OADR is projected to increase to 28 older persons per 100 working-age individuals. In Europe and Northern America, the OADR was 30 in 2019 and will sharply rise to 49 in 2050. Similar trends are expected to be observed in Eastern and South-Eastern Asia (from 18 in 2019 to 43 in 2050), Latin America and the Caribbean (from 15 in 2019 to 33 in 2050), Northern Africa and Western Asia and Central-Southern Asia (from 10 in 2019 to 22 in 2050). In 2019, Japan had the highest OADR in the world with 51 individuals aged 65 years and older per 100 persons aged 20-64 years, followed by Finland (39) and Italy (39).[2] By 2050, the three countries with the highest OADR will be Japan (81), the Republic of Korea (79) and Spain (78).

However, the OADR does not consider the heterogeneity of older individuals. Therefore, the prospective old-age dependency ratio (POADR) is calculated as the number of individuals above the age closest to a remaining life expectancy of 15 years relative to the number of persons between age 20 and that age.[23, 24] Trends in the POADR demonstrated slower increases in areas with older populations compared with those observed in the OADR. Globally, the POADR has actually declined from 12.9 in 1990 to 11.6 in 2019 (-10%), but it is projected to increase to 17.3 by 2050 (+50%).[2] The fastest

increase will be observed in Eastern and South-Eastern Asia (from 12 in 2019 to 25 in 2050, corresponding to +107%).

1.3.3. Population ageing trends in the United Kingdom

The demographic trends observed at global level are reflected also in those occurring in the United Kingdom.[25] The number of individuals aged 65 years and older has increased by 2.3 million between 2009 and 2019, from 16.2% to 18.5% of the total population.[26] Also, the older age group has grown faster compared with the younger groups, with those aged 65 years and older expanding by 22.9% and including 12.4 million individuals in 2019 versus those aged 16-64 years (that have increased by 3.2% and include 41.7 million adults). Additionally, the increase in the share of individuals aged 65 years and older was similar across the four constituent countries of the United Kingdom.

These changes have impacted on the median age of the general population in the United Kingdom. In 2019, this was 40.3 years, 1 year higher compared with 2009.[26] Wales had the highest median age in 2019 (42.5 years), followed by Scotland (42.0 years), England (40.0 years) and Northern Ireland (38.9 years). Over the previous 10 years, the median age increased in all four countries, although the largest increases were observed in Northern Ireland and England who have younger populations. Importantly, coastal and rural areas have a higher median age compared with urban areas.[27] The local authorities with the highest median age are predominantly located in the South West, around the south and east coasts of England, around the west coast of Scotland or in central and western areas of Wales. Those with the highest median age include North Norfolk (54.3 years), Rother (53.1 years), East Lindsey (52.4 years) and South Hams (51.5 years).

By 2041, the baby boomers born in 1960s will have progressed into their 70s and 80s, and by 2068 there could be an additional 8.2 million people aged 65 years and older in the United Kingdom.[27] Declining fertility and mortality rates will lead to an increase in the number of individuals 65 years and over age group to 20.4 million, accounting for 26.4% of the projected population in

2068. While in 1998 around 1 in 6 people were aged 65 years and older (15.9%), this ratio increased to 1 in every 5 people in 2018 (18.3%) and will rise to around 1 in every 4 people (24.2%) by 2038. In 1998 in the United Kingdom the OADR was 300 and by 2008 this had increased to 307. Subsequently, it decreased to 295 in 2018, although it is projected to increase again up to 360 by 2038.[27]

1.4. CHALLENGES OF MANAGING CANCER IN OLDER ADULTS

The principles of managing cancer in older individuals are the same as in younger patients. However, several aspects make the care of this specific population of patients more complex compared with other age groups. While some factors are related to the existing evidence base that should inform decision-making, many are associated with the heterogeneity of older adults with cancer.

1.4.1. Underrepresentation of older adults and barriers to their recruitment in oncology clinical trials

As the burden of cancer in older individuals is increasing at global level, studying the efficacy and toxicity of cancer therapies in this population is key and a solid amount of evidence is needed to inform decision-making.[28] Nonetheless, the available evidence is limited by the underrepresentation of older patients in oncology clinical trials.

Hutchins et al. retrospectively analysed data from 164 Southwestern Oncology Group therapeutic trials ongoing between 1993 and 1996 and showed that only 25% of patients recruited were aged ≥65 years, while in 1999 older individuals represented 63% of the cancer patient population in the United States.[29] This gap was particularly pronounced for trials enrolling patients with breast cancer: only 9% of those recruited to these trials were ≥65 years compared with 49% in the general breast cancer patient population. In 2014, Hurria et al have documented that while 28% of individuals diagnosed with cancer in the United States were aged ≥75 years, less than 10% of those enrolled onto National Cancer Institute Cooperative Group clinical trials were of the same age group.[30] Similarly, only 24% of participants in trials registered with the Food and Drug Administration in the United States are aged ≥70 years.[31, 32] Several additional analyses have reported similar findings over the last two decades.[33-38]

Even when older adults are recruited in oncology trials, they are typically fitter and have fewer comorbidities or functional impairments[39] compared with those seen routinely in clinical practice.[33, 37, 38, 40] Therefore, the evidence available on the efficacy and safety of most cancer treatment agents is derived from clinical trials conducted in healthier and younger patient populations.[31, 41] This leads to substantial disparities in the treatment and outcomes in older patients compared with their younger counterparts.[42-54]

Barriers to the recruitment of older patients with cancer in oncology therapeutic studies may include factors attributed to clinical trials, healthcare professionals, patients or caregivers.[55, 56] Trials do not usually limit eligibility of patients based on age alone. However, several inclusion and exclusion criteria may limit the participation of older patients with cancer to clinical studies. These usually involve Performance Status (PS), organ function and comorbidity conditions.[57, 58] While PS and comorbidities may impact survival rates and therefore this can be considered a logical approach to select eligible individuals who are most likely to benefit and tolerate experimental treatments in the general cancer patient population, older individuals have a higher burden of comorbid conditions. Also, in this age group PS is a poor descriptor of overall health and a poor predictor of adverse events.[46]

In a systematic review of barriers to recruitment of older individuals with cancer to clinical trials,[56] this was attributed to trials themselves in 50% of the 13 included analyses.[48, 59-63] In all these studies, these involved stringent eligibility criteria. Narrow eligibility criteria aim to limit excessive treatment-related morbidity and mortality. However, they are more challenging to meet for older patients in the context of the higher burden of comorbidities and polypharmacy and age-related organ function decline. These aspects may influence trial results and their interpretation. Interestingly, in a study by Javid et al trial participation rates, survival and toxicity rates did not differ based on age for patients eligible for clinical trials.[48] Additional challenges highlighted by Sedrak et al included language used in the consent forms[48, 59, 60] and availability of clinical studies.[59, 62] Trial eligibility criteria are instrumental to

limiting the external validity of the current evidence base and drive recommendations for the management of cancer in older patients with cancer.[64]

Sedrak et al also documented barriers attributed to healthcare providers in 75% of studies investigating obstacles to the trial recruitment of older patients with cancer.[56] In this systematic review, concerns regarding toxicities in the context of comorbidities were predominant and highlighted by 78% of studies.[48, 59-63, 65-70] However, 56% of these trials showed that hesitation was driven by patients' age alone.[48, 59-61, 68] Additional barriers included time constraints,[48, 60, 61, 68] staff shortages,[48, 59, 60] preferences for another treatment,[60, 61, 67] general bias against research,[48, 61, 65, 68, 70] lack of awareness on trial availability[61, 67] and concerns about the randomisation.[48, 68] On the other hand, a prospective analysis including 1,079 patients being considered for clinical trials involving patient and physician questionnaires showed that 11% of investigators did not offer patients enrolment within studies solely on the basis of their age.[48] The same analysis also showed that clinical trial enrolment was discussed with 76% of patients aged <65 years and with 58% of those aged ≥65 years. Among factors related to the investigators, concerns regarding the interplay between potential toxicities of experimental treatments and comorbidities are frequently cited.[40, 67] Nonetheless, the tolerance to trial treatments does not necessarily vary across age groups, even in phase 1 and phase 2 studies.[71, 72]

In the systematic review by Sedrak et al,[56] 83% of trials reported barriers attributed to patients.[48, 59-61, 63, 65-67, 69, 70] In 60% of these studies, they related to lack of patient knowledge,[48, 59, 61, 63, 65, 70] transportation issues,[48, 59, 61, 63, 65, 66] time demands or burden associated with clinical studies,[48, 59, 60, 63, 66, 69] concerns about experimental treatment efficacy and safety[48, 63, 65, 66, 69, 70] and general worries about experimentation.[48, 60, 61, 66, 67] Additional barriers included patients' treatment preferences,[48, 60, 61, 67] concerns about financial toxicity,[48, 59, 61, 66] age (e.g., patients believe they are too old)[65, 70] and emotional

burden.[59, 69] Some authors also cite a lack of autonomy over treatment decisions as being a reason for foregoing trial participation.[70] In an analysis of questionnaires and semi-structured interviews exploring attitudes of 425 older individuals diagnosed with cancer treated in a single institution, some expressed concerns regarding their contribution to shared decision-making if they enrol in a clinical trial. Additional barriers include concerns about the safety of trial treatment, the input of families and caregivers and doubts about the positive impact of trial participation on other patients with cancer.[48] Nonetheless, altruism has been documented as a powerful influencing factor in this setting.[73] Older patients have also been found to be less frequently informed about the availability of clinical trials compared with their younger counterparts, although this aspect might be at least partially influenced by literacy levels.[70] The trust in trial investigators is usually a difficult factor to interpret since this may be contribute to either enrolling or foregoing trial participation.[73] Patient perception of trial efficacy may play a relevant contribution: for example, a study of 486 patients with cancer showed that 44% of them declined trial enrolment because it compared an experimental agents with an established standard of care, while patients were more inclined to participate in trials investigating a standard treatment with or without the addition of a novel drug.[73] In this analysis, 20% of patients participated because they perceived the trial as the best treatment option, although some abstained as they favoured the standard treatment. Logistical obstacles are certainly a key barrier for the recruitment of older patients in clinical trials.[74] These challenges usually involve the need to travel long distances to specialised or academic centres, the lack of social support and financial aspects. Nonetheless, Javid et al did not necessarily document any differences in support networks and financial concerns across age groups.[48]

Finally, barriers to trial participation for older patients with cancer may also involve caregivers. In the systematic review by Sedrak et al,[56] one third of the included studies reported them (namely, caregivers' concerns[48, 59, 61, 70] and caregiver burden[48, 61]). Although caregivers are frequently key in treatment decision-making, patient advocacy and supportive care for older

patients with cancer,[75] no studies have so far directly investigated their role on trial participation in this specific population.

1.4.2. Heterogeneity of older adults with cancer and risk of under- and over-treatment

Older adults with cancer are a heterogenous population in terms of key domains that may have a significant impact on their well-being.[76] These domains include physiologic reserve, organ function, comorbidities, cognitive impairment, nutritional status, polypharmacy, disability, psychological distress and social activity and support. While chronological age alone provides relatively little information regarding the potential treatment benefits and individual tolerance, among patients of the same age there is substantial heterogeneity in the ability to undergo a number of anticancer therapeutic approaches.

In this population, the risk of under-treatment and over-treatment is substantial.[77] Traditionally, under-treatment for older patients with cancer has been defined as offering them less than recommended therapy.[30, 37, 78-80] However, this definition does not take into account the limitation that older adults are frequently excluded from the trials supporting these recommended therapies. Even when under-treatment is defined based on whether considering a less than recommended treatment actually leads to worse outcomes, these frequently involve survival metrics.[81-84] However, vulnerable older patients receiving intensive therapy may experience higher all-cause mortality as a result of treatment toxicity even in the context of lower cancer-specific mortality.[85] Importantly, survival outcomes such as progression-free survival may not necessarily correlate with patient-centred outcomes such as quality of life (QoL).[86-88] Also, QoL detriment and functional decline may outweigh survival benefits, whereas older adults often value functional and QoL as much as quantity of life.[89, 90] Although evidence on this specific aspect if sparse,[91] the balance between harms and benefits becomes even more delicate when survival gains are minimal while impacts on QoL are substantial.[92-94] Finally, age-related vulnerabilities

have a significant impact on treatment outcomes but are not accounted for in oncology clinical trials.[95-99] Omitting the assessment of domains such as comorbidities, cognition or function allows confounding by indication/contraindication,[100] with several unmeasured confounders influencing the association between treatment intensity and outcomes. Although frailer older individuals with cancer are less likely to be offered intensive treatments, in this setting a higher mortality burden may be attributed not only to the receipt of less intense therapies but also to age-related vulnerabilities.[6, 101-105] Smaller benefit gains and increased complications have been documented for frailer older individuals receiving intensive treatments endorsed by guidelines in real-world studies.[106-109]

Over-treatment is often defined as giving intensive anticancer therapy to vulnerable older patients who cannot tolerate its burden of toxicity.[110-112] Nevertheless, even lower intensity treatments can sometimes exceed the reduced physiologic reserve of vulnerable or frail older patients and correlate with functional decline or mortality.[113]

Also, a number of studies do not include fitness assessments for risk stratification and to guide interventions targeting reversible causes of frailty in older individuals.[6, 114] However, over-treatment encompasses also giving treatments which are not able to provide any meaningful benefit in an older patient's remaining lifetime. In this regard, evidence have often focused on the concept of overdiagnosis, which is frequently associated with cancers subject to screening.[115] However, over-treatment may involve also malignancies diagnosed based on symptoms. Considering the aggressiveness of the cancer in the context of patients' life expectancy to estimate whether a specific treatment is likely to provide any benefit in their remaining lifetime is crucial.[6]

Therefore, in geriatric oncology defining under- and over-treatment should emphasise additional risk factors and outcomes that are meaningful for older adults with cancer beyond simply focusing on survival measures.[116] Patients' values and preferences and QoL are particularly relevant in this setting and should be reviewed in a discussion of what outcomes matter most

to individual older patients.[117, 118] Assessing priorities is key in view of the fact that older adult may have different burdens of comorbidities and functional impairments:[119] while those that value prolonging life may wish to tolerate the burden and toxicity of more intensive therapies, older individuals prioritising quality over quantity of life may view the same approach as a harm rather than beneficial.[90]

Similar considerations apply to the clinicians' perspective. Under-emphasising patients' preferences and focusing on disease-specific and survival measures may increase the risk of over-treatment. For example, some clinicians may consider withholding radical treatment for potentially curable cancer in older patients as under-treatment due to concerns regarding cancer-specific mortality. However, in the presence of comorbidities, cognitive impairment or functional deficits, other-cause mortality may be higher and not impacted or increased by a more radical and intensive therapeutic approach. If patients and their caregivers value more function and QoL, this approach would represent over-treatment. On the other hand, for fit older individuals that value quantity of life even in the context of the potential risk of complications, declining radical treatment would represent under-treatment. In this setting, some clinicians may still consider this approach over-treatment solely on the basis of their perceived risk of adverse outcomes and chronologic age.

Therefore, a comprehensive and rigorous framework including oncologic factors and geriatric domains is crucial to inform shared decision-making for older adults with cancer.[120] In this setting, clinicians should aim to identify the seemingly frail older adults that are likely to benefit from and tolerate standard anticancer therapy and the seemingly fit older individuals who are prone to experience undue side effects and require a modified anticancer treatment plan in the context of their specific values and preferences.

1.4.3. Organ function decline

Ageing correlates with a gradual decline in organ function impacting on the resilience and ability to maintain homeostasis under conditions of

physiological stress.[5] Despite many changes in the organ function may not be apparent under normal conditions, they may become apparent under the effect of stressors such as cancer and its treatment.[121]

Aging is associated with a decline in the hepatic volume and blood flow.[122, 123] These changes may slow the first-pass metabolism and elimination of systemic agents, potentially exposing patients to higher drug concentrations for longer periods of time.[121] Liver function may also be influenced by the presence of the burden of metastatic disease that may increase the expected degree of hepatic decompensation. Therefore, clinicians should consider careful monitoring of liver function for older patients receiving systemic anticancer agents especially if they have hepatic metabolism.[124] Considering additional risk factors for hepatic damage, such as alcohol abuse and history of hepatitis, is also important for decision-making purposes.

Renal function is also a key concern for the management of older patients with cancer. The glomerular filtration rate also declines with age,[122] that correlates with a reduction in the renal mass and a gradual hyalinisation of renal vasculature. On the other hand, the loss of muscle mass associated with the ageing process makes serum creatinine concentration alone a less reliable indicator of renal function in this age group. Since the renal reserve is diminished in older individuals, volume depletion may result in exaggerated reductions in renal function.[121] For example, fluid management should be carefully monitored in this age group, especially in case patients experience gastrointestinal side effects (such as vomiting or diarrhoea) that can increase fluid loss.[124]

The ageing process correlates also with a gradual decline in the bone marrow reserve. This aspect significantly increases the risk of severe and prolonged cytopenia associated with myelosuppressive agents in this age group.[123, 125] An increased incidence of severe neutropenia in older adults compared with their younger counterparts has been observed on a number of chemotherapy regimens.[126-129] Hence, systemic anticancer therapy (SACT) dose reductions or delays may be more frequently required in this

group of patients.[124] The use of white blood cell growth factor support is also recommended for older patients receiving cytotoxic therapy, especially if the risk of febrile neutropenia is ≥20% and in the curative setting.[5, 6, 130] Anaemia is also frequently observed in older adults diagnosed with cancer as a consequence of both the malignancy and its treatments and can crucially impair their functional status.[131-133]

Normal ageing also correlates with reduced cardiac output and heart rate modulation, increased arterial stiffness, myocardial hypertrophy, impaired endothelial function and conduction abnormalities.[134] These factors may increase the risk of coronary artery disease, the frequency and severity of valvular heart disease and decrease the ventricular compliance.[122] Therefore, the possibility of exacerbating these abnormalities should be taken into account when systemic or local therapeutic approaches potentially impacting on the cardiac function are pursued.[5]

Loss of muscle mass and reduced muscular strength and power are also common changes attributed to the ageing process in this population.[135] Along with inactivity, sarcopenia may contribute to the loss of muscle mass in this population and is not necessarily associated with weight loss.[136] On the other hand, sarcopenic obesity is prevalent in the older age group.[135, 137] Its aetiology is multifactorial and involves disuse, chronic conditions, inflammation, insulin resistance, malnutrition, specific cancers and their treatments. Importantly, reduced muscle mass can impair mobility and functional status in older adults with cancer.

Additional changes possibly influencing the resilience of older adults to cancer and its treatment and their effects involve the bones (reduced bone mineral density and increased risk of fractures),[135] the digestive system (reduced acid secretion and drug absorption),[138] the central nervous system (reduced cortical volume, synaptic density, processing speed, attention and memory)[139] and the respiratory system (reduced elastic coil and lung volume and increased ventilation-perfusion inequality).[140]

1.4.4. Comorbidities

Comorbidities represent the additional burden of physical and psychological conditions diagnosed alongside the disease for which patients are being considered for treatment.[141] The burden of comorbidities increases with age.[4, 142] Frequent comorbid conditions in the older age group include anaemia, hypertension, gastrointestinal problems and cardiovascular disease (CVD).[143]

Significantly, the effect of comorbid conditions on life expectancy and treatment tolerance should be carefully evaluated when considering the risks and benefits of anticancer treatments.[144] A longitudinal observational study of 936 patients with breast cancer aged 40 to 84 years documented that those with ≥3 comorbidities had 20-fold higher mortality rate from causes other than breast cancer and a four-fold higher all-cause mortality rate compared with those with no comorbid conditions.[145] Similarly, a study of 1,255 patients with non-small cell lung cancer (NSCLC) recruited in two randomised trials in Canada showed that those aged ≥65 years were more likely to have a Charlson Comorbidity Index (CCI) ≥1 compared with their younger counterparts.[146] In this cohort, age was not an independent factor associated with survival but comorbidities were associated with increased mortality. Likewise, an analysis of 496 patients with a mean age of 67 years and undergoing surgery for colorectal cancer documented worse overall and disease-specific survival outcomes for those with a higher comorbidity burden defined based on the CCI, the National Institute on Aging and National Cancer Institute Comorbidity Index and the Adult Comorbidity Evaluation-27.[147]

Importantly, the presence of comorbidities also affects patients' ability to tolerate anticancer therapies.[148] This is particularly relevant for those diagnosed with common comorbid conditions such as CVD, diabetes and chronic renal insufficiency. An analysis of 120 patients aged ≥70 years with advanced NSCLC demonstrated that those with a CCI ≥2 were more likely to experience early chemotherapy discontinuations compared with those with a lower score.[149] A retrospective SEER-Medicare database analysis of

70,781 older adults with early-stage breast cancer showed that those diagnosed with diabetes were more likely to require hospitalisations and have a higher risk of all-cause mortality that may be attributed to either the cancer (and under-treatment) or to complications of diabetes.[150] Diabetes can also increase the risk of peripheral neuropathy for patients receiving taxanes-based chemotherapy, as documented in an analysis of 1,401 patients with cancer ≥65 years recruited in 23 Southwest Oncology Group studies.[151] Comorbidities may also compromise the effectiveness and completion of anticancer treatments as documented in a systematic review of more than 2,500 articles published between 2002 and 2012.[152]

Assessing comorbidities can provide key information on the health status and fitness of older patients with cancer that is independent of functional status. This aspect was illustrated in a study of 203 patients with cancer in whom there was no correlation between comorbidities and functional status.[153] This analysis, where comorbidities were measured by either the CCI or Cumulative Illness Rating Scale-Geriatric and functional status was assessed by Eastern Cooperative Oncology Group (ECOG) PS or activities of daily living (ADLs), suggests that comorbidity needs to be assessed independently from functional status in this population. The most important comorbidity prevalent in older patients was CVD. This may present a competing cause of mortality, and also complicates treatment delivery.

1.4.4.1. Cardiovascular risk factors and disease

In the general population, age alone appears to contribute to the higher prevalence of cardiovascular risk factors and to the development of CVD. In a cohort of more than 3.6 million individuals aged ≥40 years undergoing self-referred screening for CVD, the prevalence of any vascular disease increased significantly with each decade of life from 2.0% in those aged 40-50 years to 32.5% in those aged 91-100 years.[154] After adjusting for traditional risk factors, each additional decade of life was associated with an approximate doubling of the risk of CVD. Although all the major cardiovascular risk factors continue to be relevant in older persons,[155, 156] age may influence the relative importance of systolic, diastolic and pulse pressure, with the latter

being the strongest predictor of coronary heart disease risk above the age of 60 years.[157] Therefore, CVD is the most frequent single cause of death over the age of 65 years and is responsible for a significant burden of morbidity and disability in community-dwelling older individuals.[158]

Despite the increasing burden of CVD with increasing age, its prevalence in patients with cancer is unclear. Nonetheless, the presence of pre-existing CVD and risk factors may have significant impact on adverse outcomes on chemotherapy. The presence of CVD and risk factors is a key challenge for the management of older patients being considered for anthracycline-based chemotherapy in view of the well documented risk of cardiac toxicity on this specific class of cytotoxic agents.[159] A retrospective SEER dataset analysis including 6,388 patients aged ≥65 years and diagnosed with diffuse large B cell lymphoma (DLBCL) from 1991 and 2002 documented higher risk of congestive heart failure (CHF) in those with hypertension (hazard ratio [HR] 1.58; 95% confidence interval [CI] 1.28 to 1.95), coronary artery disease (HR 2.21; 95% CI 1.22 to 3.99) or other cardiac conditions (HR 1.53; 95% CI 1.26 to 1.84).[160] Similarly, a SEER-Medicare database study on 43,338 women aged 66 to 80 years diagnosed with stage I to III breast cancer and no history of cardiac disease showed that aside from age, the presence of hypertension and coronary artery disease were associated with increased cardiac risk (hypertension: HR 1.45; 95% CI, 1.39 to 1.52; coronary artery disease: HR 1.58; 95% CI, 1.39 to 1.79).[161] In this cohort, up to 38% of patients receiving an anthracyclines developed CHF at 10 years.

The presence of CVD and risk factors is also associated with a higher risk of complications on targeted anticancer therapies. Despite the overall low incidence of cardiac toxicity on anti-human epidermal growth factor receptor 2 (HER2) treatments,[162] this is a frequent concern in older individuals with HER2-positive breast cancer.[163] Impaired left ventricular ejection fraction (LVEF) was associated with higher risk of CHF in the registration studies of trastuzumab.[164, 165] A SEER-Medicare retrospective analysis including 9,535 patients aged ≥66 years treated with chemotherapy for stage I-III breast cancer identified higher rates of CHF compared to those reported in clinical

trials (29.4% with trastuzumab versus 18.9% without trastuzumab).[166] In this patient population, cardiac comorbidities (including coronary artery disease and hypertension) and older age were identified as risk factors. Likewise, a retrospective series of patients ≥70 years documented an increased incidence of cardiac toxicity on trastuzumab in the context of a previous history of cardiac problems.[167]

1.4.5. Functional impairment

Functional status is a patient's ability to perform routine daily tasks. These include ADLs required for basic living, such as feeding, grooming, transferring and toileting, and instrumental activities of daily living (IADLs), necessary to live independently in the community, such as shopping, managing finances, housekeeping, preparing meals and taking medications. Therefore, functional impairment involves deficits in a range of abilities related to meeting the needs of daily life, including physical, social, spiritual, psychological, and intellectual needs.[168, 169] Impairments in this key domain are prevalent among older adults with cancer.[170, 171] Also, among older individuals those diagnosed with cancer have a higher prevalence of geriatric syndromes, including functional impairment, frailty and falls, compared to those without cancer.[172]

A retrospective analysis of 9,745 older individuals in the United States showed an increased burden of limitations in ADLs and IADLs and a greater level of healthcare utilisation in those diagnosed with cancer.[173] In this analysis, the most common challenges involved walking (38%) and getting out of a chair (21%) among the ADLs and heavy housework (34%) and shopping (17%) among the IADLs. Likewise, limitations in ADLs and IADLs were seen respectively in 17% and 59% of patients with solid or hematologic malignancies in a caseload of 303 Italian patients aged ≥65 years.[171] Even in a more selected cohort of older cancer patients with a ECOG PS of 0-1, restrictions in ADLs and IADLs have been documented in 9% and 38% of patients respectively.[101] The complex interplay between functional status, other health domains and adverse outcomes of cancer and its treatment is well documented. Although there is no correlation between comorbidity burden

and functional impairments,[153] other domains relevant to the well-being of older adults may also influence functional status, such as depression.[174]

In general, functional impairments are associated with adverse outcomes of cancer and treatment complications. For example, a study of 314 patients aged ≥75 diagnosed with haematological malignancies showed higher mortality, unplanned hospitalisations and emergency room admission rates in case of decreased gait speed.[175] Also, in this study a reduced grip strength was associated with worse survival. Functional impairment also leads to institutionalisation and increased use of healthcare services: a recent analysis of 125 older patients with cancer (mostly breast cancer) with a mean age of 74 years showed that various functional problems (including IADL impairments, falls and limitations in climbing stairs) were associated with increased hospitalisations and long-term care use.[176]

Functional status is also a key predictor of chemotherapy toxicity. IADL limitations are included in the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score,[177] while the presence of falls, limitations in walking one block, the need for assistance with taking medications and reduced social activity are included in the Cancer and Aging Research Group (CARG) tools.[178-180] Another study has documented the influence of functional dependence and poorer ECOG PS on the risk of chemotherapy toxicity in a population of ovarian cancer patients aged ≥70 years.[181] Functional status also impacts on QoL. A study including 768 patients with cancer aged ≥65 years documented an association of patient-reported decreased levels of activities and function with poor health-related QoL assessed by Functional Assessment of Cancer Therapy-General and Patient-Reported Outcomes Measurement Information System measures.[182]

Therefore, a number of studies have investigated the impact of adapting anticancer treatment strategies based on functional assessments for older patients with cancer.[183-185] Functional status is a key meaningful endpoint for oncology clinical trials: while some older patients with cancer may be willing to trade compromised function in exchange for prolonged survival, many may

still favour functional independence and QoL over its quantity.[89, 186, 187] The International Society of Geriatric Oncology (SIOG) and the American Society of Clinical Oncology (ASCO) have developed guidelines that recognize functional status as a core domain of the evaluation of older patients with cancer and endorse its use in informing management of cancer in this population.[6, 188]

1.4.6. Polypharmacy

Polypharmacy is defined as the use of an increased number of medications, potentially inappropriate medication (PIM) use or medication duplication.[5, 189] Comorbidities, prescribing medications to treat complications derived from another medication (the “prescribing cascade”) and care fragmentation across multiple specialist services can increase the risk of polypharmacy.[190-193]

Polypharmacy is a common problem in the general geriatric population.[194] Older ambulatory patients use approximately three times as many medications as their younger counterparts,[195] with an average of at least four medications per patients and at least 90% taking at least one. In the population of older patients with cancer, the prevalence of polypharmacy has been reported to be 80%.[196] An analysis of 500 patients with cancer aged ≥65 years and treated in seven academic institutions documented that 48% used ≥5 medications at chemotherapy initiation.[189] Moreover, the use of complementary medicines including vitamins and supplements is also prevalent in patients with cancer.[197] Polypharmacy is also associated with a higher risk of taking PIM:[198] based on the Beers criteria,[199] the Screening Tool of Older Person's Prescriptions (STOPP) criteria[200] and the Healthcare Effectiveness Data and Information Set (HEDIS) criteria,[201] PIM have been documented in up to 51% of older individuals with cancer.[191]

Polypharmacy can lead to a significantly increased risk of drug interactions, morbidity and adverse events. Potential drug interactions are associated with an increased risk of toxicity for older patients with cancer receiving

chemotherapy and supportive care medications.[202] Medications inhibiting the cytochrome P450 enzymes (particularly CYP3A4) have the potential to increase the toxicity of cytotoxic agents either by reducing their conversion to nontoxic metabolites or by increasing their conversion to toxic metabolites. On the other hand, agents inducing enzymes in the P450 pathway (for example, dexamethasone, anticonvulsants, alcohol) can decrease the therapeutic effectiveness of cytotoxic agents by increasing the metabolism of active drug. Physiologic changes associated with the ageing process also have a major impact on drug pharmacokinetics and pharmacodynamics[121] and may increase the risk of adverse drug events in older individuals.

In the general older population, polypharmacy is also associated with functional impairments, falls and longitudinal functional decline.[203, 204] Similar effects have been documented also in older patients with cancer: in a cross-sectional study of 439 patients with advanced cancer initiating a new line of SACT, polypharmacy (defined as taking ≥8 medications) and PIM were associated with worse ADL and IADL.[205] Importantly, in this age group non-prescription medications (such as non-steroidal anti-inflammatory drugs and sleep aids) should also be considered PIMs since they may lead to adverse events including acute kidney injury, gastrointestinal bleeding, stroke, cognitive decline and falls;[206, 207] they may also interact with each other and with prescription medications including anticancer agents.

Therefore, evaluating polypharmacy and PIM in older patients with cancer is key as sometimes they might derive more harm than benefit from the use of many medications (for example, statins and antidiabetics) especially in the context of the shorter life expectancy of this age group and when cancer has a significant impact on their prognosis. The strategy of “deprescribing” (the planned discontinuation of medications) has been investigated in community-dwelling older adults to optimise medication use.[208] In the oncology setting, pharmacist input have been effectively implemented in the clinic to identify polypharmacy[191] and PIMs and a pharmacist-led deprescribing intervention have been shown to be feasible in the management of older adults with cancer.[209] Furthermore, providing to oncologists information on patients’

medications increases in-clinic conversations about medicine optimisation.[210]

1.4.7. Malnutrition

Nutritional status is a key health domain for older adults. In this population, malnutrition is frequently defined based on the presence of ≥1 of the following factors: ≥5% weight loss in one month or ≥10% in 6 months or a on Mini-Nutritional Assessment (MNA) score of <17/30 or a serum albumin <35 g/L or a body mass index (BMI) <21 kg/m^2.[211] Nonetheless, a high BMI does not necessarily exclude a diagnosis of malnutrition as this is a key feature of sarcopenic obesity.[212]

In the general older population, weight loss or low BMI have an adverse effect on general health even in the absence of a cancer diagnosis.[213-217] A study of 4,714 community-dwelling individuals aged ≥65 years documented the association of weight loss ≥5% with an increased mortality risk.[215] Similarly, an analysis of 7,527 adults aged ≥70 years showed that those with a BMI <19.4 Kg/m^2 (the lowest 10% of the population) were at higher risk of mortality.[213]

Despite individuals diagnosed with cancer are at risk of malnutrition due to cancer and its treatments, older patients are at particularly increased risk. More than 66% of older patients with cancer have been found to be malnourished in a study of 657 community-dwelling adults aged ≥70 years with or without cancer.[218] In this study, the risk of malnutrition increased by 14 times in the presence of a cancer diagnosis; depression, impaired functional status and psychological distress were also associated with malnutrition. In a study of 88 older patients hospitalised with advanced cancer, 71% were found to have experienced a weight loss decline ≥10%.[219] This was documented in 42.5% of patients in an analysis of 1,556 community-dwelling Italian older adults with cancer.[220] A study of community-dwelling older patients with cancer from France documented malnutrition in 13.3% of those diagnosed with non-gastrointestinal malignancies and 28.6% in those diagnosed with

gastrointestinal tumours.[221] More recently, the GAP70 study documented nutritional impairment in 61.1% of patients aged ≥70 years with advanced cancer and ≥1 impairments on geriatric assessment in 40 community practices in the United States.[9]

Among older patients with cancer, a study of 3,047 individuals enrolled in 12 ECOG trials confirmed the deleterious effect of weight loss on survival outcomes.[222] In this analysis, weight loss was an independent predictor of survival and was associated with poorer PS. Interestingly, weight loss was also associated with reduced response rates in patients with breast cancer (but not with those diagnosed with other tumours). Importantly, also limited weight loss ≤5% can be clinically significant for older patients with cancer. A number of studies have demonstrated similar results in older adults with cancer receiving chemotherapy.[223-225] A recent meta-analysis conducted including 71 studies confirmed a negative impact of malnutrition on intermediate- and long-term mortality;[226] in this meta-analysis, malnourished patients were also less likely to complete anticancer treatments and required more frequent healthcare utilisation.

Malnutrition is also associated with additional adverse outcomes in older individuals with cancer. These may include major depression and frailty, as shown in a cross-sectional study of 454 patients aged ≥65 years with cancer.[227] Malnutrition can also result in sarcopenia and frailty.[228] A recent study of 336 patients aged ≥60 years with gastrointestinal malignancies seen in a single Institution documented that malnutrition is associated with a higher prevalence of falls, IADL impairments and frailty.[229] In this analysis, the presence of malnutrition was also associated with worse health-related QoL involving both physical and mental domains.

Furthermore, malnutrition is associated with more frequent toxicities in older patients receiving chemotherapy.[177, 230, 231] A secondary analysis of a prospective multicentre study recruiting 750 patients aged ≥65 years receiving chemotherapy documented higher grade ≥3 chemotherapy toxicities associated with low albumin levels.[230] A cohort study including 993 patients

aged ≥70 years with a newly diagnosed malignancy showed that malnutrition can double their mortality.[232] Nutritional status is also a key item included in the CRASH chemotherapy toxicity prediction tool and associated with non-haematological complications.[177]

Obesity is another significant concern for cancer survivors in the context of its impact on comorbidities and QoL.[233, 234] However, there is paucity of data on the prevalence and the impact of obesity in older adults with cancer.[235] Ageing may correlate with an increase in body fat despite declining food intake.[236] Therefore, older adults are at increased risk of malnutrition even in the context of obesity due to the impact of cancer and its treatments.

Since a number of nutritional interventions can be pursued to maximise the health of older individuals with cancer, regular screening for older patients with cancer is recommended by international guidelines.[237, 238]

1.4.7.1. Sarcopenia

Sarcopenia results from an imbalance in the muscle protein turnover and is common in older individuals, with a prevalence ranging from 11 to 74% in different analyses.[239, 240] In older adults with cancer, sarcopenia may result from the ageing process or be a consequence of cancer and its treatment.[241]

Sarcopenia correlates with less anticancer treatment tolerability, increased risk of postoperative complications and shorter survival in patients with cancer regardless of age, type of tumour and stage.[193, 240, 242] The significant impact on survival outcomes may be related to more limited physical reserve. However, higher non-cancer-related mortality has also been documented during and after anticancer therapy in sarcopenic older patients with cancer.[243] Similar findings have been confirmed in a recent meta-analysis of 56 trials.[244]

A higher incidence of severe chemotherapy toxicity has been shown in patients with lower muscle mass or lower lean body mass, especially when they receive cytotoxic agents dosed based on body surface area.[245]

Sarcopenia has also been correlated with decreased health-related QoL, functional impairments and frailty in various cross-sectional studies.[246-249]

1.4.8. Cognitive impairment

Cognitive function is a key domain for the well-being of older adults with cancer. Several diagnostic criteria are available, but they can have significant impact on the prevalence of dementia.[250] Based on the Diagnostic and Statistical Manual-5, a diagnosis of dementia requires significant cognitive impairment in ≥1 of six domains based on history and clinical assessment (learning and memory, language, executive function, complex attention, perceptual-motor function and social cognition).[251] The prevalence of dementia is estimated to be approximately 6% in individuals aged ≥65 years and 30% in those aged ≥90 years.[252] Nonetheless, cognitive impairment is often under-diagnosed in many patients. The impact of routine screening for cognitive impairments in older individuals is unclear.[253] However, assessing decisional capacity in older adults with cancer is critical in view of the complexity of cancer treatment decisions and the implications of even mild cognitive impairment on the risk of developing dementia.[254]

In older patients with cancer, the optimal method to identify and measure pre-existing cognitive impairment is unknown.[255] Based on a SEER Medicare dataset analysis, the prevalence of memory loss and dementia in older adults diagnosed with cancer has been estimated to be approximately 12%.[172] More recently, cognitive problems have been documented in 36.4% of older patients aged ≥70 years with at least one geriatric assessment impairment and receiving SACT in a prospective study recruiting 718 patients in 40 community oncology practices in the United States.[9] Guidelines recommend that older patients with cancer are screened for cognitive impairment to evaluate cognitive capacity.[5] A number of studies showed that the prevalence of cognitive impairment detected on screening ranges between 24% and 38%.[101, 141, 183, 256-258]

Cognitive impairment may have substantial impact on morbidity and mortality in older individuals and dramatic implications treatment decisions and outcomes. In the general older population, dementia is an independent prognostic factor for survival. In a study of 821 subjects aged ≥65 years and screened for cognitive impairment, survival was almost halved in the presence of Alzheimer's disease, possible Alzheimer's disease or vascular dementia compared with the overall cohort.[259]

However, few studies have assessed these effects in older individuals with cancer. Those with cognitive impairment may find it more challenging to understand the nature of the cancer and their prognosis, along with risks and benefits associated with anticancer treatment. Cognitive problems may also affect the ability to process instructions on treatment regimens and side effect reporting and ultimately impact on treatment and cancer-related outcomes.[255] Additional concerns involve the ability to report cancer-related symptoms and its impact on palliative interventions and QoL.

A key additional concern in this population is the presence of mild cognitive impairment. Typically, this is recognised as greater cognitive impairment compared with what expected based on chronological age, but it does not impact function. Longitudinal population studies of older individuals using different definitions estimated it from 3% to 19%, with a 11-33% risk of progression to dementia in 2 years.[260, 261] A diagnosis of mild cognitive impairment does not necessarily imply lack of capacity to make decisions and consent since most of these patients are still able to understand the risks and benefits of treatment and participate in research.[262] However, this capacity may fluctuate based on the task and the complexity of decision.[263] Nonetheless, its specific prevalence in older patients with cancer is unclear.

In older patients with cancer, cognitive impairment can impact on cancer diagnosis and treatment. A SEER-Medicare database analysis including 17,507 adults aged ≥67 years with colon cancer treated in 1993-1996 showed that those with dementia were twice as likely to have colon cancer diagnosed on autopsy compared with those without cognitive impairment.[45] In this

study, patients with dementia were also less likely to undergo a surgical resection or adjuvant chemotherapy. Likewise, a study including 50,460 patients with breast cancer aged ≥65 years confirmed an association of dementia with later-stage diagnosis.[264] A retrospective cohort study of 106,061 patients aged ≥68 years with breast, colon and prostate cancer documented similar findings.[265] Cognitive impairment is also an independent predictor of functional disability, as demonstrated by a recent analysis of 304 patients with cancer aged ≥65 years referred for geriatric assessments and enrolled in the French Physical Frailty in Elderly Cancer patients study.[266] This association has also been previously demonstrated in the general older adult population.[267]

ASCO guidelines[6] recommend cognitive screening with validated tools[268, 269] to inform the management of older patients with cancer. Nevertheless, more research is warranted on this specific topic.[270]

One aspect of cognitive impairment which can present a particular challenge is delirium, which is distressing for patients and families, can interfere with recognition and management of symptoms such as pain, and is associated with increased mortality.

1.4.8.1. Delirium

Delirium is characterised by the acute onset of disturbance in attention, awareness and cognition not caused by pre-existing cognitive problems.[271] Age and cancer diagnoses correlate with increased risk of delirium.[272, 273] Nonetheless, delirium is also frequently under-diagnosed in older individuals. The prevalence of delirium has been estimated around 10-50% of patients undergoing surgery for cancer[274-278] and 20-90% among patients with advanced malignancy receiving palliative care.[279-281] In a study of 416 patients aged ≥75 years with solid tumours being considered for surgery, comorbidities, IADL dependence and a history of falls have been found to be predictors of postoperative delirium.[282]

On the other hand, delirium can have a significant impact on morbidity, mortality and decision-making in this population.[283-285] Additional relevant consequences in older individuals include functional decline,[286] cognitive decline[287, 288] and caregiver burden and distress.[289-291] Delirium is also potentially preventable in 30-40% of patients with non-pharmacologic interventions.[292-294] However, while most studies have investigated its prevalence in hospitalised general medicine patients or in those undergoing surgery, its prevalence in older patients with cancer and in the outpatient setting (where most of cancer care is delivered) remains unclear.[295]

1.4.9. Psychological distress

Cross-sectional studies have shown that approximately one third of older patients with cancer experience psychological distress.[296, 297] This was confirmed more recently also by the GAP70 study that recruited 715 patients aged ≥70 years diagnosed with advanced cancer and documented an overall prevalence of psychological status impairment in 28.6% of them.[9] Psychological distress may frequently take the form of depression or anxiety and have significant consequences on the well-being of older patients with cancer. However, it remains still poorly investigated in this specific population and most available data are derived from the general geriatric population.[298]

1.4.9.1. Depression

The prevalence of major depressive disorder ranges between 1 and 5% in community-dwelling older individuals, whereas this was documented in up to 42% of those residing in long-term care facilities.[299, 300] Despite the higher prevalence of depression in younger adults, its burden varies substantially in the older age group and increases significantly above the age of 80 years.[300, 301] Social isolation is a critical concern and increases the risk of depression in the older age group,[302, 303] alongside increased mortality and more frequent cognitive decline. A similar effect of social isolation has been demonstrated in a study of breast cancer survivors.[304] In older patients with cancer, the prevalence of depression is estimated to be 3-25%[296] and therefore ASCO guidelines recommend adequate screening.[6]

Depression has a worse trajectory in older adults[305, 306] and depressive episodes are more likely to recur in this age group.[307] Interestingly, in older adults depression may not necessarily involve dysphoria, but also irritability or withdrawal.[308] While sense of guilt and thoughts that life is not worth living are significantly less frequent in individuals aged ≥60 years compared with their younger counterparts,[309] a recent meta-analysis showed that older adults experience more psychomotor agitation, gastrointestinal somatic symptoms and general somatic symptoms.[310] On the other hand, depressive disorders include also minor depression, subthreshold disorders and dysthymia that may have significant clinical impact in this age group.[300, 311]

Symptom recognition remains a key challenge in routine practice for older patients with cancer experiencing depressive disorders. Patients and clinicians may perceive depression as expected for individuals diagnosed with cancer.[312, 313] In a significant proportion of older patients these issues remain undiagnosed and untreated despite the availability of effective treatment options.[299, 312, 314] Somatic symptoms may also be perceived as part of the ageing process or as an effect of the cancer,[299, 312, 313, 315, 316] since they frequently involve decreased appetite, weight loss, sleep disturbance, fatigue and diminished concentration.

In the general older adult population, major and minor depressive disorders may have a significant negative impact on functional impairment and QoL.[311] Similar effects have been documented on physical, social and role functioning also in older individuals with subthreshold depressive disorders.[317] Although evidence is mixed, some analyses have found an association between comorbid depression and cancer progression and related mortality.[318, 319] Similarly, non-dysphoric depression has been associated with increased mortality and daily activities impairments in individuals aged ≥65 years in a cohort study including 6,610 subjects in the United States.[308] Depression is associated with increased utilisation of healthcare resources as documented in a study of 6,649 patients aged >70 years where the presence

of depressive symptoms correlated with the need of more hours of informal caregiving.[320]

1.4.9.2. Anxiety

Anxiety is prevalent in patients with cancer and cancer survivors[321] and may be more common than depression across different age groups.[322, 323] In older individuals, cancer may be perceived by patients as one of multiple threats associated with multiple risks of morbidity and mortality and add further complexity to the management of anxiety.[324, 325] Moreover, in this age group the higher prevalence of frailty, comorbidities, functional impairments, lack of social support and cognitive decline may contribute to increasing anxiety, along with cancer-related symptoms and side effects of its treatments.[326]

Various studies have estimated the prevalence of clinically significant anxiety in older patients with cancer around 40%.[327-329] Although the burden of anxiety may reduce over time,[330] approximately 50% of older adults with cancer have been found to report anxiety ≥5 years after the initial cancer diagnosis.[331] This aspect highlights that anxiety may be a chronic condition also in this specific population.

Nonetheless, also anxiety is frequently under-treated in older patients with cancer:[332] among 1,211 patients aged ≥75 years being considered for surgery and referred to the geriatrics service in a comprehensive cancer centre, only one quarter of those with high distress were received mental health care.[333] Lack of knowledge on the prevalence, impacts and management of anxiety in this specific population remains a key challenge for oncology teams.[334] Also, identifying anxiety may be more challenging in older individuals in view of the higher burden of comorbidities and frailty in this age group:[335] while pain, dyspnoea and delirium may present as anxiety, metabolic and endocrine abnormalities, the use of steroids and specific antiemetics may also contribute to similar symptoms.

In patients with cancer, anxiety may correlate with physical symptoms including fatigue, nausea, pain, shortness of breath, worse social and cognitive function and poor QoL.[336-344] Anxiety may also interfere with decision-making and create challenges including poor communication with the healthcare team and treatment adherence.[345-347] Anxiety has also been associated with longer hospitalisations and higher mortality in this population.[348, 349] Finally, anxiety may also impact on patients' understanding of prognosis and treatment decisions, as shown in two analyses of patients with prostate cancer documenting earlier systemic treatment initiations in those reporting higher anxiety burden at baseline with no impact on survival outcomes but significant effects on QoL.[350, 351]

1.4.10. Lack of social support and activity

Social support includes the network of family, friends, neighbours and community members available to provide psychological, physical and financial assistance to patients with cancer. Social support include four domains: emotional, instrumental, informational and appraisal support.[352] Older adults may experience a reduction of their social support in the context of life events such as widowhood and retirement and these may increase the risk of social isolation.[353]

Evaluating social support in older patients is complex in view of the fact that perceived levels might differ from received ones[354] and its complexity involving characteristics specific to each individual.[355] Also, very limited data exist on the prevalence of social support needs in older adults with cancer. However, a recent analysis of 1,460 Medicare beneficiaries in the United States aged ≥65 years and diagnosed with various types of cancer showed that 67.5% of them had ≥1 social support need.[356] In this analysis, social needs were classified as physical, emotional, informational, practical and medical support. In 45% of these patients, these needs were unmet, especially pertaining to medical support (39%), but also informational (35%), physical (30%), emotional (28%) and practical support (20%). Interestingly, unmet social needs were more prevalent in those from ethnic minorities, those who

were not married, those with lower income and in those with a higher symptom burden.

Several studies showed that social support may directly impact on physical and emotional health and on overall survival (OS) in patients with cancer.[357, 358] Specifically, individuals with high levels of social support have lower risk of mortality compared with those with social needs, who have also increased risk of cancer progression.[359-363] The effect of a larger social network on cancer mortality was estimated around 20% in a meta-analysis of 87 controlled studies,[360] that documented also different degrees of impact according to specific malignancies. Belonging to a social network can also positively influence treatment adherence and illness-management behaviours, but it is also important to support participation in cancer care and several aspects such as symptom management, care coordination, assistance with ADL and emotional support.[364]

Studies on the impact of social support on disease-specific outcomes in older patients with cancer are more sparce. Positive effects on survival outcomes and decreased risk of de novo metastatic presentation have been shown in a number of studies.[365-367] However, in a pre-planned analysis of the Cancer and Leukemia Group B (CALGB) 49907 study recruiting 331 patients ≥65 years with early breast cancer receiving adjuvant chemotherapy, social support did not predict survival, treatment completion and adverse events.[368] Nevertheless, these findings may be attributed to the selection bias with patients with greater social support being recruited within the clinical trial.

Social support may also impact on additional outcomes relevant to older adults with cancer. Social support was found to correlate with a lower prevalence of fatigue and depression and better QoL in a prospective study of 94 patients with cancer aged ≥65 years and receiving chemotherapy.[369] Similarly, a secondary analysis of the CALGB 369901 study of 1,280 older patients with non-metastatic breast cancer monitored for 7 years, those with tangible social support (i.e., having someone able to take them to medical appointments if

needed) was associated with less risk of declining health-related QoL.[370] In a cross-sectional study of 1,457 patients with cancer aged ≥65 years, having emotional and physical needs (i.e., needing someone to listen when needing to talk or someone to help when fatigued) were also predictors of poorer health-related QoL.[371]

Finally, social support can also affect anticancer treatment tolerance in this specific population. A prospective study of 500 older adults initiating a new line of SACT, social activity was found to be a predictor of side effects.[178, 179] Therefore, this item was included in the CARG chemotherapy toxicity prediction tool.

1.5. USE OF FUNCTIONAL AND PHYSIOLOGICAL AGE TO GUIDE MANAGEMENT OF OLDER ADULTS WITH CANCER

Chronological age is a poor indicator of the physiological and functional status of older adults, and therefore it should not be the main factor guiding treatment decisions in oncology. Considering potential treatment benefits and complications in the context of life expectancy and patients' preferences is key in this specific population.

1.5.1. Estimation of life expectancy

A key challenge for the management of older individuals with cancer is balancing expected treatment benefits and outcomes compared with risks.[5] Estimating life expectancy should be the first question to address when evaluating this specific group of patients. The increased burden of competing risks of morbidity and mortality in this population may impact both cancer treatment and patients' prognosis. Moreover failing to consider life expectancy within shared decision-making may lead to both under-treatment and over-treatment.[372] An estimate of life expectancy should be considered in the context of the risk of cancer recurrence or cancer-related mortality within this specific time period in order to wisely inform treatment decisions. Epidemiological data have been used to develop tools able to predict the risk of death in older adults accounting for comorbidities, functional parameters and geriatric assessments.[372, 373]

Life tables, such as those published by the WHO, are a simple method to estimate life expectancy.[374] Nonetheless, they may be imprecise and do not address individual characteristics and functional status.[76] Additional tools have been developed and validated to predict more accurately absolute all-cause mortality in older adults.[372, 373] They include functional measures that can be easily obtained from geriatric assessments and are applicable in various settings (including community, nursing homes, hospitals and hospices). These life expectancy calculators are available on the ePrognosis website.[375] For example, among those relevant to community-dwelling older

individuals, the Gagne index was validated to predict 1-year mortality and takes into account comorbidities,[376] while the Carey index accounts for age, gender and physical function to estimate mortality at 2 years.[377] On the other hand, the Lee index can predict the risk of death at 4-10 years based on age, gender, comorbidities, physical function and nutritional measures.[378] Additionally, hospitalisations are included in the validation model of the Schonberg index predicting mortality at 5-14 years.[379] Finally, the combined Lee-Schonberg index takes into account age, gender, physical function, nutrition, comorbidities, hospitalisations, cognitive status and presence of depression to estimate mortality at 4-14 years.[380]

However, these tools are not disease specific, and their validation studies have been conducted only in specific geographical areas (typically, high-income countries). More recently, the Suemoto index has been developed using data from 5 longitudinal studies of community-dwelling adults including 23,615 participants ≥60 years from 16 countries and validated in 11,752 participants within the same age group.[381] This model takes into account age, comorbidities, cancer diagnosis, smoking habit, alcohol use, nutritional status, physical function and self-reported health. Despite limitations related to the retrospective nature of its validation study, this model had good calibration with less than 7% difference between estimated and observed mortality rates at 10 years. Nonetheless, the role of life expectancy prediction tools is yet to be validated in older individuals with cancer.

1.5.2. Estimation of treatment benefit

Treatment goals are an additional key consideration for the management of cancer in older individuals. These should be clearly defined in order to guide shared decision-making for patients suitable for treatments with curative versus palliative intent.[76] In the curative setting, an estimate of the risk of cancer-related mortality should be balanced against other causes of death in order to gain insight into the potential treatment benefits. A number of clinical and biomolecular prediction tools are available for routine use to support

treatment decisions for patients with different tumours. These should be weighed against estimated life expectancy and patient preferences.

For patients with early-stage breast cancer, PREDICT was developed based on cancer registry data from the United Kingdom and is available to predict the efficacy of various systemic treatment options, including chemotherapy, endocrine therapy, trastuzumab and bisphosphonates.[382] The primary outcome of this model is breast cancer-mortality. In an independent analysis of data on 2,012 patients included in the population-based FOCUS-cohort study, PREDICT was found to accurately estimate OS at 5 years and to overestimate it at 10 years.[383] Furthermore, PREDICT did not accurately predict OS in patients aged ≥85 years and in those with a higher comorbidity burden since competing risks are not included in this specific model. Similarly, despite this tool is no longer available, Adjuvant! Online was shown to overestimate overall and recurrence-free survival in patients with curable breast cancer aged ≥65 years.[384] The Bridging The Age Gap study decision tool integrates considerations on breast cancer characteristics (grade, size, nodal involvement, oestrogen receptor [ER] status, human epidermal growth factor receptor 2 [HER2] status) along with chronological age, comorbidities and ADL data to predict overall survival outcomes at 2 and 5 years with surgery versus primary endocrine therapy alone and with or without adjuvant chemotherapy.[385] While this specific tool may facilitate shared decision-making and impact on treatment decisions,[386] its performance has not been prospectively validated.[387]

Conversely, Adjuvant! Online was accurate in predicting the risk of recurrence and death at 5 years with or without adjuvant chemotherapy in an analysis including individual data on 2,967 patients with early-stage colon cancer aged ≥70 years.[388] Nonetheless, this study confirmed the significant impact of comorbidities on predicted survival estimates also in this population. Additional tools such as Numeracy! have been found to accurately predict recurrence-free survival in patients with early colon cancer aged ≥70 years,[389] although OS outcomes have not been validated in this age group.

For patients with prostate cancer being considered for radical prostatectomy, a normogram was developed and validated at the Memorial Sloan Kettering Cancer Center.[390] However, in this model life expectancy is calculated exclusively based on comorbidities and the validation study included a population of 6,279 patients with a median age of 60 years.[391] Likewise, the Roswell Park Prostate Cancer Calculator estimates on life expectancy and prostate cancer-specific mortality are derived simply using life tables.[392]

1.5.3. Recognition of patient preferences

The National Comprehensive Cancer Network (NCCN) guidelines recommend involving older patients in a shared decision-making process.[5] The United States Food and Drug Administration also advocates for increasing incorporation of patient preferences into treatment decision-making.[393] Capturing patient preference remains a key challenge in routine shared decision-making.[394-398] Systematic reviews have consistently shown discordance between physician perceptions of patients' priorities and their actual preferences.[398, 399] Patient distress during treatment discussions, complex cancer care and time constraints have been associated with higher likelihood of discordance.[400-402]

Moreover, patients may value differently various treatment outcomes.[90, 403-405] While some individuals may favour maximising long-term survival even in the context of additional side effects, others may prioritise maintaining QoL. QoL, functional status and cognitive function are important treatment goals in older individuals and may be more relevant than survival benefits.[89] In this context, assessments of the disease and the patients' overall health are insufficient to guide personalised treatment recommendations without understanding their preferences.[406]

Nonetheless, most clinical trials in oncology include survival benefits as their primary measure of success, while patient-centred outcomes (QoL and functional capacity and independence) are either included as secondary endpoints or not considered.[407, 408] Furthermore, older adults with cancer

are frequently offered treatment options involving competing outcomes that may benefit one specific aspect of their health status while negatively affecting others.[409] Patients in this age group are less likely to deem the survival gains associated with specific treatments as worthwhile.[410] These considerations on goals and motivational priorities are a crucial part of the treatment decision-making process for older individuals with cancer. In this population, shared decision-making requires investigating what matters to patients, understanding their underlying priorities, acknowledging the fears and hopes motivating their choices and integrating these factors with considerations on overall health and prognosis.[411]

1.6. GERIATRIC ASSESSMENTS IN OLDER ADULTS WITH CANCER

In view of the lack of easily measurable or precise markers of ageing, clinical tools are the gold standard to comprehensively evaluate older individuals with cancer and their overall health. In this population, there is a need to identify seemingly frail older individuals who are likely to benefit from and tolerate standard therapy, as well as seemingly fit older patients who are apt to experience undue side effects and require a modified anticancer treatment plan. Detailed information about specific issues involving these various domains may guide interventions that can improve the ability to undergo cancer treatment. A comprehensive geriatric assessment (CGA) evaluating the factors that can influence the well-being of older adults and the outcomes of anticancer therapies is useful in addressing these needs.

1.6.1. Comprehensive geriatric assessment: applying general geriatrics to oncology

Addressing these challenges is crucial to the development of a coordinated anticancer treatment plan and to guide appropriate personalised interventions for older individuals with cancer in view of their significant impact on therapeutic decisions and outcomes. In the absence of an easily measurable or precise marker of ageing, clinical tools remain the gold standard for the holistic evaluation of this patient population. CGA is a multidimensional and multidisciplinary diagnostic and therapeutic process encompassing important domains for the well-being of older adults,[188] including comorbidities, functional status, cognition, nutritional status, psychological state, social support and activity, fatigue, polypharmacy and geriatric syndromes (Table 1.1). Geriatric assessments are feasible in both daily clinical practice and in oncology clinical trials.[412] Consensus guidelines from the ASCO, the NCCN, and the SIOG recommend the routine use of geriatric assessments to inform treatment decisions for older patients with cancer.[5, 6, 188, 413]

Nevertheless, CGA is frequently perceived as time consuming and may not be required for every patient. Hence, screening tools have been developed to identify more vulnerable patients requiring a CGA and their use is recommended by international guidelines (Table 1.2).[414] On the other hand, screening tools are not fit to replace CGA for those patients requiring a more in-depth assessment: while they remain as useful to predict prognosis, they have not been demonstrated to identify problems that can be followed up specifically to improve outcomes.

The ASCO guidelines establish a minimum dataset for geriatric assessments in older patients with cancer (Table 1.3).[6] These instruments include the IADL for function, a thorough past medical history or using a validated tool (e.g., the Cumulative Illness Rating Scale-Geriatrics)[415] to assess and rate comorbidities, a single question for falls ("how many falls have you had in the last six months or since your last visit?"), the Geriatric Depression scale to screen for depression, the Mini-Cog[268] or the Blessed Orientation-Memory-Concentration test[269] to screen for cognitive issues, and assessment of unintentional weight loss to evaluate nutrition.

1.6.2. Benefits of integrating geriatric assessments and guided interventions in cancer care

Several studies have demonstrated a wide range of benefits from using CGA in older patients with cancer. These include predicting complications and side effects from anticancer treatment,[177, 181, 416-419] anticipating functional decline,[224, 420] estimating survival,[417, 421-424] assisting cancer treatment decisions,[425-427] detecting problems not found by routine history and physical examination during the initial evaluation,[101, 418, 425, 428, 429] identifying and addressing new emerging problems during follow-up care,[429, 430] improving mental health, well-being and pain control.[431]

Importantly, the aim of geriatric assessments is to guide treatment decisions and trigger interventions to maximise the general health of older adults before anticancer treatment initiation. Benefits of geriatric assessment-guided

interventions have been demonstrated and are well established in older patients without cancer.[432, 433] In the older cancer patient population, two systematic reviews have shown that geriatric assessment not only has the potential to reveal many unrecognised health issues, but also impacts on treatment decisions.[421, 434] More recently, a systematic review of 34 studies of geriatric assessments in older adults with cancer documented impacts on treatment decision in up to one half of patients.[435] This analysis included 18 prospective, 11 cross-sectional and 5 retrospective studies. However, none were randomised studies specifically designed to evaluate the effectiveness of geriatric assessments regarding medical decision-making. In this systematic review, three studies focusing on impact on treatment decision-making showed that decisions were changed for fewer than 50% of patients undergoing geriatric assessments. Seven studies examined the ability of CGA to predict treatment toxicity and complications but reported conflicting findings. Eleven studies evaluating the ability of CGA to predict mortality documented an association of geriatric assessment deficits with higher mortality.

However, a large multicentre study found that only 26% of interventions recommended by a geriatric oncology team were used in the anticancer treatment decision-making process for older patients with cancer.[425] This is a key challenge related to the fact that the treating oncologist, and not the geriatric team, was responsible for implementing the therapeutic interventions and recommendations. On the other hand, the uptake of geriatric assessment-driven interventions increased up to 70% in studies including recommendations issues by geriatric healthcare professionals.[421] These considerations support the routine integration of geriatric assessments and driven intervention in routine cancer care.[436]

Information derived from CGA can be used in a number of ways to assist in decision-making regarding the overall management of older patients with cancer. For example, some authors have classified the older population into specific groups for the purpose of selecting the treatment strategy, based upon their functional status, rehabilitative potential, life expectancy and tolerance of stress.[183-185, 437] Prognostic indices and nomograms have been

developed based upon domains and elements of the CGA that predict the probability of one-, two- and three-year OS for older individuals with cancer.[223, 438] A frailty index derived from information obtained from the CGA has been used to predict the likelihood of discontinuing chemotherapy and hospitalisation in older patients.[439] In older adults with lung cancer, chemotherapy treatment allocation based on CGA results is associated with reduced treatment toxicity and treatment failures compared with treatment allocated based on PS and age alone.[419] The information obtained from the CGA has also been combined with other information, including the proposed chemotherapy regimen, hematologic and renal function, hearing impairment, and cancer type, to derive a model used to predict chemotherapy toxicity in the older adult population.[178] This predictive model was developed (studying a cohort of 500 patients) and validated (in a cohort of 250 patients) in a prospective multicentre trial.[46] A cohort of geriatric oncology experts developed algorithms for geriatric assessment-guided care processes and developed geriatric assessment-guided interventions in view of the potential effect of impairment in a specific geriatric assessment domains on anticancer treatment decision-making.[440]

Recently, randomised clinical trials (RCTs) of geriatric oncology care delivery with CGA and CGA-driven interventions have investigated the effect of this approach on treatment toxicity, QoL, healthcare utilisation and survival. The GAP 70 cluster randomised study enrolled 718 patients ≥70 years with stage III-IV cancer and more than 1 impaired geriatric assessment domain other than polypharmacy and due to start a new chemotherapy regimen in 41 private oncology practices.[9] Recommendations based on geriatric assessments were sent to the primary oncologist by the University of Rochester geriatric oncology team and outcomes were compared versus usual care. The primary endpoint of the study was the rate of severe (grade 3-5) toxicity and secondary endpoints included non-haematological toxicity, survival and impact on treatment decisions. The study documented a statistically significant reduction in the rate of severe toxicities in the experimental arm compared with the standard arm (50.1% versus 71.0%) along with a reduction in non-haematological toxicities (31.8% versus 51.8%). The initial dose of systemic

treatment was also more frequently reduced in the intervention group whilst subsequent dose reductions were more frequent in the control group despite there was no difference in OS at 6 months in the two cohorts.

The GAIN study enrolled 600 patients ≥65 years with solid tumours of any stage and due to initiate a new line of chemotherapy.[7] Patients were randomised to usual care plus geriatric assessment-driven interventions versus standard care following a baseline CGA. The trial explored multidisciplinary team recommendations implemented by the primary team supported by a geriatric nurse practitioner. The primary endpoint was the rate of grade 3-5 chemotherapy toxicity and secondary endpoints included advanced directive completion, unplanned hospitalisations, emergency room visits and average length of inpatient stay. In this population, the study documented a statistically significant reduction in the rate of grade 3-5 chemotherapy-related toxicities (50% versus 60.4%) and statistically significant increase in the completion of advance directives (24.1% versus 10.4%) in the absence of any differences in A&E visits, hospitalisations and average length of stay.

The INTEGERATE study enrolled 154 patients ≥70 years with solid tumours or DLBCL due to receive chemotherapy, targeted therapy or immunotherapy.[10] Patients were randomised to integrated oncogeriatric care involving a geriatrician-led CGA and guided management versus usual care. The primary outcome of the study was a health-related QoL measured by the validated Elderly Functional Index score and secondary endpoints included healthcare utilisation, treatment delivery, function, hospitalisation, mood, nutrition, health utility and survival. The study showed an improvement in QoL, along with less frequent emergency presentations (-39%), unplanned hospitalisations (-41%), unplanned hospital overnight bed-days (-24%) and lower early treatment discontinuations, in the absence of any differences in treatment reduction, escalation and delay.

A study focusing on the perioperative oncogeriatric management for patients undergoing surgery for gastrointestinal malignancies enrolled 160 patients ≥65

years due to undergo a surgical resection.[441] These patients were randomised to an intervention arm including a preoperative meeting with geriatric assessment and guided recommendations followed by a post-operative inpatient consultation versus usual care. The primary endpoint was the postoperative length of stay and secondary endpoints included ICU use, rate of readmissions, symptom burden and QoL. The intention-to-treat analysis documented a reduction in the burden of symptoms and depression and the per protocol analysis showed a reduction in the length of hospital stay and postoperative intensive care unit use.

Additional RCTs of CGA and CGA-driven interventions are ongoing in the United States,[442-445] France[446] and Canada.[447]

In conclusion, the incidence of breast cancer and a number of common malignancies increases with increasing age. As a result, the burden of cancer in older individuals is projected to increase in the context of the ageing population and the improvements in cancer detection and management. However, cancer outcomes remain poorer in older adults compared with their younger counterparts. Also, several challenges may influence treatment selection in this specific population, where minimising the risk of both over-treatment and under-treatment is key. Therefore, identifying where these risks might be occurring and what are the possible drivers of over-treatment and under-treatment in this population is critical in order to minimise these hazards and better inform shared decision-making for older individuals diagnosed with cancer.

1.7. REFERENCES

1. Medicare.gov: What's Medicare? [cited 2022 18/07/2022]; Available from: https://www.medicare.gov/what-medicare-covers/your-medicare-coverage-choices/whats-medicare.
2. World Population Ageing 2019 (ST/ESA/SER.A/444). 2019, United Nations Department of Economic and Social Affairs, Population Division: New York.
3. Kowal, P.R., K. Peachey, and O. World Health, Information needs for research, policy and action on ageing and older adults: a report of the follow-up meeting to the 2000 Harare MDS Workshop : indicators for the minimum data set project on ageing: a critical review in sub-Saharan Africa, 21 and 22 June 2001, Dar es Salaam, United Republic of Tanzania. 2001, World Health Organization: Geneva.
4. Yancik, R. and L.A. Ries, Cancer in older persons. Magnitude of the problem--how do we apply what we know? Cancer, 1994. 74(7 Suppl): p. 1995-2003.
5. Older Adult Oncology (Version 2.2022). 2022.
6. Mohile, S.G., et al., Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Chemotherapy: ASCO Guideline for Geriatric Oncology. J Clin Oncol, 2018. 36(22): p. 2326-2347.
7. Li, D., et al., Geriatric Assessment-Driven Intervention (GAIN) on Chemotherapy-Related Toxic Effects in Older Adults With Cancer: A Randomized Clinical Trial. JAMA Oncol, 2021.
8. Wyld, L., et al., Programme Grants for Applied Research, in Improving outcomes for women aged 70 years or above with early breast cancer: research programme including a cluster RCT. 2022, National Institute for Health and Care Research
9. Mohile, S.G., et al., Evaluation of geriatric assessment and management on the toxic effects of cancer treatment (GAP70+): a cluster-randomised study. Lancet, 2021.
10. Soo, W.-K., et al., Integrated geriatric assessment and treatment (INTEGERATE) in older people with cancer planned for systemic

anticancer therapy. Journal of Clinical Oncology, 2020. 38(15_suppl): p. 12011-12011.
11. Howlader, N., et al., SEER Cancer Statistics Review, 1975-2018. 2021, National Cancer Institute: Bethesda, MD.
12. Yancik, R. and L.A. Ries, Cancer in older persons: an international issue in an aging world. Semin Oncol, 2004. 31(2): p. 128-36.
13. CancerData. [cited 2021 12/06/2021]; Available from: https://www.cancerdata.nhs.uk/.
14. Cancer Statistics for the UK. 12/06/2021]; Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics-for-the-uk.
15. Quaresma, M., M.P. Coleman, and B. Rachet, 40-year trends in an index of survival for all cancers combined and survival adjusted for age and sex for each cancer in England and Wales, 1971-2011: a population-based study. Lancet, 2015. 385(9974): p. 1206-18.
16. Cancer registration statistics, England: 2017. Office for National Statistics.
17. Pantazis, A. and S.J. Clark, A parsimonious characterization of change in global age-specific and total fertility rates. PLOS ONE, 2018. 13(1): p. e0190574.
18. World Population Ageing 2020 Highlights: Living arrangements of older persons (ST/ESA/SER.A/451). 2020, United Nations Department of Economic and Social Affairs, Population Division: New York.
19. Lee, R. and Y. Zhou, Does Fertility or Mortality Drive Contemporary Population Aging? The Revisionist View Revisited. Population and Development Review, 2017. 43(2): p. 285-301.
20. Murphy, M., Demographic Determinants of Population Aging in Europe since 1850. Population and Development Review, 2017. 43(2): p. 257-283.
21. Preston, S.H. and A. Stokes, Sources of Population Aging in More and Less Developed Countries. Population and Development Review, 2012. 38(2): p. 221-236.

22. Skirbekk, V.F., U.M. Staudinger, and J.E. Cohen, How to Measure Population Aging? The Answer Is Less than Obvious: A Review. Gerontology, 2019. 65(2): p. 136-144.
23. Sanderson, W.C. and S. Scherbov, Average remaining lifetimes can increase as human populations age. Nature, 2005. 435(7043): p. 811-3.
24. Sanderson, W.C. and S. Scherbov, A new perspective on population aging. Demographic Research, 2007. 16(2): p. 27-58.
25. Shaw, C., United Kingdom population trends in the 21st century. Popul Trends, 2001(103): p. 37-46.
26. Population estimates for the UK, England and Wales, Scotland and Northern Ireland: mid-2019. 2020 20/06/2021]; Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/annualmidyearpopulationestimates/latest#ageing.
27. Overview of the UK population: August 2019. 2019 20/06/2021]; Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/articles/overviewoftheukpopulation/august2019.
28. Scher, K.S. and A. Hurria, Under-representation of older adults in cancer registration trials: known problem, little progress. J Clin Oncol, 2012. 30(17): p. 2036-8.
29. Hutchins, L.F., et al., Underrepresentation of patients 65 years of age or older in cancer-treatment trials. N Engl J Med, 1999. 341(27): p. 2061-7.
30. Hurria, A., et al., Designing therapeutic clinical trials for older and frail adults with cancer: U13 conference recommendations. J Clin Oncol, 2014. 32(24): p. 2587-94.
31. Singh, H., et al., FDA analysis of enrollment of older adults in clinical trials for cancer drug registration: A 10-year experience by the U.S. Food and Drug Administration. Journal of Clinical Oncology, 2017. 35(15_suppl): p. 10009-10009.

32. Talarico, L., G. Chen, and R. Pazdur, Enrollment of elderly patients in clinical trials for cancer drug registration: a 7-year experience by the US Food and Drug Administration. J Clin Oncol, 2004. 22(22): p. 4626-31.
33. Lewis, J.H., et al., Participation of patients 65 years of age or older in cancer clinical trials. J Clin Oncol, 2003. 21(7): p. 1383-9.
34. Murthy, V.H., H.M. Krumholz, and C.P. Gross, Participation in cancer clinical trials: race-, sex-, and age-based disparities. Jama, 2004. 291(22): p. 2720-6.
35. Stewart, J.H., et al., Participation in surgical oncology clinical trials: gender-, race/ethnicity-, and age-based disparities. Ann Surg Oncol, 2007. 14(12): p. 3328-34.
36. Kumar, A., et al., Treatment tolerance and efficacy in geriatric oncology: a systematic review of phase III randomized trials conducted by five National Cancer Institute-sponsored cooperative groups. J Clin Oncol, 2007. 25(10): p. 1272-6.
37. Ludmir, E.B., et al., Factors Associated With Age Disparities Among Cancer Clinical Trial Participants. JAMA Oncol, 2019. 5(12): p. 1769-1773.
38. Ludmir, E.B., et al., Decreasing incidence of upper age restriction enrollment criteria among cancer clinical trials. Journal of Geriatric Oncology, 2020. 11(3): p. 451-454.
39. Bernard, M.A., J.A. Clayton, and M.S. Lauer, Inclusion Across the Lifespan: NIH Policy for Clinical Research. Jama, 2018. 320(15): p. 1535-1536.
40. Yee, K.W., et al., Enrollment of older patients in cancer treatment trials in Canada: why is age a barrier? J Clin Oncol, 2003. 21(8): p. 1618-23.
41. Singh, H., et al., Enrollment of older adults on oncology trials: An FDA perspective. J Geriatr Oncol, 2017. 8(3): p. 149-150.
42. Berry, M.F., et al., Variability in the treatment of elderly patients with stage IIIA (N2) non-small-cell lung cancer. J Thorac Oncol, 2013. 8(6): p. 744-52.
43. Bonadonna, G. and P. Valagussa, Dose-response effect of adjuvant chemotherapy in breast cancer. N Engl J Med, 1981. 304(1): p. 10-5.

44. Cress, R.D., et al., Patterns of chemotherapy use for women with ovarian cancer: a population-based study. J Clin Oncol, 2003. 21(8): p. 1530-5.
45. Gupta, S.K. and E.B. Lamont, Patterns of presentation, diagnosis, and treatment in older patients with colon cancer and comorbid dementia. J Am Geriatr Soc, 2004. 52(10): p. 1681-7.
46. Hurria, A., et al., Validation of a Prediction Tool for Chemotherapy Toxicity in Older Adults With Cancer. J Clin Oncol, 2016. 34(20): p. 2366-71.
47. Hurria, A., et al., Role of age and health in treatment recommendations for older adults with breast cancer: the perspective of oncologists and primary care providers. Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 2008. 26(33): p. 5386-5392.
48. Javid, S.H., et al., A prospective analysis of the influence of older age on physician and patient decision-making when considering enrollment in breast cancer clinical trials (SWOG S0316). The oncologist, 2012. 17(9): p. 1180-1190.
49. Lyman, G.H., et al., Incidence and predictors of low chemotherapy dose-intensity in aggressive non-Hodgkin's lymphoma: a nationwide study. J Clin Oncol, 2004. 22(21): p. 4302-11.
50. Mandelblatt, J.S., et al., Breast cancer adjuvant chemotherapy decisions in older women: the role of patient preference and interactions with physicians. J Clin Oncol, 2010. 28(19): p. 3146-53.
51. Merchant, T.E., et al., The influence of older age on breast cancer treatment decisions and outcome. Int J Radiat Oncol Biol Phys, 1996. 34(3): p. 565-70.
52. O'Neill, C.B., et al., Treatment-related toxicities in older adults with head and neck cancer: A population-based analysis. Cancer, 2015. 121(12): p. 2083-9.
53. Sargent, D.J., et al., A Pooled Analysis of Adjuvant Chemotherapy for Resected Colon Cancer in Elderly Patients. New England Journal of Medicine, 2001. 345(15): p. 1091-1097.

54. Schrag, D., et al., Age and Adjuvant Chemotherapy Use After Surgery for Stage III Colon Cancer. JNCI: Journal of the National Cancer Institute, 2001. 93(11): p. 850-857.
55. Trimble, E.L., et al., Representation of older patients in cancer treatment trials. Cancer, 1994. 74(7 Suppl): p. 2208-14.
56. Sedrak, M.S., et al., Older adult participation in cancer clinical trials: A systematic review of barriers and interventions. CA: A Cancer Journal for Clinicians, 2021. 71(1): p. 78-92.
57. Garrido-Laguna, I., et al., Validation of the Royal Marsden Hospital prognostic score in patients treated in the Phase I Clinical Trials Program at the MD Anderson Cancer Center. Cancer, 2012. 118(5): p. 1422-8.
58. van Heeckeren, W.J., et al., Safety and tolerability of phase I/II clinical trials among older and younger patients with acute myelogenous leukemia. Journal of Geriatric Oncology, 2011. 2(3): p. 215-221.
59. Freedman, R.A., et al., Promoting Accrual of Older Patients with Cancer to Clinical Trials: An Alliance for Clinical Trials in Oncology Member Survey (A171602). Oncologist, 2018. 23(9): p. 1016-1023.
60. Hamaker, M.E., et al., Slow accrual of elderly patients with metastatic breast cancer in the Dutch multicentre OMEGA study. Breast, 2013. 22(4): p. 556-9.
61. Kornblith, A.B., et al., Survey of oncologists' perceptions of barriers to accrual of older patients with breast carcinoma to clinical trials. Cancer, 2002. 95(5): p. 989-96.
62. Moore, D.H., et al., An assessment of age and other factors influencing protocol versus alternative treatments for patients with epithelial ovarian cancer referred to member institutions: a Gynecologic Oncology Group study. Gynecol Oncol, 2004. 94(2): p. 368-74.
63. Prieske, K., et al., Participation of elderly gynecological cancer patients in clinical trials. Arch Gynecol Obstet, 2018. 298(4): p. 797-804.
64. Battisti, N.M.L., M. Sehovic, and M. Extermann, Assessment of the External Validity of the National Comprehensive Cancer Network and European Society for Medical Oncology Guidelines for Non-Small-Cell

Lung Cancer in a Population of Patients Aged 80 Years and Older. Clin Lung Cancer, 2017. 18(5): p. 460-471.
65. Ayodele, O., et al., Comparing attitudes of younger and older patients towards cancer clinical trials. J Geriatr Oncol, 2016. 7(3): p. 162-8.
66. Basche, M., et al., Barriers to enrollment of elderly adults in early-phase cancer clinical trials. J Oncol Pract, 2008. 4(4): p. 162-8.
67. Kemeny, M.M., et al., Barriers to clinical trial participation by older women with breast cancer. J Clin Oncol, 2003. 21(12): p. 2268-75.
68. McCleary, N.J., et al., Challenges of conducting a prospective clinical trial for older patients: Lessons learned from NCCTG N0949 (alliance). J Geriatr Oncol, 2018. 9(1): p. 24-31.
69. Puts, M.T., et al., Participation of older newly-diagnosed cancer patients in an observational prospective pilot study: an example of recruitment and retention. BMC Cancer, 2009. 9: p. 277.
70. Townsley, C.A., et al., Understanding the attitudes of the elderly towards enrolment into cancer clinical trials. BMC Cancer, 2006. 6: p. 34.
71. LoConte, N.K., et al., Amongst eligible patients, age and comorbidity do not predict for dose-limiting toxicity from phase I chemotherapy. Cancer Chemother Pharmacol, 2010. 65(4): p. 775-80.
72. Giovanazzi-Bannon, S., et al., Treatment tolerance of elderly cancer patients entered onto phase II clinical trials: an Illinois Cancer Center study. Journal of Clinical Oncology, 1994. 12(11): p. 2447-2452.
73. Jenkins, V., et al., Drivers and barriers to patient participation in RCTs. Br J Cancer, 2013. 108(7): p. 1402-7.
74. Umutyan, A., et al., Overcoming barriers to cancer clinical trial accrual: impact of a mass media campaign. Cancer, 2008. 112(1): p. 212-9.
75. Kadambi, S., et al., Older adults with cancer and their caregivers - current landscape and future directions for clinical care. Nature reviews. Clinical oncology, 2020. 17(12): p. 742-755.
76. Soto-Perez-de-Celis, E., et al., Functional versus chronological age: geriatric assessments to guide decision making in older patients with cancer. Lancet Oncol, 2018. 19(6): p. e305-e316.

77. DuMontier, C., et al., Defining Undertreatment and Overtreatment in Older Adults With Cancer: A Scoping Literature Review. J Clin Oncol, 2020. 38(22): p. 2558-2569.
78. Passaro, A., et al., Immunotherapy in Non-Small-Cell Lung Cancer Patients With Performance Status 2: Clinical Decision Making With Scant Evidence. J Clin Oncol, 2019. 37(22): p. 1863-1867.
79. Sanoff, H.K., et al., Sorafenib Effectiveness in Advanced Hepatocellular Carcinoma. Oncologist, 2016. 21(9): p. 1113-20.
80. Burstein, H.J., et al., Clinical Cancer Advances 2017: Annual Report on Progress Against Cancer From the American Society of Clinical Oncology. J Clin Oncol, 2017. 35(12): p. 1341-1367.
81. Al-Refaie, W.B., et al., Extremity soft tissue sarcoma care in the elderly: insights into the generalizability of NCI Cancer Trials. Ann Surg Oncol, 2010. 17(7): p. 1732-8.
82. Kaloshi, G., et al., Supratentorial low-grade gliomas in older patients. Neurology, 2009. 73(24): p. 2093-8.
83. Akre, O., et al., Mortality among men with locally advanced prostate cancer managed with noncurative intent: a nationwide study in PCBaSe Sweden. Eur Urol, 2011. 60(3): p. 554-63.
84. Takuwa, H., W. Tsuji, and F. Yotsumoto, Overall survival of elderly patients with breast cancer is not related to breast-cancer specific survival: A single institution experience in Japan. Breast Dis, 2018. 37(4): p. 177-183.
85. Mailankody, S. and V. Prasad, Overall Survival vs Disease-Specific Survival-Reply. JAMA Oncol, 2018. 4(4): p. 586-587.
86. Hwang, T.J. and B. Gyawali, Association between progression-free survival and patients' quality of life in cancer clinical trials. Int J Cancer, 2019. 144(7): p. 1746-1751.
87. Chen, E.Y., V. Raghunathan, and V. Prasad, An Overview of Cancer Drugs Approved by the US Food and Drug Administration Based on the Surrogate End Point of Response Rate. JAMA Intern Med, 2019. 179(7): p. 915-921.

88. Gyawali, B., S.P. Hey, and A.S. Kesselheim, Assessment of the Clinical Benefit of Cancer Drugs Receiving Accelerated Approval. JAMA Intern Med, 2019. 179(7): p. 906-913.
89. Fried, T.R., et al., Understanding the treatment preferences of seriously ill patients. N Engl J Med, 2002. 346(14): p. 1061-6.
90. Loh, K.P., et al., Willingness to bear adversity and beliefs about the curability of advanced cancer in older adults. Cancer, 2019. 125(14): p. 2506-2513.
91. Rocque, G.B. and G.R. Williams, Bridging the Data-Free Zone: Decision Making for Older Adults With Cancer. J Clin Oncol, 2019. 37(36): p. 3469-3471.
92. Gyawali, B. and S. Niraula, Cancer treatment in the last 6 months of life: when inaction can outperform action. Ecancermedicalscience, 2018. 12: p. 826.
93. Patient-centered care for older adults with multiple chronic conditions: a stepwise approach from the American Geriatrics Society: American Geriatrics Society Expert Panel on the Care of Older Adults with Multimorbidity. J Am Geriatr Soc, 2012. 60(10): p. 1957-68.
94. Lee, H., S.M. Shi, and D.H. Kim, Home Time as a Patient-Centered Outcome in Administrative Claims Data. J Am Geriatr Soc, 2019. 67(2): p. 347-351.
95. Van Leeuwen, B.L., et al., The effect of under-treatment of breast cancer in women 80 years of age and older. Crit Rev Oncol Hematol, 2011. 79(3): p. 315-20.
96. Zouaoui, S., et al., Oncological patterns of care and outcomes for 265 elderly patients with newly diagnosed glioblastoma in France. Neurosurg Rev, 2014. 37(3): p. 415-23; discussion 423-4.
97. Camilon, P.R., et al., Are the elderly with oropharyngeal carcinoma undertreated? Laryngoscope, 2014. 124(9): p. 2057-63.
98. Fourcadier, E., et al., Under-treatment of elderly patients with ovarian cancer: a population based study. BMC Cancer, 2015. 15: p. 937.
99. Inwald, E.C., et al., Screening-relevant age threshold of 70 years and older is a stronger determinant for the choice of adjuvant treatment in

breast cancer patients than tumor biology. Breast Cancer Res Treat, 2017. 163(1): p. 119-130.

100. Cnossen, M.C., et al., Adjusting for confounding by indication in observational studies: a case study in traumatic brain injury. Clin Epidemiol, 2018. 10: p. 841-852.
101. Repetto, L., et al., Comprehensive geriatric assessment adds information to Eastern Cooperative Oncology Group performance status in elderly cancer patients: an Italian Group for Geriatric Oncology Study. J Clin Oncol, 2002. 20(2): p. 494-502.
102. Clough-Gorr, K.M., et al., Older breast cancer survivors: geriatric assessment domains are associated with poor tolerance of treatment adverse effects and predict mortality over 7 years of follow-up. J Clin Oncol, 2010. 28(3): p. 380-6.
103. Mohile, S.G., et al., Community Oncologists' Decision-Making for Treatment of Older Patients With Cancer. J Natl Compr Canc Netw, 2018. 16(3): p. 301-309.
104. Guerard, E.J., et al., Frailty Index Developed From a Cancer-Specific Geriatric Assessment and the Association With Mortality Among Older Adults With Cancer. J Natl Compr Canc Netw, 2017. 15(7): p. 894-902.
105. Chaïbi, P., et al., Influence of geriatric consultation with comprehensive geriatric assessment on final therapeutic decision in elderly cancer patients. Crit Rev Oncol Hematol, 2011. 79(3): p. 302-7.
106. Ethun, C.G., et al., Frailty and cancer: Implications for oncology surgery, medical oncology, and radiation oncology. CA Cancer J Clin, 2017. 67(5): p. 362-377.
107. Clough-Gorr, K.M., et al., Examining five- and ten-year survival in older women with breast cancer using cancer-specific geriatric assessment. Eur J Cancer, 2012. 48(6): p. 805-12.
108. Kantarjian, H., et al., Intensive chemotherapy does not benefit most older patients (age 70 years or older) with acute myeloid leukemia. Blood, 2010. 116(22): p. 4422-9.
109. Caires-Lima, R., et al., Palliative chemotherapy outcomes in patients with ECOG-PS higher than 1. Ecancermedicalscience, 2018. 12: p. 831.

110. Audisio, R.A., Preoperative evaluation of the older patient with cancer. J Geriatr Oncol, 2016. 7(6): p. 409-412.
111. Björkholm, M., E. Svedmyr, and J. Sjöberg, How we treat elderly patients with Hodgkin lymphoma. Curr Opin Oncol, 2011. 23(5): p. 421-8.
112. Rosko, A., et al., Myeloma in Elderly Patients: When Less Is More and More Is More. Am Soc Clin Oncol Educ Book, 2017. 37: p. 575-585.
113. Tang, V., et al., Functional Status and Survival After Breast Cancer Surgery in Nursing Home Residents. JAMA Surg, 2018. 153(12): p. 1090-1096.
114. Wynter-Blyth, V. and K. Moorthy, Prehabilitation: preparing patients for surgery. Bmj, 2017. 358: p. j3702.
115. NCI Dictionary of Cancer Terms: Overtreatment. [cited 2021 17/07/2021]; Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/overtreatment.
116. Le Saux, O., et al., Changes in the use of end points in clinical trials for elderly cancer patients over time. Ann Oncol, 2017. 28(10): p. 2606-2611.
117. Tinetti, M., et al., Challenges and strategies in patients' health priorities-aligned decision-making for older adults with multiple chronic conditions. PLoS One, 2019. 14(6): p. e0218249.
118. Tinetti, M.E., et al., Association of Patient Priorities-Aligned Decision-Making With Patient Outcomes and Ambulatory Health Care Burden Among Older Adults With Multiple Chronic Conditions: A Nonrandomized Clinical Trial. JAMA Intern Med, 2019. 179(12): p. 1688-97.
119. Fried, T.R., et al., Health outcome prioritization as a tool for decision making among older persons with multiple chronic conditions. Arch Intern Med, 2011. 171(20): p. 1854-6.
120. Djulbegovic, B., S. Elqayam, and W. Dale, Rational decision making in medicine: Implications for overuse and underuse. J Eval Clin Pract, 2018. 24(3): p. 655-665.

121. Crimmin, J., T. Fulop, and N.M.L. Battisti, Biological aspects of aging that influence response to anticancer treatments. Curr Opin Support Palliat Care, 2021. 15(1): p. 29-38.
122. Sawhney, R., M. Sehl, and A. Naeim, Physiologic aspects of aging: impact on cancer management and decision making, part I. Cancer J, 2005. 11(6): p. 449-60.
123. Sehl, M., R. Sawhney, and A. Naeim, Physiologic aspects of aging: impact on cancer management and decision making, part II. Cancer J, 2005. 11(6): p. 461-73.
124. Battisti, N.M.L., et al., Systemic Therapy of Common Tumours in Older Patients: Challenges and Opportunities. A Young International Society of Geriatric Oncology Review Paper. Curr Oncol Rep, 2020. 22(10): p. 98.
125. Baraldi-Junkins, C.A., A.C. Beck, and G. Rothstein, Hematopoiesis and cytokines. Relevance to cancer and aging. Hematol Oncol Clin North Am, 2000. 14(1): p. 45-61, viii.
126. Crivellari, D., et al., Burdens and benefits of adjuvant cyclophosphamide, methotrexate, and fluorouracil and tamoxifen for elderly patients with breast cancer: the International Breast Cancer Study Group Trial VII. J Clin Oncol, 2000. 18(7): p. 1412-22.
127. Dees, E.C., et al., A prospective pharmacologic evaluation of age-related toxicity of adjuvant chemotherapy in women with breast cancer. Cancer Invest, 2000. 18(6): p. 521-9.
128. Gómez, H., et al., Elderly patients with aggressive non-Hodgkin's lymphoma treated with CHOP chemotherapy plus granulocyte-macrophage colony-stimulating factor: identification of two age subgroups with differing hematologic toxicity. J Clin Oncol, 1998. 16(7): p. 2352-8.
129. Schild, S.E., et al., The outcome of combined-modality therapy for stage III non-small-cell lung cancer in the elderly. J Clin Oncol, 2003. 21(17): p. 3201-6.
130. Smith, T.J., et al., 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol, 2006. 24(19): p. 3187-205.

131. Anía, B.J., et al., Prevalence of anemia in medical practice: community versus referral patients. Mayo Clin Proc, 1994. 69(8): p. 730-5.
132. Anía, B.J., et al., Incidence of anemia in older people: an epidemiologic study in a well defined population. J Am Geriatr Soc, 1997. 45(7): p. 825-31.
133. Chaves, P.H., et al., Looking at the relationship between hemoglobin concentration and prevalent mobility difficulty in older women. Should the criteria currently used to define anemia in older people be reevaluated? J Am Geriatr Soc, 2002. 50(7): p. 1257-64.
134. North, B.J. and D.A. Sinclair, The intersection between aging and cardiovascular disease. Circ Res, 2012. 110(8): p. 1097-108.
135. Edwards, M.H., et al., Osteoporosis and sarcopenia in older age. Bone, 2015. 80: p. 126-130.
136. Baumgartner, R.N., et al., Epidemiology of sarcopenia among the elderly in New Mexico. Am J Epidemiol, 1998. 147(8): p. 755-63.
137. Rolland, Y., et al., Difficulties with physical function associated with obesity, sarcopenia, and sarcopenic-obesity in community-dwelling elderly women: the EPIDOS (EPIDemiologie de l'OSteoporose) Study. Am J Clin Nutr, 2009. 89(6): p. 1895-900.
138. Mangoni, A.A. and S.H. Jackson, Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. Br J Clin Pharmacol, 2004. 57(1): p. 6-14.
139. Harada, C.N., M.C. Natelson Love, and K.L. Triebel, Normal cognitive aging. Clin Geriatr Med, 2013. 29(4): p. 737-52.
140. Vaz Fragoso, C.A. and T.M. Gill, Respiratory impairment and the aging lung: a novel paradigm for assessing pulmonary function. J Gerontol A Biol Sci Med Sci, 2012. 67(3): p. 264-75.
141. Extermann, M. and M. Aapro, Assessment of the older cancer patient. Hematol Oncol Clin North Am, 2000. 14(1): p. 63-77, viii-ix.
142. Yancik, R., Cancer burden in the aged: an epidemiologic and demographic overview. Cancer, 1997. 80(7): p. 1273-83.
143. Yancik, R., et al., Comorbidity and age as predictors of risk for early mortality of male and female colon carcinoma patients: a population-based study. Cancer, 1998. 82(11): p. 2123-34.

144. Welch, H.G., et al., Estimating treatment benefits for the elderly: the effect of competing risks. Ann Intern Med, 1996. 124(6): p. 577-84.
145. Satariano, W.A. and D.R. Ragland, The effect of comorbidity on 3-year survival of women with primary breast cancer. Ann Intern Med, 1994. 120(2): p. 104-10.
146. Asmis, T.R., et al., Age and comorbidity as independent prognostic factors in the treatment of non small-cell lung cancer: a review of National Cancer Institute of Canada Clinical Trials Group trials. J Clin Oncol, 2008. 26(1): p. 54-9.
147. Hines, R.B., et al., Predictive capacity of three comorbidity indices in estimating mortality after surgery for colon cancer. J Clin Oncol, 2009. 27(26): p. 4339-45.
148. Williams, G.R., et al., Comorbidity in older adults with cancer. J Geriatr Oncol, 2016. 7(4): p. 249-57.
149. Frasci, G., et al., Gemcitabine plus vinorelbine versus vinorelbine alone in elderly patients with advanced non-small-cell lung cancer. J Clin Oncol, 2000. 18(13): p. 2529-36.
150. Srokowski, T.P., et al., Impact of diabetes mellitus on complications and outcomes of adjuvant chemotherapy in older patients with breast cancer. J Clin Oncol, 2009. 27(13): p. 2170-6.
151. Hershman, D.L., et al., Comorbidities and Risk of Chemotherapy-Induced Peripheral Neuropathy Among Participants 65 Years or Older in Southwest Oncology Group Clinical Trials. J Clin Oncol, 2016. 34(25): p. 3014-22.
152. Søgaard, M., et al., The impact of comorbidity on cancer survival: a review. Clin Epidemiol, 2013. 5(Suppl 1): p. 3-29.
153. Extermann, M., et al., Comorbidity and functional status are independent in older cancer patients. J Clin Oncol, 1998. 16(4): p. 1582-7.
154. Savji, N., et al., Association between advanced age and vascular disease in different arterial territories: a population database of over 3.6 million subjects. J Am Coll Cardiol, 2013. 61(16): p. 1736-43.

155. Harris, T., et al., Proportional hazards analysis of risk factors for coronary heart disease in individuals aged 65 or older. The Framingham Heart Study. J Am Geriatr Soc, 1988. 36(11): p. 1023-8.
156. Wilson, P.W. and W.B. Kannel, Hypercholesterolemia and Coronary Risk in the Elderly: The Framingham Study. Am J Geriatr Cardiol, 1993. 2(2): p. 56.
157. Franklin, S.S., et al., Does the relation of blood pressure to coronary heart disease risk change with aging? The Framingham Heart Study. Circulation, 2001. 103(9): p. 1245-9.
158. Wei, J.Y. and B.J. Gersh, Heart disease in the elderly. Curr Probl Cardiol, 1987. 12(1): p. 1-65.
159. Gianni, L., et al., Anthracycline cardiotoxicity: from bench to bedside. J Clin Oncol, 2008. 26(22): p. 3777-84.
160. Hershman, D.L., et al., Doxorubicin, cardiac risk factors, and cardiac toxicity in elderly patients with diffuse B-cell non-Hodgkin's lymphoma. J Clin Oncol, 2008. 26(19): p. 3159-65.
161. Pinder, M.C., et al., Congestive heart failure in older women treated with adjuvant anthracycline chemotherapy for breast cancer. J Clin Oncol, 2007. 25(25): p. 3808-15.
162. Martín, M., et al., Minimizing cardiotoxicity while optimizing treatment efficacy with trastuzumab: review and expert recommendations. Oncologist, 2009. 14(1): p. 1-11.
163. Biganzoli, L., et al., Updated recommendations regarding the management of older patients with breast cancer: a joint paper from the European Society of Breast Cancer Specialists (EUSOMA) and the International Society of Geriatric Oncology (SIOG). Lancet Oncol, 2021. 22(7): p. e327-e340.
164. Tan-Chiu, E., et al., Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. J Clin Oncol, 2005. 23(31): p. 7811-9.
165. Perez, E.A., et al., Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in

the North Central Cancer Treatment Group N9831 adjuvant breast cancer trial. J Clin Oncol, 2008. 26(8): p. 1231-8.

166. Chavez-MacGregor, M., et al., Trastuzumab-related cardiotoxicity among older patients with breast cancer. J Clin Oncol, 2013. 31(33): p. 4222-8.
167. Serrano, C., et al., Trastuzumab-related cardiotoxicity in the elderly: a role for cardiovascular risk factors. Ann Oncol, 2012. 23(4): p. 897-902.
168. International classification of functioning, disability and health (ICF). 2001, World Health Organization: Geneva.
169. Wang, T.J., Concept analysis of functional status. Int J Nurs Stud, 2004. 41(4): p. 457-62.
170. Hurria, A., et al., Functional Decline and Resilience in Older Women Receiving Adjuvant Chemotherapy for Breast Cancer. J Am Geriatr Soc, 2019. 67(5): p. 920-927.
171. Serraino, D., L. Fratino, and V. Zagonel, Prevalence of functional disability among elderly patients with cancer. Crit Rev Oncol Hematol, 2001. 39(3): p. 269-73.
172. Mohile, S.G., et al., Association of cancer with geriatric syndromes in older Medicare beneficiaries. J Clin Oncol, 2011. 29(11): p. 1458-64.
173. Stafford, R.S. and P.L. Cyr, The impact of cancer on the physical function of the elderly and their utilization of health care. Cancer, 1997. 80(10): p. 1973-80.
174. Penninx, B.W., et al., Depressive symptoms and physical decline in community-dwelling older persons. Jama, 1998. 279(21): p. 1720-6.
175. Liu, M.A., et al., Gait speed, grip strength, and clinical outcomes in older patients with hematologic malignancies. Blood, 2019. 134(4): p. 374-382.
176. Williams, G.R., et al., Geriatric Assessment Predicts Hospitalization Frequency and Long-Term Care Use in Older Adult Cancer Survivors. J Oncol Pract, 2019. 15(5): p. e399-e409.
177. Extermann, M., et al., Predicting the risk of chemotherapy toxicity in older patients: the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score. Cancer, 2012. 118(13): p. 3377-86.

178. Hurria, A., et al., Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. J Clin Oncol, 2011. 29(25): p. 3457-65.
179. Hurria A, M.A., Gross CP, Twe WP, Klepin HD, Wildes TM, Muss HB, Dotan E, Freedman R, O'Connor T, Dale W, Cohen HJ, Katheria V, Arsenyan A, Levi A, Kim H, Sun C-L, Development and validation of a chemotherapy toxicity (Chemo Tox) risk score for older patients (Pts) with breast cancer (BC) receiving adjuvant/neoadjuvant treatment (Adjuvant Tx): A R01 and BCRF funded prospective multicenter study. [GS6-04], in San Antonio Breast Cancer Symposium. 2018: San Antonio, TX, USA.
180. Magnuson, A., et al., Development and Validation of a Risk Tool for Predicting Severe Toxicity in Older Adults Receiving Chemotherapy for Early-Stage Breast Cancer. J Clin Oncol, 2021. 39(6): p. 608-618.
181. Freyer, G., et al., Comprehensive geriatric assessment predicts tolerance to chemotherapy and survival in elderly patients with advanced ovarian carcinoma: a GINECO study. Ann Oncol, 2005. 16(11): p. 1795-800.
182. Pergolotti, M., et al., Activities, function, and health-related quality of life (HRQOL) of older adults with cancer. J Geriatr Oncol, 2017. 8(4): p. 249-254.
183. Caillet, P., et al., Comprehensive geriatric assessment in the decision-making process in elderly patients with cancer: ELCAPA study. J Clin Oncol, 2011. 29(27): p. 3636-42.
184. Olivieri, A., et al., Tailored therapy in an unselected population of 91 elderly patients with DLBCL prospectively evaluated using a simplified CGA. Oncologist, 2012. 17(5): p. 663-72.
185. Spina, M., et al., Modulated chemotherapy according to modified comprehensive geriatric assessment in 100 consecutive elderly patients with diffuse large B-cell lymphoma. Oncologist, 2012. 17(6): p. 838-46.
186. Lichtman, S.M., A. Hurria, and P.B. Jacobsen, Geriatric oncology: an overview. J Clin Oncol, 2014. 32(24): p. 2521-2.

187. López-Otín, C., et al., The hallmarks of aging. Cell, 2013. 153(6): p. 1194-1217.
188. Wildiers, H., et al., International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. J Clin Oncol, 2014. 32(24): p. 2595-603.
189. Maggiore, R.J., et al., Polypharmacy and potentially inappropriate medication use in older adults with cancer undergoing chemotherapy: effect on chemotherapy-related toxicity and hospitalization during treatment. J Am Geriatr Soc, 2014. 62(8): p. 1505-12.
190. Maggiore, R.J., C.P. Gross, and A. Hurria, Polypharmacy in older adults with cancer. Oncologist, 2010. 15(5): p. 507-22.
191. Nightingale, G., et al., Evaluation of a pharmacist-led medication assessment used to identify prevalence of and associations with polypharmacy and potentially inappropriate medication use among ambulatory senior adults with cancer. J Clin Oncol, 2015. 33(13): p. 1453-9.
192. Rochon, P.A. and J.H. Gurwitz, The prescribing cascade revisited. Lancet, 2017. 389(10081): p. 1778-1780.
193. Sharma, M., et al., Polypharmacy and potentially inappropriate medication use in geriatric oncology. J Geriatr Oncol, 2016. 7(5): p. 346-53.
194. Gurwitz, J.H., Polypharmacy: a new paradigm for quality drug therapy in the elderly? Arch Intern Med, 2004. 164(18): p. 1957-9.
195. Vestal, R.E., Aging and pharmacology. Cancer, 1997. 80(7): p. 1302-10.
196. Prithviraj, G.K., et al., Patient Characteristics Associated with Polypharmacy and Inappropriate Prescribing of Medications among Older Adults with Cancer. J Geriatr Oncol, 2012. 3(3): p. 228-237.
197. Richardson, M.A., et al., Complementary/alternative medicine use in a comprehensive cancer center and the implications for oncology. J Clin Oncol, 2000. 18(13): p. 2505-14.
198. Cannon, K.T., M.M. Choi, and M.A. Zuniga, Potentially inappropriate medication use in elderly patients receiving home health care: a

retrospective data analysis. Am J Geriatr Pharmacother, 2006. 4(2): p. 134-43.

199. American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc, 2019. 67(4): p. 674-694.
200. O'Mahony, D., et al., STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age and Ageing, 2014. 44(2): p. 213-218.
201. Medication Management in Older Adults (DAE/DDE). [cited 2021 31/07/2021]; Available from: https://www.ncqa.org/hedis/measures/medication-management-in-the-elderly/.
202. Popa, M.A., et al., Potential drug interactions and chemotoxicity in older patients with cancer receiving chemotherapy. J Geriatr Oncol, 2014. 5(3): p. 307-14.
203. Fried, T.R., et al., Health outcomes associated with polypharmacy in community-dwelling older adults: a systematic review. J Am Geriatr Soc, 2014. 62(12): p. 2261-72.
204. Jyrkkä, J., et al., Association of polypharmacy with nutritional status, functional ability and cognitive capacity over a three-year period in an elderly population. Pharmacoepidemiol Drug Saf, 2011. 20(5): p. 514-22.
205. Mohamed, M.R., et al., Association of Polypharmacy and Potentially Inappropriate Medications With Physical Functional Impairments in Older Adults With Cancer. J Natl Compr Canc Netw, 2021: p. 1-8.
206. Roumie, C.L. and M.R. Griffin, Over-the-counter analgesics in older adults: a call for improved labelling and consumer education. Drugs Aging, 2004. 21(8): p. 485-98.
207. Abraham, O., L. Schleiden, and S.M. Albert, Over-the-counter medications containing diphenhydramine and doxylamine used by older adults to improve sleep. Int J Clin Pharm, 2017. 39(4): p. 808-817.
208. Page, A.T., et al., The feasibility and effect of deprescribing in older adults on mortality and health: a systematic review and meta-analysis. Br J Clin Pharmacol, 2016. 82(3): p. 583-623.

209. Whitman, A., et al., Pharmacist-led medication assessment and deprescribing intervention for older adults with cancer and polypharmacy: a pilot study. Support Care Cancer, 2018. 26(12): p. 4105-4113.
210. Ramsdale, E., et al., Geriatric assessment-driven polypharmacy discussions between oncologists, older patients, and their caregivers. J Geriatr Oncol, 2018. 9(5): p. 534-539.
211. Nutritional support strategy for protein-energy malnutrition in the elderly: clinical practice guidelines. 2007, Haute Autorité de Santé.
212. Batsis, J.A., et al., Normal Weight Obesity and Mortality in United States Subjects ≥60 Years of Age (from the Third National Health and Nutrition Examination Survey). The American Journal of Cardiology, 2013. 112(10): p. 1592-1598.
213. Grabowski, D.C. and J.E. Ellis, High body mass index does not predict mortality in older people: analysis of the Longitudinal Study of Aging. J Am Geriatr Soc, 2001. 49(7): p. 968-79.
214. Landi, F., et al., Body mass index and mortality among hospitalized patients. Arch Intern Med, 2000. 160(17): p. 2641-4.
215. Newman, A.B., et al., Weight change in old age and its association with mortality. J Am Geriatr Soc, 2001. 49(10): p. 1309-18.
216. Reynolds, M.W., et al., Weight, weight change, mortality in a random sample of older community-dwelling women. J Am Geriatr Soc, 1999. 47(12): p. 1409-14.
217. Wallace, J.I., et al., Involuntary weight loss in older outpatients: incidence and clinical significance. J Am Geriatr Soc, 1995. 43(4): p. 329-37.
218. Van Den Broeke, C., et al., Occurrence of Malnutrition and Associated Factors in Community-Dwelling Older Adults: Those with a Recent Diagnosis of Cancer Are at Higher Risk. J Nutr Health Aging, 2018. 22(2): p. 191-198.
219. Paillaud, E., et al., Increased risk of alteration of nutritional status in hospitalized elderly patients with advanced cancer. J Nutr Health Aging, 2006. 10(2): p. 91-5.

220. Mariani, L., S. Lo Vullo, and F. Bozzetti, Weight loss in cancer patients: a plea for a better awareness of the issue. Support Care Cancer, 2012. 20(2): p. 301-9.
221. Paillaud, E., et al., Geriatric syndromes increased the nutritional risk in elderly cancer patients independently from tumour site and metastatic status. The ELCAPA-05 cohort study. Clin Nutr, 2014. 33(2): p. 330-5.
222. Dewys, W.D., et al., Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. Am J Med, 1980. 69(4): p. 491-7.
223. Kanesvaran, R., et al., Analysis of prognostic factors of comprehensive geriatric assessment and development of a clinical scoring system in elderly Asian patients with cancer. J Clin Oncol, 2011. 29(27): p. 3620-7.
224. Hoppe, S., et al., Functional decline in older patients with cancer receiving first-line chemotherapy. J Clin Oncol, 2013. 31(31): p. 3877-82.
225. Soubeyran, P., et al., Predictors of early death risk in older patients treated with first-line chemotherapy for cancer. J Clin Oncol, 2012. 30(15): p. 1829-34.
226. Hamaker, M.E., et al., Nutritional status and interventions for patients with cancer - A systematic review. J Geriatr Oncol, 2021. 12(1): p. 6-21.
227. Zhang, X., et al., Prevalence and factors associated with malnutrition in older patients with cancer. J Geriatr Oncol, 2019. 10(5): p. 763-769.
228. Williams, G.R., et al., Sarcopenia in the Older Adult With Cancer. J Clin Oncol, 2021. 39(19): p. 2068-2078.
229. Williams, G.R., et al., Association of malnutrition with geriatric assessment impairments and health-related quality of life among older adults with gastrointestinal malignancies. Cancer, 2020. 126(23): p. 5147-5155.
230. Dotan, E., et al., Associations between nutritional factors and chemotherapy toxicity in older adults with solid tumors. Cancer, 2020. 126(8): p. 1708-1716.

231. Nishijima, T.F., et al., The incremental value of a geriatric assessment-derived three-item scale on estimating overall survival in older adults with cancer. J Geriatr Oncol, 2018. 9(4): p. 329-336.
232. Ferrat, E., et al., Predictors of 1-Year Mortality in a Prospective Cohort of Elderly Patients With Cancer. J Gerontol A Biol Sci Med Sci, 2015. 70(9): p. 1148-55.
233. Bray, G.A., et al., Management of obesity. Lancet, 2016. 387(10031): p. 1947-56.
234. Ligibel, J.A., et al., Recommendations for Obesity Clinical Trials in Cancer Survivors: American Society of Clinical Oncology Statement. J Clin Oncol, 2015. 33(33): p. 3961-7.
235. Presley, C.J., et al., Gaps in nutritional research among older adults with cancer. J Geriatr Oncol, 2016. 7(4): p. 281-92.
236. Morley, J.E., Anorexia of aging: physiologic and pathologic. Am J Clin Nutr, 1997. 66(4): p. 760-73.
237. Arends, J., et al., ESPEN guidelines on nutrition in cancer patients. Clin Nutr, 2017. 36(1): p. 11-48.
238. Mislang, A.R., et al., Nutritional management of older adults with gastrointestinal cancers: An International Society of Geriatric Oncology (SIOG) review paper. J Geriatr Oncol, 2018. 9(4): p. 382-392.
239. Shachar, S.S., et al., Prognostic value of sarcopenia in adults with solid tumours: A meta-analysis and systematic review. Eur J Cancer, 2016. 57: p. 58-67.
240. Dunne, R.F., et al., Characterizing cancer cachexia in the geriatric oncology population. J Geriatr Oncol, 2019. 10(3): p. 415-419.
241. Williams, G.R., et al., Sarcopenia & aging in cancer. J Geriatr Oncol, 2019. 10(3): p. 374-377.
242. Broughman, J.R., et al., Prevalence of sarcopenia in older patients with colorectal cancer. J Geriatr Oncol, 2015. 6(6): p. 442-5.
243. McDonald, A.M., et al., CT Measures of Bone Mineral Density and Muscle Mass Can Be Used to Predict Noncancer Death in Men with Prostate Cancer. Radiology, 2017. 282(2): p. 475-483.
244. Xu, J., et al., Sarcopenia Is Associated with Mortality in Adults: A Systematic Review and Meta-Analysis. Gerontology, 2021: p. 1-16.

245. Hopkins, J.J. and M.B. Sawyer, Interactions of lean soft-tissue and chemotherapy toxicities in patients receiving anti-cancer treatments. Cancer Chemotherapy and Pharmacology, 2018. 82(1): p. 1-29.
246. Williams, G.R., et al., Frailty and skeletal muscle in older adults with cancer. Journal of geriatric oncology, 2018. 9(1): p. 68-73.
247. Williams, G.R., et al., Skeletal muscle measures and physical function in older adults with cancer: sarcopenia or myopenia? Oncotarget, 2017. 8(20): p. 33658-33665.
248. Nipp, R.D., et al., Sarcopenia Is Associated with Quality of Life and Depression in Patients with Advanced Cancer. Oncologist, 2018. 23(1): p. 97-104.
249. Rier, H.N., et al., Severe sarcopenia might be associated with a decline of physical independence in older patients undergoing chemotherapeutic treatment. Support Care Cancer, 2018. 26(6): p. 1781-1789.
250. Erkinjuntti, T., et al., The effect of different diagnostic criteria on the prevalence of dementia. N Engl J Med, 1997. 337(23): p. 1667-74.
251. Knopman, D.S., et al., Practice parameter: diagnosis of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology, 2001. 56(9): p. 1143-53.
252. Butler, R., Dementia. Am Family Physician Clin Evid Handb, 2014. 2: p. 89.
253. Boustani, M., et al., Implementing a screening and diagnosis program for dementia in primary care. J Gen Intern Med, 2005. 20(7): p. 572-7.
254. Farias, S.T., et al., Progression of mild cognitive impairment to dementia in clinic- vs community-based cohorts. Arch Neurol, 2009. 66(9): p. 1151-7.
255. Karuturi, M., et al., Understanding cognition in older patients with cancer. J Geriatr Oncol, 2016. 7(4): p. 258-69.
256. Klepin, H., S. Mohile, and A. Hurria, Geriatric assessment in older patients with breast cancer. J Natl Compr Canc Netw, 2009. 7(2): p. 226-36.

257. Mohile, S.G., et al., A pilot study of the vulnerable elders survey-13 compared with the comprehensive geriatric assessment for identifying disability in older patients with prostate cancer who receive androgen ablation. Cancer, 2007. 109(4): p. 802-10.
258. Thein, M.S., et al., Mini-Cog: A brief screening tool for cognitive impairment in older cancer patients. Journal of Clinical Oncology, 2010. 28(15_suppl): p. 9064-9064.
259. Wolfson, C., et al., A reevaluation of the duration of survival after the onset of dementia. N Engl J Med, 2001. 344(15): p. 1111-6.
260. Ritchie, K., Mild cognitive impairment: an epidemiological perspective. Dialogues Clin Neurosci, 2004. 6(4): p. 401-8.
261. Gauthier, S., et al., Mild cognitive impairment. Lancet, 2006. 367(9518): p. 1262-70.
262. Kim, S.Y., J.H. Karlawish, and E.D. Caine, Current state of research on decision-making competence of cognitively impaired elderly persons. Am J Geriatr Psychiatry, 2002. 10(2): p. 151-65.
263. High, D.M., Research with Alzheimer's disease subjects: informed consent and proxy decision making. J Am Geriatr Soc, 1992. 40(9): p. 950-7.
264. Gorin, S.S., et al., Treatment for breast cancer in patients with Alzheimer's disease. J Am Geriatr Soc, 2005. 53(11): p. 1897-904.
265. Raji, M.A., et al., Effect of a dementia diagnosis on survival of older patients after a diagnosis of breast, colon, or prostate cancer: implications for cancer care. Arch Intern Med, 2008. 168(18): p. 2033-40.
266. Pamoukdjian, F., et al., Impaired mobility, depressed mood, cognitive impairment and polypharmacy are independently associated with disability in older cancer outpatients: The prospective Physical Frailty in Elderly Cancer patients (PF-EC) cohort study. J Geriatr Oncol, 2017. 8(3): p. 190-195.
267. Kuo, H.K., et al., Cognitive function, habitual gait speed, and late-life disability in the National Health and Nutrition Examination Survey (NHANES) 1999-2002. Gerontology, 2007. 53(2): p. 102-10.

268. Borson, S., et al., The mini-cog: a cognitive 'vital signs' measure for dementia screening in multi-lingual elderly. Int J Geriatr Psychiatry, 2000. 15(11): p. 1021-7.
269. Kawas, C., et al., Reliability of the Blessed Telephone Information-Memory-Concentration Test. J Geriatr Psychiatry Neurol, 1995. 8(4): p. 238-42.
270. Pergolotti, M., et al., Embracing the complexity: Older adults with cancer-related cognitive decline-A Young International Society of Geriatric Oncology position paper. J Geriatr Oncol, 2020. 11(2): p. 237-243.
271. Association, A.P., Diagnostic and Statistical Manual of Mental Disorders: DSM-5. 5th ed. 2013, Washington, DC: American Psychiatric Association.
272. Martinez, J.A., et al., Derivation and validation of a clinical prediction rule for delirium in patients admitted to a medical ward: an observational study. BMJ Open, 2012. 2(5).
273. Kobayashi, D., et al., A prediction rule for the development of delirium among patients in medical wards: Chi-Square Automatic Interaction Detector (CHAID) decision tree analysis model. Am J Geriatr Psychiatry, 2013. 21(10): p. 957-62.
274. Takeuchi, D., et al., Postoperative complications in elderly patients with gastric cancer. J Surg Res, 2015. 198(2): p. 317-26.
275. Tominaga, T., et al., Short-term outcomes of laparoscopic surgery for colorectal cancer in oldest-old patients. Dig Surg, 2015. 32(1): p. 32-8.
276. Takeuchi, M., et al., Incidence and risk factors of postoperative delirium in patients with esophageal cancer. Ann Surg Oncol, 2012. 19(12): p. 3963-70.
277. Tei, M., et al., Risk factors for postoperative delirium in elderly patients with colorectal cancer. Surg Endosc, 2010. 24(9): p. 2135-9.
278. Yamagata, K., et al., Risk factors for postoperative delirium in patients undergoing head and neck cancer surgery. Int J Oral Maxillofac Surg, 2005. 34(1): p. 33-6.

279. Hui, D., et al., Acute symptomatic complications among patients with advanced cancer admitted to acute palliative care units: A prospective observational study. Palliat Med, 2015. 29(9): p. 826-33.
280. Fang, C.K., et al., Prevalence, detection and treatment of delirium in terminal cancer inpatients: a prospective survey. Jpn J Clin Oncol, 2008. 38(1): p. 56-63.
281. Rainsford, S., J.P. Rosenberg, and T. Bullen, Delirium in advanced cancer: screening for the incidence on admission to an inpatient hospice unit. J Palliat Med, 2014. 17(9): p. 1045-8.
282. Korc-Grodzicki, B., et al., Geriatric Assessment as a Predictor of Delirium and Other Outcomes in Elderly Patients With Cancer. Ann Surg, 2015. 261(6): p. 1085-90.
283. de la Cruz, M., et al., The frequency of missed delirium in patients referred to palliative care in a comprehensive cancer center. Support Care Cancer, 2015. 23(8): p. 2427-33.
284. Kiely, D.K., et al., Persistent delirium predicts greater mortality. J Am Geriatr Soc, 2009. 57(1): p. 55-61.
285. Witlox, J., et al., Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. Jama, 2010. 304(4): p. 443-51.
286. Rudolph, J.L., et al., Delirium: an independent predictor of functional decline after cardiac surgery. J Am Geriatr Soc, 2010. 58(4): p. 643-9.
287. Fong, T.G., et al., Delirium accelerates cognitive decline in Alzheimer disease. Neurology, 2009. 72(18): p. 1570-5.
288. Saczynski, J.S., et al., Cognitive trajectories after postoperative delirium. N Engl J Med, 2012. 367(1): p. 30-9.
289. Toye, C., et al., Experiences, understandings and support needs of family carers of older patients with delirium: a descriptive mixed methods study in a hospital delirium unit. Int J Older People Nurs, 2014. 9(3): p. 200-8.
290. Cohen, M.Z., et al., Delirium in advanced cancer leading to distress in patients and family caregivers. J Palliat Care, 2009. 25(3): p. 164-71.

291. Bruera, E., et al., Impact of delirium and recall on the level of distress in patients with advanced cancer and their family caregivers. Cancer, 2009. 115(9): p. 2004-12.
292. Inouye, S.K., et al., A multicomponent intervention to prevent delirium in hospitalized older patients. N Engl J Med, 1999. 340(9): p. 669-76.
293. Inouye, S.K., R.G. Westendorp, and J.S. Saczynski, Delirium in elderly people. Lancet, 2014. 383(9920): p. 911-22.
294. Hshieh, T.T., et al., Effectiveness of multicomponent nonpharmacological delirium interventions: a meta-analysis. JAMA Intern Med, 2015. 175(4): p. 512-20.
295. Bond, S.M., et al., Delirium in patients with head and neck cancer in the outpatient treatment setting. Support Care Cancer, 2012. 20(5): p. 1023-30.
296. Kua, J., The prevalence of psychological and psychiatric sequelae of cancer in the elderly - how much do we know? Ann Acad Med Singap, 2005. 34(3): p. 250-6.
297. Vinokur, A.D., et al., The process of recovery from breast cancer for younger and older patients. Changes during the first year. Cancer, 1990. 65(5): p. 1242-54.
298. Saracino, R.M. and C.J. Nelson, Identification and treatment of depressive disorders in older adults with cancer. J Geriatr Oncol, 2019. 10(5): p. 680-684.
299. Fiske, A., J.L. Wetherell, and M. Gatz, Depression in Older Adults. Annual Review of Clinical Psychology, 2009. 5(1): p. 363-389.
300. Luppa, M., et al., Age- and gender-specific prevalence of depression in latest-life – Systematic review and meta-analysis. Journal of Affective Disorders, 2012. 136(3): p. 212-221.
301. Steffens, D.C., et al., Prevalence of depression among older Americans: the Aging, Demographics and Memory Study. Int Psychogeriatr, 2009. 21(5): p. 879-88.
302. Cornwell, E.Y. and L.J. Waite, Social Disconnectedness, Perceived Isolation, and Health among Older Adults. Journal of Health and Social Behavior, 2009. 50(1): p. 31-48.

303. Max L. Stek, M.D., Ph.D. ,, et al., Is Depression in Old Age Fatal Only When People Feel Lonely? American Journal of Psychiatry, 2005. 162(1): p. 178-180.
304. Kornblith, A.B., et al., Long-term adjustment of survivors of early-stage breast carcinoma, 20 years after adjuvant chemotherapy. Cancer, 2003. 98(4): p. 679-89.
305. Alex J. Mitchell, M.R.C.Psych. , and and Hari Subramaniam, M.R.C.Psych., Prognosis of Depression in Old Age Compared to Middle Age: A Systematic Review of Comparative Studies. American Journal of Psychiatry, 2005. 162(9): p. 1588-1601.
306. Comijs, H.C., et al., The two-year course of late-life depression; results from the Netherlands study of depression in older persons. BMC Psychiatry, 2015. 15: p. 20.
307. Haigh, E.A.P., et al., Depression Among Older Adults: A 20-Year Update on Five Common Myths and Misconceptions. The American Journal of Geriatric Psychiatry, 2018. 26(1): p. 107-122.
308. Gallo, J.J., J.C. Anthony, and B.O. Muthen, Age Differences in the Symptoms of Depression: A Latent Trait Analysis. Journal of Gerontology, 1994. 49(6): p. P251-P264.
309. Gallagher, D., et al., Late life depression: a comparison of risk factors and symptoms according to age of onset in community dwelling older adults. Int J Geriatr Psychiatry, 2010. 25(10): p. 981-7.
310. Hegeman, J.M., et al., Phenomenology of depression in older compared with younger adults: meta-analysis. Br J Psychiatry, 2012. 200(4): p. 275-81.
311. Dan G. Blazer, Depression in Late Life: Review and Commentary. FOCUS, 2009. 7(1): p. 118-136.
312. Rhondali, W., et al., Frequency of depression among oncology outpatients and association with other symptoms. Supportive Care in Cancer, 2012. 20(11): p. 2795-2802.
313. Weinberger, M.I., et al., Depression and barriers to mental health care in older cancer patients. International Journal of Geriatric Psychiatry, 2011. 26(1): p. 21-26.

314. Pascoe, S., S. Edelman, and A. Kidman, Prevalence of psychological distress and use of support services by cancer patients at Sydney hospitals. Aust N Z J Psychiatry, 2000. 34(5): p. 785-91.
315. Cavanaugh, S.V.A., Depression in the Medically Ill: Critical Issues in Diagnostic Assessment. Psychosomatics, 1995. 36(1): p. 48-59.
316. Simon, G.E. and M. Von Korff, Medical co-morbidity and validity of DSM-IV depression criteria. Psychological Medicine, 2006. 36(1): p. 27-36.
317. Beekman, A.T., et al., The natural history of late-life depression: a 6-year prospective study in the community. Arch Gen Psychiatry, 2002. 59(7): p. 605-11.
318. Spiegel, D. and J. Giese-Davis, Depression and cancer: mechanisms and disease progression. Biological Psychiatry, 2003. 54(3): p. 269-282.
319. Pinquart, M. and P.R. Duberstein, Depression and cancer mortality: a meta-analysis. Psychol Med, 2010. 40(11): p. 1797-810.
320. Langa, K.M., et al., Extent and cost of informal caregiving for older Americans with symptoms of depression. Am J Psychiatry, 2004. 161(5): p. 857-63.
321. Stark, D.P. and A. House, Anxiety in cancer patients. Br J Cancer, 2000. 83(10): p. 1261-7.
322. Mitchell, A.J., et al., Depression and anxiety in long-term cancer survivors compared with spouses and healthy controls: a systematic review and meta-analysis. The Lancet Oncology, 2013. 14(8): p. 721-732.
323. Puigpinós-Riera, R., et al., Anxiety and depression in women with breast cancer: Social and clinical determinants and influence of the social network and social support (DAMA cohort). Cancer Epidemiology, 2018. 55: p. 123-129.
324. Kypriotakis, G., et al., Correlated and Coupled Trajectories of Cancer-Related Worries and Depressive Symptoms among Long-Term Cancer Survivors. Behavioral Medicine, 2016. 42(2): p. 82-92.

325. Deimling, G.T., K.F. Bowman, and L.J. Wagner, The effects of cancer-related pain and fatigue on functioning of older adult, long-term cancer survivors. Cancer Nurs, 2007. 30(6): p. 421-33.
326. Trevino, K.M., R.M. Saracino, and A.J. Roth, Symptomatology, assessment, and treatment of anxiety in older adults with cancer. J Geriatr Oncol, 2021. 12(2): p. 316-319.
327. Kasparian, N.A., J.K. McLoone, and P.N. Butow, Psychological responses and coping strategies among patients with malignant melanoma: a systematic review of the literature. Arch Dermatol, 2009. 145(12): p. 1415-27.
328. Nelson, C.J., E.M. Balk, and A.J. Roth, Distress, anxiety, depression, and emotional well-being in African-American men with prostate cancer. Psycho-Oncology, 2010. 19(10): p. 1052-1060.
329. Teunissen, S.C., et al., Does age matter in palliative care? Critical Reviews in Oncology/Hematology, 2006. 60(2): p. 152-158.
330. Pang, L., et al., Symptom frequency and change of oldest old cancer patients. Supportive Care in Cancer, 2019. 27(11): p. 4165-4170.
331. Deimling, G.T., et al., Cancer-related health worries and psychological distress among older adult, long-term cancer survivors. Psycho-Oncology, 2006. 15(4): p. 306-320.
332. Zebrack, B., et al., A Practice-Based Evaluation of Distress Screening Protocol Adherence and Medical Service Utilization. J Natl Compr Canc Netw, 2017. 15(7): p. 903-912.
333. Trevino, K.M., et al., Is screening for psychosocial risk factors associated with mental health care in older adults with cancer undergoing surgery? Cancer, 2020. 126(3): p. 602-610.
334. Trevino, K.M., et al., Improving implementation of psychological interventions to older adult patients with cancer: Convening older adults, caregivers, providers, researchers. J Geriatr Oncol, 2018. 9(5): p. 423-429.
335. Roth, A.J. and R. Modi, Psychiatric issues in older cancer patients. Critical Reviews in Oncology/Hematology, 2003. 48(2): p. 185-197.

336. Fujii, M., et al., Manifest Anxiety Scale for evaluation of effects of granisetron in chemotherapy with CDDP and 5FU for head and neck cancer. Support Care Cancer, 2001. 9(5): p. 366-71.
337. Brown, L.F. and K. Kroenke, Cancer-related fatigue and its associations with depression and anxiety: a systematic review. Psychosomatics, 2009. 50(5): p. 440-7.
338. Reddy, S.K., et al., Characteristics and correlates of dyspnea in patients with advanced cancer. J Palliat Med, 2009. 12(1): p. 29-36.
339. Salvo, N., et al., Frequency of reporting and predictive factors for anxiety and depression in patients with advanced cancer. Clin Oncol (R Coll Radiol), 2012. 24(2): p. 139-48.
340. Andrykowski, M.A., The role of anxiety in the development of anticipatory nausea in cancer chemotherapy: a review and synthesis. Psychosom Med, 1990. 52(4): p. 458-75.
341. Horney, D.J., et al., Associations between quality of life, coping styles, optimism, and anxiety and depression in pretreatment patients with head and neck cancer. Head Neck, 2011. 33(1): p. 65-71.
342. Smith, E.M., S.A. Gomm, and C.M. Dickens, Assessing the independent contribution to quality of life from anxiety and depression in patients with advanced cancer. Palliat Med, 2003. 17(6): p. 509-13.
343. Delgado-Guay, M., et al., Symptom distress in advanced cancer patients with anxiety and depression in the palliative care setting. Support Care Cancer, 2009. 17(5): p. 573-9.
344. Bruera, E., et al., The frequency and correlates of dyspnea in patients with advanced cancer. J Pain Symptom Manage, 2000. 19(5): p. 357-62.
345. Schag, C.A. and R.L. Heinrich, Anxiety in medical situations: adult cancer patients. J Clin Psychol, 1989. 45(1): p. 20-7.
346. Pedersen, A.E., J.A. Sawatzky, and T.F. Hack, The sequelae of anxiety in breast cancer: a human response to illness model. Oncol Nurs Forum, 2010. 37(4): p. 469-75.
347. Greer, J.A., et al., Behavioral and psychological predictors of chemotherapy adherence in patients with advanced non-small cell lung cancer. J Psychosom Res, 2008. 65(6): p. 549-52.

348. Prieto, J.M., et al., Psychiatric morbidity and impact on hospital length of stay among hematologic cancer patients receiving stem-cell transplantation. J Clin Oncol, 2002. 20(7): p. 1907-17.
349. Chan, C.M., et al., Effects of depression and anxiety on mortality in a mixed cancer group: a longitudinal approach using standardised diagnostic interviews. Psychooncology, 2015. 24(6): p. 718-25.
350. Dale, W., et al., Patient anxiety about prostate cancer independently predicts early initiation of androgen deprivation therapy for biochemical cancer recurrence in older men: a prospective cohort study. J Clin Oncol, 2009. 27(10): p. 1557-63.
351. Latini, D.M., et al., The relationship between anxiety and time to treatment for patients with prostate cancer on surveillance. J Urol, 2007. 178(3 Pt 1): p. 826-31; discussion 831-2.
352. Langford, C.P., et al., Social support: a conceptual analysis. J Adv Nurs, 1997. 25(1): p. 95-100.
353. Kadambi, S., et al., Social support for older adults with cancer: Young International Society of Geriatric Oncology review paper. J Geriatr Oncol, 2020. 11(2): p. 217-224.
354. Lyyra, T.M. and R.L. Heikkinen, Perceived social support and mortality in older people. J Gerontol B Psychol Sci Soc Sci, 2006. 61(3): p. S147-52.
355. Walker, K.N., A. MacBride, and M.L.S. Vachon, Social support networks and the crisis of bereavement. Social Science & Medicine (1967), 1977. 11(1): p. 35-41.
356. Williams, G.R., et al., Unmet social support needs among older adults with cancer. Cancer, 2019. 125(3): p. 473-481.
357. Usta, Y.Y., Importance of social support in cancer patients. Asian Pac J Cancer Prev, 2012. 13(8): p. 3569-72.
358. Nausheen, B., et al., Social support and cancer progression: A systematic review. Journal of Psychosomatic Research, 2009. 67(5): p. 403-415.
359. Reiche, E.M.V., S.O.V. Nunes, and H.K. Morimoto, Stress, depression, the immune system, and cancer. The Lancet Oncology, 2004. 5(10): p. 617-625.

360. Pinquart, M. and P.R. Duberstein, Associations of social networks with cancer mortality: A meta-analysis. Critical Reviews in Oncology/Hematology, 2010. 75(2): p. 122-137.
361. Boen, C.E., et al., Social Relationships, Inflammation, and Cancer Survival. Cancer Epidemiology Biomarkers & Prevention, 2018. 27(5): p. 541-549.
362. Penwell, L.M. and K.T. Larkin, Social support and risk for cardiovascular disease and cancer: a qualitative review examining the role of inflammatory processes. Health Psychology Review, 2010. 4(1): p. 42-55.
363. Yang, Y.C., T. Li, and Y. Ji, Impact of social integration on metabolic functions: evidence from a nationally representative longitudinal study of US older adults. BMC Public Health, 2013. 13: p. 1210.
364. Gallant, M.P., Social Networks, Social Support, and Health-Related Behavior, ed. L.R.M.a.M.R. DiMatteo. 2013: Oxford University Press.
365. Cavalli-Björkman, N., et al., Lower treatment intensity and poorer survival in metastatic colorectal cancer patients who live alone. British Journal of Cancer, 2012. 107(1): p. 189-194.
366. Aizer, A.A., et al., Marital status and survival in patients with cancer. J Clin Oncol, 2013. 31(31): p. 3869-76.
367. Lutgendorf, S.K., et al., Social influences on clinical outcomes of patients with ovarian cancer. J Clin Oncol, 2012. 30(23): p. 2885-90.
368. Jatoi, A., et al., Social support and its implications in older, early-stage breast cancer patients in CALGB 49907 (Alliance A171301). Psychooncology, 2016. 25(4): p. 441-6.
369. Robb, C., et al., Health and personal resources in older patients with cancer undergoing chemotherapy. J Geriatr Oncol, 2013. 4(2): p. 166-73.
370. Durá-Ferrandis, E., et al., Personality, coping, and social support as predictors of long-term quality-of-life trajectories in older breast cancer survivors: CALGB protocol 369901 (Alliance). Psychooncology, 2017. 26(11): p. 1914-1921.

371. Pisu, M., et al., Most impactful factors on the health-related quality of life of a geriatric population with cancer. Cancer, 2018. 124(3): p. 596-605.
372. Yourman, L.C., et al., Prognostic indices for older adults: a systematic review. Jama, 2012. 307(2): p. 182-92.
373. Cruz, M., et al., Predicting 10-year mortality for older adults. Jama, 2013. 309(9): p. 874-6.
374. Global Health Estimates: Life expectancy and leading causes of death and disability. 2021 13/08/2021]; Available from: https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates.
375. ePrognosis. 13/08/2021]; Available from: https://eprognosis.ucsf.edu/.
376. Gagne, J.J., et al., A combined comorbidity score predicted mortality in elderly patients better than existing scores. J Clin Epidemiol, 2011. 64(7): p. 749-59.
377. Carey, E.C., et al., Development and validation of a functional morbidity index to predict mortality in community-dwelling elders. J Gen Intern Med, 2004. 19(10): p. 1027-33.
378. Lee, S.J., et al., Development and validation of a prognostic index for 4-year mortality in older adults. Jama, 2006. 295(7): p. 801-8.
379. Schonberg, M.A., et al., Index to predict 5-year mortality of community-dwelling adults aged 65 and older using data from the National Health Interview Survey. J Gen Intern Med, 2009. 24(10): p. 1115-22.
380. Lee, S.J., et al., Individualizing life expectancy estimates for older adults using the Gompertz Law of Human Mortality. PLoS One, 2014. 9(9): p. e108540.
381. Suemoto, C.K., et al., Development and Validation of a 10-Year Mortality Prediction Model: Meta-Analysis of Individual Participant Data From Five Cohorts of Older Adults in Developed and Developing Countries. J Gerontol A Biol Sci Med Sci, 2017. 72(3): p. 410-416.
382. Candido dos Reis, F.J., et al., An updated PREDICT breast cancer prognostication and treatment benefit prediction model with independent validation. Breast Cancer Research, 2017. 19(1): p. 58.

383. de Glas, N.A., et al., Validity of the online PREDICT tool in older patients with breast cancer: a population-based study. Br J Cancer, 2016. 114(4): p. 395-400.
384. de Glas, N.A., et al., Validity of Adjuvant! Online program in older patients with breast cancer: a population-based study. Lancet Oncol, 2014. 15(7): p. 722-9.
385. Age Gap Decision Tool. 25/03/2021]; Available from: https://agegap.shef.ac.uk/.
386. Wyld, L., et al., Bridging the age gap in breast cancer: cluster randomized trial of two decision support interventions for older women with operable breast cancer on quality of life, survival, decision quality, and treatment choices. Br J Surg, 2021. 108(5): p. 499-510.
387. Burton, M., et al., Process evaluation of the Bridging the Age Gap in Breast Cancer decision support intervention cluster randomised trial. Trials, 2021. 22(1): p. 447.
388. Papamichael, D., et al., Validity of Adjuvant! Online in older patients with stage III colon cancer based on 2967 patients from the ACCENT database. J Geriatr Oncol, 2016. 7(6): p. 422-429.
389. Renfro, L.A., et al., ACCENT-based web calculators to predict recurrence and overall survival in stage III colon cancer. J Natl Cancer Inst, 2014. 106(12).
390. Memorial Sloan Kettering Cancer Center pre-radical prostatectomy normogram. 13/08/2021]; Available from: https://www.mskcc.org/nomograms/prostate/pre_op.
391. Stephenson, A.J., et al., Prostate cancer-specific mortality after radical prostatectomy for patients treated in the prostate-specific antigen era. J Clin Oncol, 2009. 27(26): p. 4300-5.
392. Albertsen, P.C., J.A. Hanley, and J. Fine, 20-year outcomes following conservative management of clinically localized prostate cancer. Jama, 2005. 293(17): p. 2095-101.
393. Hunter, N.L., K.M. O'Callaghan, and R.M. Califf, Engaging Patients Across the Spectrum of Medical Product Development: View From the US Food and Drug Administration. Jama, 2015. 314(23): p. 2499-500.

394. Aiello Bowles, E.J., et al., Understanding high-quality cancer care: a summary of expert perspectives. Cancer, 2008. 112(4): p. 934-42.
395. Wagner, E.H., et al., The quality of cancer patient experience: perspectives of patients, family members, providers and experts. Qual Saf Health Care, 2010. 19(6): p. 484-9.
396. Beaussant, Y., et al., Is shared decision-making vanishing at the end-of-life? A descriptive and qualitative study of advanced cancer patients' involvement in specific therapies decision-making. BMC Palliat Care, 2015. 14: p. 61.
397. Brom, L., et al., Challenges in shared decision making in advanced cancer care: a qualitative longitudinal observational and interview study. Health Expect, 2017. 20(1): p. 69-84.
398. Harrison, M., et al., Do patients and health care providers have discordant preferences about which aspects of treatments matter most? Evidence from a systematic review of discrete choice experiments. BMJ Open, 2017. 7(5): p. e014719.
399. Mühlbacher, A.C. and C. Juhnke, Patient preferences versus physicians' judgement: does it make a difference in healthcare decision making? Appl Health Econ Health Policy, 2013. 11(3): p. 163-80.
400. Covvey, J.R., et al., Barriers and facilitators to shared decision-making in oncology: a systematic review of the literature. Support Care Cancer, 2019. 27(5): p. 1613-1637.
401. Pel-Littel, R.E., et al., Barriers and facilitators for shared decision making in older patients with multiple chronic conditions: a systematic review. BMC Geriatr, 2021. 21(1): p. 112.
402. Thorne, S., J.L. Oliffe, and K.I. Stajduhar, Communicating shared decision-making: cancer patient perspectives. Patient Educ Couns, 2013. 90(3): p. 291-6.
403. Richardson, D.R., et al., Age at Diagnosis and Patient Preferences for Treatment Outcomes in AML: A Discrete Choice Experiment to Explore Meaningful Benefits. Cancer Epidemiol Biomarkers Prev, 2020. 29(5): p. 942-948.

404. Bien, D.R., et al., Patients' Preferences for Outcome, Process and Cost Attributes in Cancer Treatment: A Systematic Review of Discrete Choice Experiments. Patient, 2017. 10(5): p. 553-565.
405. Bridges, J.F., et al., Patients' preferences for treatment outcomes for advanced non-small cell lung cancer: a conjoint analysis. Lung Cancer, 2012. 77(1): p. 224-31.
406. Rocque, G., et al., Engaging Multidisciplinary Stakeholders to Drive Shared Decision-Making in Oncology. J Palliat Care, 2019. 34(1): p. 29-31.
407. Hamaker, M.E., R. Stauder, and B.C. van Munster, On-going clinical trials for elderly patients with a hematological malignancy: are we addressing the right end points? Ann Oncol, 2014. 25(3): p. 675-681.
408. Wildiers, H., et al., End points and trial design in geriatric oncology research: a joint European organisation for research and treatment of cancer--Alliance for Clinical Trials in Oncology--International Society Of Geriatric Oncology position article. J Clin Oncol, 2013. 31(29): p. 3711-8.
409. Case, S.M., T.R. Fried, and J. O'Leary, How to ask: older adults' preferred tools in health outcome prioritization. Patient Educ Couns, 2013. 91(1): p. 29-36.
410. Lux, M.P., et al., Shared decision-making in metastatic breast cancer: discrepancy between the expected prolongation of life and treatment efficacy between patients and physicians, and influencing factors. Breast Cancer Res Treat, 2013. 139(2): p. 429-40.
411. Rostoft, S., et al., Shared decision-making in older patients with cancer - What does the patient want? J Geriatr Oncol, 2021. 12(3): p. 339-342.
412. Puts, M.T., et al., Use of geriatric assessment for older adults in the oncology setting: a systematic review. J Natl Cancer Inst, 2012. 104(15): p. 1133-63.
413. Extermann, M., et al., Use of comprehensive geriatric assessment in older cancer patients: recommendations from the task force on CGA of the International Society of Geriatric Oncology (SIOG). Crit Rev Oncol Hematol, 2005. 55(3): p. 241-52.

414. Decoster, L., et al., Screening tools for multidimensional health problems warranting a geriatric assessment in older cancer patients: an update on SIOG recommendations†. Ann Oncol, 2015. 26(2): p. 288-300.
415. Linn, B.S., M.W. Linn, and L. Gurel, Cumulative illness rating scale. J Am Geriatr Soc, 1968. 16(5): p. 622-6.
416. Extermann, M., et al., MAX2--a convenient index to estimate the average per patient risk for chemotherapy toxicity; validation in ECOG trials. Eur J Cancer, 2004. 40(8): p. 1193-8.
417. Ramjaun, A., et al., Improved targeting of cancer care for older patients: a systematic review of the utility of comprehensive geriatric assessment. J Geriatr Oncol, 2013. 4(3): p. 271-81.
418. Hamaker, M.E., M.C. Prins, and R. Stauder, The relevance of a geriatric assessment for elderly patients with a haematological malignancy--a systematic review. Leuk Res, 2014. 38(3): p. 275-83.
419. Corre, R., et al., Use of a Comprehensive Geriatric Assessment for the Management of Elderly Patients With Advanced Non-Small-Cell Lung Cancer: The Phase III Randomized ESOGIA-GFPC-GECP 08-02 Study. J Clin Oncol, 2016. 34(13): p. 1476-83.
420. Kenis, C., et al., Functional decline in older patients with cancer receiving chemotherapy: A multicenter prospective study. J Geriatr Oncol, 2017. 8(3): p. 196-205.
421. Hamaker, M.E., et al., The effect of a geriatric evaluation on treatment decisions for older cancer patients--a systematic review. Acta Oncol, 2014. 53(3): p. 289-96.
422. Maione, P., et al., Pretreatment quality of life and functional status assessment significantly predict survival of elderly patients with advanced non-small-cell lung cancer receiving chemotherapy: a prognostic analysis of the multicenter Italian lung cancer in the elderly study. J Clin Oncol, 2005. 23(28): p. 6865-72.
423. Klepin, H.D., et al., Geriatric assessment predicts survival for older adults receiving induction chemotherapy for acute myelogenous leukemia. Blood, 2013. 121(21): p. 4287-94.

424. Shahrokni, A., et al., Geriatric Assessment, Not ASA Physical Status, Is Associated With 6-Month Postoperative Survival in Patients With Cancer Aged ≥75 Years. J Natl Compr Canc Netw, 2019. 17(6): p. 687-694.
425. Kenis, C., et al., Relevance of a systematic geriatric screening and assessment in older patients with cancer: results of a prospective multicentric study. Ann Oncol, 2013. 24(5): p. 1306-12.
426. Tucci, A., et al., A comprehensive geriatric assessment is more effective than clinical judgment to identify elderly diffuse large cell lymphoma patients who benefit from aggressive therapy. Cancer, 2009. 115(19): p. 4547-53.
427. Cudennec, T., et al., Use of a simplified geriatric evaluation in thoracic oncology. Lung Cancer, 2010. 67(2): p. 232-6.
428. Balducci, L. and M. Extermann, Management of cancer in the older person: a practical approach. Oncologist, 2000. 5(3): p. 224-37.
429. Extermann, M., et al., A comprehensive geriatric intervention detects multiple problems in older breast cancer patients. Crit Rev Oncol Hematol, 2004. 49(1): p. 69-75.
430. Chen, H., et al., Can older cancer patients tolerate chemotherapy? A prospective pilot study. Cancer, 2003. 97(4): p. 1107-14.
431. Rao, A.V., et al., Geriatric evaluation and management units in the care of the frail elderly cancer patient. J Gerontol A Biol Sci Med Sci, 2005. 60(6): p. 798-803.
432. Stuck, A.E., et al., Comprehensive geriatric assessment: a meta-analysis of controlled trials. Lancet, 1993. 342(8878): p. 1032-6.
433. Beswick, A.D., et al., Complex interventions to improve physical function and maintain independent living in elderly people: a systematic review and meta-analysis. Lancet, 2008. 371(9614): p. 725-35.
434. Caillet, P., et al., Optimal management of elderly cancer patients: usefulness of the Comprehensive Geriatric Assessment. Clin Interv Aging, 2014. 9: p. 1645-60.
435. Puts, M.T., et al., An update on a systematic review of the use of geriatric assessment for older adults in oncology. Ann Oncol, 2014. 25(2): p. 307-15.

436. Battisti, N.M.L. and E. Dotan, Integrating Geriatric Oncology into Clinical Pathways and Guidelines, in Geriatric Oncology, M. Extermann, Editor. 2018, Springer.
437. Hamerman, D., Toward an understanding of frailty. Ann Intern Med, 1999. 130(11): p. 945-50.
438. Brunello, A., et al., Development of an oncological-multidimensional prognostic index (Onco-MPI) for mortality prediction in older cancer patients. J Cancer Res Clin Oncol, 2016. 142(5): p. 1069-77.
439. Cohen, H.J., et al., Frailty as determined by a comprehensive geriatric assessment-derived deficit-accumulation index in older patients with cancer who receive chemotherapy. Cancer, 2016. 122(24): p. 3865-3872.
440. Mohile, S.G., et al., Geriatric Assessment-Guided Care Processes for Older Adults: A Delphi Consensus of Geriatric Oncology Experts. J Natl Compr Canc Netw, 2015. 13(9): p. 1120-30.
441. Qian, C.L., et al., Randomized trial of a perioperative geriatric intervention for older adults with cancer. Journal of Clinical Oncology, 2020. 38(15_suppl): p. 12012-12012.
442. Geriatric assessment in predicting chemotherapy toxicity and vulnerabilities in older patients with cancer (NCT02517034). 05/07/2020]; Available from: https://clinicaltrials.gov/ct2/show/NCT02517034.
443. Francescatti, A.B., et al. Improving surgical care and outcomes through the OPTI-Surg toolkit. 05/07/2020]; Available from: http://bulletin.facs.org/2018/03/improving-surgical-care-and-outcomes-through-the-opti-surg-toolkit/#
444. Magnuson, A., et al., Geriatric assessment with management intervention in older adults with cancer: a randomized pilot study. Support Care Cancer, 2018. 26(2): p. 605-613.
445. Mohile, S.G., et al., Communication With Older Patients With Cancer Using Geriatric Assessment: A Cluster-Randomized Clinical Trial From the National Cancer Institute Community Oncology Research Program. JAMA Oncol, 2019. 6(2): p. 1-9.

446. Role of geriatric intervention in treatment of older patients with cancer (PREPARE) (NCT02704832).
447. Puts, M.T.E., et al., A randomized phase II trial of geriatric assessment and management for older cancer patients. Support Care Cancer, 2018. 26(1): p. 109-117.

1.8. TABLES

Table 1.1 – Comprehensive geriatric assessment domains and examples of tools.

Domain	Tool	Time to administer	Abnormal score
Demographic and social status	Conditions of living, marital status, educational level, financial resources, social activities, family support Identification of the caregiver and burden (Zarit Burden Interview)	10 min 15-20 min	 >20
Comorbidities	Charlson comorbidity index CIRS CIRS-G Physical Health Section (subscale of OARS) Simplified comorbidity score	2 min	
Polypharmacy	Beers criteria STOPP and START criteria		
Functional status	ADL (Katz index) IADL (Lawton scale) Visual and/or hearing impairment, regardless of use of glasses or hearing aids Mobility problem (requiring help or use of walking aid) Timed Get Up and Go Hand grip strength Walking problems, gait assessment, and gait speed Self-reported no. of falls (within different time frames)		<6 <8 ≥14s <1m/s
Cognition	Mini Mental State Examination Montreal Cognitive Assessment Clock-drawing test Blessed Orientation-Memory-Concentration Test Mini-Cog	10-15 min	<24 <26 <5 >4 <4
Mood	Geriatric Depression Scale (mini-GDS, GDS-15, GDS-30)	15 min	Mini GDS: <1; GDS-15: >5; GDS-30: >10

	Hospital Anxiety and Depression Scale Distress thermometer		>7
Nutrition	Body-mass index (weight and height) Weight loss (unintentional loss in 3 or 6 months) Mini Nutritional Assessment Dentition		<23 <24
Fatigue	MOB-T		
Geriatric syndromes[188]	Dementia Delirium Incontinence (faecal and/or urinary) Osteoporosis or spontaneous fractures Neglect or abuse Failure to thrive Pressure ulcer Sarcopenia		

Abbreviations: ADL, activity of daily living; CIRS-G, Cumulative Illness Rating Scale-Geriatrics; ECOG, Eastern Cooperative Oncology Group; GA, geriatric assessment; IADL, instrumental activity of daily living; MOB-T, Mobility Tiredness Test; PS, performance status; START, Screening Tool to Alert Doctors to Right Treatment; STOPP, Screening Tool of Older Person's Prescriptions

Table 1.2 – Selected geriatric screening tools

Tool	Number of items	Score range	Time to perform (min)	Abnormal score	Sensitivity for abnormal CGA	Specificity for abnormal CGA	PPV	NPV	% screen positive
G8	8	0-17	4.4	≤14	65-92%	3-75%	44-86%	8-78%	64-94%
VES-13	13	0-10	5.7	≥3	39-88%	62-100%	60-100%	18-88%	29-60%
TRST	5	0-6	2	≥1	91-92%	42-50%	81-87%	63%	74-82%
GFI	15	0-15	N/A	≥4	30-66%	47-87%	86-94%	40-59%	64-79%
Abbreviated CGA	15	--	4	≥1	51%	97%	97%	48%	68%
Fried frailty criteria	5	--	5	≥3	37-87%	49-86%	77-95%	16-66%	66-88%
SAOP2	27	--	N/A	≥1	100%	40%	90%	100%	84%

Abbreviations: G8, Geriatric 8; VES-13, Vulnerable Elders Survey-13; TRST, Triage Risk Screening Tool; GFI, Groningen Frailty Index; CGA, comprehensive geriatric assessment; SAOP2, Senior Adult Oncology Program 2; PPV, Positive predictive value; NPV, Negative predictive value

Table 1.3 – Geriatric assessment minimum dataset recommended by the American Society of Clinical Oncology.

Predict chemotherapy toxicity (if clinically applicable): Cancer and Aging Research Group or Chemotherapy Risk Assessment Scale for High-Age Patients tools
Estimate (noncancer) life expectancy (if clinically applicable): ePrognosis
Functional assessment: Instrumental Activities of Daily Living
Comorbidity assessment: Medical record review or validated tool
Screening for falls, one question: How many falls or falls with an injury have you had in the previous 6 months (or since your last visit)?
Screening for depression: Geriatric Depression Scale or other validated tool
Screening for cognitive impairment: Mini-Cog or Blessed Orientation-Memory-Concentration test
Screening for malnutrition: Weight loss/body mass index

Table 1.4 – Geriatric interventions recommended by ASCO.

Geriatric assessment measure	Geriatric assessment: Guided interventions
Function and falls Instrumental activities of daily living deficit History of falls	Physical therapy and/or occupational therapy referrals to prescribe strength and balance training, assist device evaluation, home exercise program, and safety evaluation Fall prevention discussion Home safety evaluation
Comorbidity domain Comorbidity and polypharmacy considerations	Involve caregiver in discussions to assess risks of therapy and management of comorbidities Involve primary care physician and/or geriatrician in decision making for treatment and management of comorbidities; consider referral to geriatrician Review medication list and minimize medications as much as possible; consider involving a pharmacist Assess adherence to medications; have patient bring in medications to review
Cognition Screen positive on validated cognitive screen	Assess decision-making capacity and ability to consent for treatment Identification of health care proxy and involve proxy in decision making for treatment, including signing consent forms with patient Delirium risk counseling for patient and family Medication review to minimize medications with higher risk of delirium Consider further workup with geriatrician or cognitive specialist
Depression Geriatric Depression Scale >5	Consider referral for psychotherapy/psychiatry Consider cognitive-behavioral therapy Social work involvement Consider pharmacologic therapy
Nutrition Weight loss >10%	Nutrition counseling Referral to nutritionist/dietician Assess need for extra support for meal preparation and institute support interventions if necessary (e.g., caregiver, *Meals on Wheels*)

CHAPTER 2. OBSERVATIONAL COHORT STUDY OF EFFECTS OF CHEMOTHERAPY AND TRASTUZUMAB ON RECURRENCE AND SURVIVAL IN OLDER WOMEN WITH EARLY BREAST CANCER

2.1. ABSTRACT

Chemotherapy improves outcomes for high-risk early breast cancer (EBC) patients but is infrequently offered to older individuals. This study determined if there are fit older patients with high-risk disease who may benefit from chemotherapy.

A multicentre, prospective, observational study was performed to determine chemotherapy (with or without trastuzumab) usage and survival and quality of life (QoL) outcomes in EBC patients aged ≥70 years. Propensity score matching adjusted for variation in baseline age, fitness and tumour stage.

3416 women were recruited from 56 UK centres between 2013-2018. 2,811 (82%) had surgery. 1,520/2,811 (54%) had high-risk EBC and 2059/2,811 (73%) were fit. Chemotherapy was given to 306/1,100 (27.8%) fit patients with high-risk EBC. Unmatched comparison of chemotherapy versus no chemotherapy demonstrated reduced metastatic recurrence risk in high-risk patients (hazard ratio [HR] 0.36 [95% CI 0.19-0.68]) and in 541 age, stage and fitness-matched patients (adjusted HR 0.43 [95% CI 0.20-0.92]) but no benefit to overall survival (OS) or breast cancer-specific survival (BCSS) in either group. Chemotherapy improved survival in women with oestrogen receptor (ER)-negative cancer (OS: HR 0.20 [95% CI 0.08-0.49]; BCSS: HR 0.12 [95% CI 0.03-0.44]).

Chemotherapy was associated with reduced risk of metastatic recurrence, but survival benefits were only seen in patients with ER-negative cancer.

2.2. INTRODUCTION

In 2014-2016 over 18,500 women per year aged ≥70 years were diagnosed with breast cancer in the UK, representing 34% of all diagnoses.[1] Breast cancer survival is worse in older patients[2] who have not experienced similar outcome improvements compared with younger individuals in the past 3 decades.[3] This may reflect late presentation, more comorbidities or under-treatment. Significant treatment variations between centres are frequently reported in older adults.[4, 5] However, interpreting such data can be challenging without information on fitness, which may mitigate treatment benefits, due to competing mortality risks and increased treatment-related toxicity.

Chemotherapy benefit in older women with early breast cancer (EBC) is controversial. Whilst there have been many high-quality randomised clinical trials (RCTs) to evaluate the impact of systemic chemotherapy, the majority of trials excluded or recruited poorly amongst older patients, and tended to enrol fitter individuals.[6] This reflects clinicians' and patients' toxicity concerns and reticence from trialists about diluting the study power by introducing higher morbidity rates and competing causes of death in less fit older patients.

As a population, older adults derive less benefit from chemotherapy compared to younger patients. Benefit is present between the ages of 70 and 80, although data for women aged over 80 years are scarce.[7] The Bridging the Age Gap study was designed to recruit a large, real-world, cohort of older women with breast cancer including detailed baseline fitness data and information about the cancer, treatment received and outcomes. The objectives of this study analysis were to determine health status-stratified outcomes for EBC patients aged ≥70 according to whether they received guideline concordant or non-concordant care with a particular focus on chemotherapy use. In this study, the age- and risk-stratified patterns of receipt of adjuvant systemic therapy are described in older EBC patients, with propensity score-matched analysis of disease recurrence and survival outcomes.

The Bridging the Age Gap study had completed recruitment by the time of registration of my research degree. Within this study, I have been responsible for the cleaning of the study database, the statistical analysis in conjunction with the trial statistician and the formulation of specific research questions to be investigated in the study cohort.

2.3. METHODS

2.3.1. Regulatory approval

Ethics approval (IRAS: 12 LO 1808) and research governance approval were obtained. All patients (or their proxies, if cognitively impaired) gave written informed consent.

2.3.2. Study design

Bridging the Age Gap is a prospective multicentre, observational cohort study. Patients were recruited from 56 UK centres in England and Wales (Supplementary table 2.1). Eligible patients were women ≥70 years at diagnosis of primary operable invasive breast cancer (TNM stages: T1-3 [plus operable T4b], N0-1, M0). Those unsuitable for surgery or with previous EBC within five years were not eligible.

2.3.3. Baseline data collection

Patients were recruited at the time of EBC diagnosis and before commencing treatment and could participate at three levels: full, partial (no requirement to complete quality of life [QoL] assessments) or by proxy (simple third-party data collection for those with cognitive impairment).

Baseline data were collected about the primary tumour including: cancer type, grade, nodal status, tumour size, oestrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2) status and Recurrence Score on Oncotype DX. Staging was performed if clinically indicated. Surgical, radiotherapy and systemic therapy data were collected.

At baseline, patients underwent assessments using validated tools including: comorbidities (Charlson comorbidity index [CCI]),[8] nutrition (Abridged Patient Generated Subjective Global Assessment [aPG-SGA]),[9, 10] functional status (Activities of Daily Living [ADL]),[11] advanced functional status (Instrumental Activities of Daily Living [IADL]),[12] dementia (Mini

Mental State Examination [MMSE]),[13] Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) and medication list.

QoL was evaluated using four questionnaires (Supplementary table 2.2). The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaires (QLQ)-C30 includes five functions (physical, role, emotional, cognitive and social), nine symptoms (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties) and global health status.[14] The EORTC-QLQ-BR23 comprises 23 questions evaluating body image, sexual functioning and enjoyment, future perspective, systemic therapy side effects, breast symptoms, arm symptoms and frustration with hair loss.[15] The EORTC-QLQ-ELD15 contains five scales (functional independence, relationships with family and friends, worries about the future, autonomy and burden of illness).[16] The 5-level Euroqol-5D (EQ-5D-5L) version consists of 2 pages: the EQ-5D descriptive system (comprising five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and the EQ visual analogue scale (recording the patient's self-rated health on a vertical visual analogue scale).[17] In this study, the EQ-5D-5L was used to assess overall QoL and individual questions were scored separately from 1-5.

2.3.4. Follow-up and outcomes

Patients were followed up at 6 weeks, and 6, 12, 18 and 24 months. Survival outcomes (date and cause of death) were obtained at 52 months median follow-up from the UK cancer registry. All patients were assessed for recurrence and QoL at each visit. Complications were categorised using the Common Terminology Criteria for Adverse Events system (CTCAE v4.0).

Chemotherapy-related mortality was defined as death within 30 days of chemotherapy or if chemotherapy was documented as a contributing cause. Deaths were categorised as disease-related or other causes. Deaths were reviewed by the chief investigator blind to treatment decisions. Deaths were classified as disease related if the death was related to the initial breast

cancer. Patients for whom the cause could not be established were excluded from cause specific analyses.

2.3.5. Statistical analyses

Analyses were performed in IBM SPSS statistics version 24 and R version 3.6.3.[18] A $p<0.05$ was considered statistically significant.

2.3.5.1. Chemotherapy use and impacts analysis

The relationships between systemic therapy use and tumour and patient characteristics were evaluated using univariable and multivariable logistic regression. High-risk EBC was defined if any of the following criteria were present: node-positive, ER-negative, HER2-positive, grade 3, or Recurrence Score ≥25 (Table 2.1). Additional analyses were conducted in patients with ER-negative and HER2-positive tumours, where the benefits from chemotherapy might be anticipated. Fitness was defined based on geriatric assessments and categorized into fit, vulnerable and frail according to a cumulative score including measures of functional status, comorbidities, polypharmacy, nutritional status and cognitive status (Table 2.2).

Both OS and BCSS were compared in treated and untreated patients. A Cox proportional hazards model was fitted using regression-based adjustment based on covariates of: treatment; age; categories of aPG-SGA, ADL, IADL, CCI, MMSE, ECOG, medications, and Nottingham Prognostic Index (NPI)[19] and HER2 for all high risk patients. Hazard ratios (HR) and corresponding 95% confidence intervals (CIs) were calculated.

Propensity score matching was used to limit the impact of confounders on the effects of chemotherapy on recurrence and survival outcomes. Propensity scores were calculated for each participants using a logistic regression model. The scores represent the probability to fall into one category of the exposure variable (chemotherapy receipt) as opposed to the other. A propensity score adjustment among sufficiently similar high-risk patients was fitted using a Cox model with a shared frailty term (or random effect) for matched patients.

Participants were matched exactly on NPI category and HER2 status, and logistic regression was used to calculate propensity scores for treatment in relation to age, aPG-SGA category, ADL category, IADL category, MMSE category, CCI category, ECOG PS category and number of medications. The ratio and calliper widths of the propensity scores were chosen following examination of the propensity score overlaps for several combinations of ratios and callipers. The calliper is the fixed distance by which the propensity scores of matched individuals (receiving chemotherapy or not) differ at most. A narrower calliper involves matching more similar subjects thus reducing bias and the number of participants included in the analysis. A 1:3 ratio for chemotherapy versus no chemotherapy and a calliper of 0.25 times the propensity scores' standard deviation was used to ensure participants were closely matched whilst retaining as many patients as possible.

2.3.5.2. Radiotherapy use and impacts analysis

The relationships between radiotherapy use, tumour and patient characteristics were evaluated using univariate and multivariable logistic regression for patients undergoing breast-conserving surgery (BCS) or mastectomy.

Patients undergoing BCS were considered at high risk of recurrence if the tumour was ≥3cm, ER-negative, HER2-positive, node-positive, or grade 3 (Table 2.3).[20] Those undergoing mastectomy where considered high-risk if the tumour was T3, T4, or if ≥4 lymph nodes were involved (Table 2.3).[21, 22] Fitness was defined based on geriatric assessments in order to categorize women as fit, vulnerable or frail (Table 2.1). Radiotherapy use was reported by recurrence risk and fitness.

2.3.5.3. Quality of life analyses

The questionnaires were scored according to the EORTC Scoring Manual (3rd Edition).[23] Missing data were managed accordingly. The analysis of the impact of chemotherapy on QoL included high-risk EBC patients where QoL questionnaires were available. On the other hand, the analysis of the impact of radiotherapy included patients undergoing surgery and not receiving

chemotherapy (due to its significant effect on QoL): however, the analysis was conducted separately for patients undergoing BCS or mastectomy.

The mean difference (95% CI) of the domain scores at each time point, adjusted for baseline scores, was calculated with linear regression models for high-risk participants. Effect sizes after analyses of the EORTC-QLQ-C30 were categorised as either trivial, small, medium or large according to pre-specified thresholds for each domain.[24]

The chemotherapy effect on the global health score over time for high-risk patients was estimated using a mixed-effect linear model. The model allowed for time, treatment, treatment-time interaction, and baseline global health status. Differences between the chemotherapy and non-chemotherapy groups were derived at each timepoint using linear contrasts. The model was fitted to high-risk patients and to the propensity score-matched patients only. For the unmatched analysis the model also adjusted for age and baseline functionality scores.

We also performed propensity score-matching to compare the EORTC-QLQ-C30 global health score and the EQ-5D-5L usual activities score in a matched cohort receiving chemotherapy versus patients not receiving it. Logistic regression was used to calculate propensity scores for treatment allocation in high-risk patients. These were used to match chemotherapy patients to those who did not receive chemotherapy based on ADL, IADL, MMSE, ECOG, aPG-SGA, CCI, number of medications, and age. The ratio and calliper widths of the propensity scores were chosen based on examination of propensity score overlaps for several combinations of ratios and callipers. A 1:3 ratio for chemotherapy to no chemotherapy and a calliper of 0.25 times the propensity scores standard deviation was used to optimally match quality and numbers. Participants were matched on NPI category (good ≤3.4, moderate 3.5-5.4, poor >5.4) and HER2 status.

2.4. RESULTS

Between January 2013 and June 2018, 3456 women were recruited from 56 centres in England and Wales (Supplementary table 2.1). This analysis was restricted to the 2,811 women who underwent surgery within 6 months of diagnosis (STROBE diagram [Figure 2.1]).[25] The key findings on patients' characteristics according to geriatric assessments, tumour characteristics, postoperative histology and surgery performed are shown in Table 2.4; detailed findings are presented in Supplementary table 2.3.

Of the 2,811 patients, 397 (14.1%) received chemotherapy (365 [91.9%] in the adjuvant setting, 30 [7.5%] in neoadjuvant setting, and 2 [0.5%] unknown). Of those 380 patients for whom the chemotherapy regimen received was known, 132 (34.7%) received an anthracycline-taxane combination, 124 (32.6%) a taxane (without anthracycline), 123 (32.4%) an anthracycline and 1 cyclophosphamide, methotrexate and fluorouracil (CMF). 332 patients (11.8%) had HER2-positive EBC. Of these patients, 150 (45.1%) received chemotherapy plus trastuzumab, 13 (3.9%) trastuzumab without chemotherapy, and 9 (2.7%) chemotherapy without trastuzumab. Overall, 1,753/2,811 (62.4%) patients received radiotherapy and 2,239/2,354 (95.1%) ER-positive patients received endocrine therapy.

Chemotherapy receipt according to tumour and patient characteristics is shown in Tables 2.5 and 2.6 and Supplementary tables 2.4 and 2.5. Univariate and multivariate analyses are shown in Table 2.7 and 2.8. Younger, less dependent patients with high-risk tumours and with fewer comorbidities were more likely to receive chemotherapy.

High-risk tumours were present in 1,520 (54.1%) patients and 376/1,520 (24.7%) received chemotherapy compared with 21/1,291 (1.6%) of patients with non-high-risk tumours (Table 2.9 and Table 2.10). 2,059 patients (73.2%) were fit and 752 vulnerable or frail (26.7%) (Table 2.10). Of those who were fit, 1,100 also had high-risk EBC, and of these patients 306 (27.8%) received chemotherapy (Table 2.11).

At a median follow-up of 52 months, mortality status was available for 98.3% (1,495/1,520) of high-risk patients (371 in the chemotherapy group, 1,124 in the no chemotherapy group). Chemotherapy was associated with a longer OS, but the difference was not statistically significant when adjusted for other covariates (unadjusted HR 0.55 [95% CI 0.40-0.73, p<0.001] and adjusted HR 0.87 [95% CI 0.58- 1.28, p=0.469] (Figure 2.2). In a propensity score-matched analysis 200 patients receiving chemotherapy were matched to 350 who did not receive it. Supplementary table 2.6 shows the characteristics of the matched dataset and the matching process and quality are summarised in Figure 2.3. Mortality status was available for 542 (98.5%) of the matched patients. Chemotherapy was associated with a longer OS although this was not statistically significant (HR 0.79 [95% CI 0.50-1.26, p=0.320]) (Figure 2.4).

BCSS was available for 97.8% (1,486/1,520) of patients in the high-risk population. Chemotherapy was not associated with improved BCSS (unadjusted HR 0.76 [95% CI 0.53-1.10, p=0.147] and adjusted HR 0.92 [95% CI 0.56-1.53, p=0.758]) (Figure 2.5). In the propensity score-matched population, BCSS was available for 539 patients (98.0%). Chemotherapy was also not found to be associated with improved BCSS (HR 0.93 [95% CI 0.52-1.66, p=0.798]) (Figure 2.6).

Metastatic recurrence data were available for 1,498 high-risk patients (98.5%). Chemotherapy was associated with a significantly lower risk of metastatic recurrence in the unmatched population (unadjusted HR 0.67 [95% CI 0.43-1.04, p=0.077] and adjusted HR 0.36 [95% CI 0.19-0.68, p=0.002]) (Figure 2.7). In 541 matched patients (98.0%), chemotherapy was also associated with a lower metastatic recurrence risk (HR 0.53 [95% CI 0.26-1.07, p=0.076]) (Figure 2.8).

Additional post-hoc exploratory analyses were performed in disease subgroups. Out of 369 patients with ER-negative EBC and known mortality status, 132 (35.8%) received chemotherapy. In a propensity score-matched analysis in 136 patients, chemotherapy was associated with better OS (HR

0.20 [0.08-0.49]) and BCSS (HR 0.12 [0.03-0.44]) (Figure 2.9, 2.10, 2.11 and 2.12). 326 patients with HER2-positive EBC and known mortality status of whom 156 (47.9%) received chemotherapy with or without trastuzumab. Fewer deaths from breast cancer and other causes occurred in those receiving chemotherapy with or without trastuzumab. However, in a matched analysis in 137 patients, the differences were not statistically significant for OS (HR 0.63 [0.27-1.48]) or BCSS (HR 0.50 ([0.16-1.63]) (Figure 2.13, 2.14, 2.15 and 2.16 and Table 2.12).

Table 2.13 and 2.14 outline chemotherapy toxicity. Among 397 patients receiving chemotherapy, there was one chemotherapy-related death (0.2%) (due to congestive heart failure [CHF]) and 132 (33.2%) had an episode of infection, which was grade 3 or 4 in 50 (12.6%). Among the 163 patients who received trastuzumab, 4 (2.5%) experienced CHF within the first 6 months and 12 (6.7%) within the first year.

2.5. DISCUSSION

There has been a considerable debate for several years about the absolute benefit of adjuvant chemotherapy in older patients with EBC. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis including trial data on patients randomised to adjuvant chemotherapy versus not, showed a survival benefit from polychemotherapy for patients ≤69 years.[26] However, for those ≥70 years, the proportional reductions in risk of recurrence were similar, but no longer statistically significant, potentially reflecting the smaller number of older patients included. The small number of older patients enrolled in such trials would support specific trials for older patients to address this question.

In 2006, a retrospective Surveillance, Epidemiology, and End Results (SEER) analysis of 5,081 patients ≥65 years with hormone receptor-negative EBC showed a 15% reduction in mortality for women treated with chemotherapy,[27] although chemotherapy uptake was lower for those ≥70 years. A SEER database analysis of 41,390 stage I-III patients ≥65 years showed similar results, including lower chemotherapy use after the age of 75 years and a survival benefit for those with ER-negative, node-positive EBC receiving chemotherapy.[28] Conversely, the study did not show any advantage for patients with ER-positive or ER-negative, node-negative disease. A National Cancer Database analysis, including patients ≥70 years with node-positive, ER-positive, HER2-negative EBC with a Charlson/Deyo comorbidity score of 2-3 and treated in 2010-2014, showed that chemotherapy improves OS also in the context of competing risks.[29] However, selection bias remains a significant concern with these retrospective analyses of registry data.[30]

On the other hand, relatively few studies have directly investigated the role of adjuvant chemotherapy in older patients in a randomised fashion. The French Adjuvant Study Group 08 (FASG 08) study recruited 388 patients aged ≥65 who were randomised to tamoxifen and epirubicin-based chemotherapy versus endocrine therapy alone and showed lower risk of recurrence in

patients with node-positive disease, especially in those with ER-negative disease.[31] However, no OS benefit was seen. The Ibandronate with or without Capecitabine in Elderly Patients (ICE) study investigated the effect of oral capecitabine (along with ibandronate and, where indicated, endocrine therapy) versus ibandronate with or without endocrine therapy in 1,358 patients aged ≥65 with node-positive or node-negative, high-risk EBC (defined as ≥2cm, grade 2-3 or HR negative).[32] Whilst 83.3% of patients managed to complete six cycles of chemotherapy, the study did not show any survival advantage with capecitabine. Whether this finding reflects the chosen agent or a limited benefit from chemotherapy in the patient population is unclear. FASG 08 and ICE are the only studies prospectively addressing the absolute benefits of chemotherapy in older adults with EBC by comparing outcomes for those receiving chemotherapy versus not. Other trials of a similar design, such as the ACTION and the CASA study, closed early due to poor recruitment.[33] Overall, prospective and retrospective evidence shows that adjuvant chemotherapy improves disease-specific survival and overall mortality, at least for older adults with ER-negative EBC. Nevertheless, these findings argue for conducting a prospective cohort study.

Data on the use of chemotherapy in older adults diagnosed with breast cancer suggests some potential risk of under-treatment in this population. The Adjuvant chemotherapy in elderly women with breast cancer (ACheW) study included data on 803 patients ≥70 years diagnosed with EBC in the UK.[34] In the overall population, 14% of patients were offered chemotherapy and 8% received it. However, only 30% of those with high-risk disease were offered chemotherapy, and 17% received it. Frequent reasons for foregoing chemotherapy included the availability of additional systemic treatments (such as endocrine therapy for ER-positive tumours) and the small magnitude of perceived benefits. Importantly, the study documented considerable variation in treatments offered between centres.

The Age is no Barrier to Chemotherapy analysis included cancer registry data on 49,378 patients aged ≥18 years diagnosed with stage II-III breast cancer in England in 2013-2015 and compared use of chemotherapy between those

aged 18-69 years and those aged ≥70 years.[4] While chemotherapy rates differed between the two age groups (70% for patients aged 18-69 compared with 18% aged ≥70 years), this gap persisted also for those diagnosed with ER-negative disease (92% for patients aged 18-69 years compared with 33% for those aged ≥70 years). Similarly to the ACheW study, this analysis documented a larger variation in the case-mix adjusted systemic anticancer treatment rates between hospitals in the older age group.

The Bridging the Age Gap study represents one of the largest prospective cohort studies conducted in older women with breast cancer and provides valuable data on tumour characteristics and health of older EBC patients. As expected, most patients had relatively good prognosis tumours, with relatively low rates of nodal involvement and adverse biology as determined by ER and HER2 status. A key finding of this study is that 28% of fit high-risk EBC older patients received chemotherapy. In the ACheW study 30% of high-risk EBC patients were offered chemotherapy and 17% received it.[34] Analyses of European and US registry data report similar findings.[5, 35, 36] These analyses did not consider recurrence risk (as determined by histopathological variables) and patients' fitness (to not only receive treatment but also to live long enough to benefit). The current study overcomes these limitations, by defining recurrence risk and fitness, and still demonstrates low chemotherapy uptake. This may be due to uncertainty on chemotherapy benefit in older adults, toxicity concerns and patients' and carers' choice.

In order to investigate the survival benefits of chemotherapy for older EBC patients, we conducted survival analyses in those at high risk of recurrence. Ideally this question should be addressed by RCTs. Recruiting older patients into RCTs comparing different chemotherapy regimens is feasible,[37] but trials comparing chemotherapy with no chemotherapy have failed to recruit.[33, 38] Moreover, older patients enrolled in RCTs may be fitter and not necessarily representative of a real-world population.[6] In contrast, this cohort study recruited well, and recruited patients with a broad fitness range.

Our analyses attempted to correct for confounders, specifically the fact that younger, fitter patients might be more likely to receive chemotherapy, but also are biologically more likely to survive longer irrespective of chemotherapy effect. This effect is perhaps most apparent when comparing the unmatched and matched OS analyses (Figure 2.2 and 2.4).

In the high-risk population chemotherapy reduced the risks of metastatic recurrence, which did not translate into better survival. This may be because the benefit was modest and the fact that median OS for ER-positive metastatic disease patients often exceeds 3 years with contemporary therapies.[39] Irrespective, a reduction in metastatic relapses, with their symptomatic, psychological and financial implications, may be sufficient grounds on which to offer treatment even in the absence of a survival benefit. Longer term follow-up will be required to further explore this.

Chemotherapy benefits are expected to be small for most ER-positive, HER2-negative EBC patients. Therefore, we performed exploratory analyses in patients with the more chemotherapy-sensitive subtypes, i.e., ER-negative and HER2-positive disease. In ER-negative EBC patients there was an apparent reduction of breast cancer deaths with chemotherapy. These data are consistent with an US SEER analysis suggesting that adjuvant chemotherapy benefit in older patients were restricted to those with ER-negative disease (28).[28] In HER2-positive EBC patients, fewer breast cancer deaths occurred in those who received chemotherapy with or without trastuzumab although the differences were not statistically significant in a matched analysis. This could be explained by the small numbers in this subgroup analysis. However, a retrospective study demonstrated that HER2-positive EBC older patients do not have inferior long-term outcomes compared with younger adults not receiving chemotherapy.[40] Low Ki67 and high bcl2 expression in the older cohort of HER2-positive patients might explain this better prognosis and also relative chemo-resistance.[40] Our study found that mortality rates from chemotherapy were very low and side-effects consistent with previous analyses.[41] Follow up of the cohort is planned at 10 years and may provide data about longer term benefits, although it should be recognised

that with longer follow-up competing mortality causes are likely have a greater impact.

A key strength of this study is that patients were recruited from a broad range of academic and general centres across the UK and were likely to reflect contemporary practice and outcomes. However, despite the inclusive entry criteria and low level of intervention a key limitation is still the possibility of selection bias. In a separate analysis of this study we found that patients who did not enter the trial following screening were older and had worse functional ability.[42] An additional limitation of the study involves the definition of high-risk EBC: this was determined by use of one individual clinico-pathological feature rather than considering these variables together. Since patients were not randomised, an additional limitation involves unmeasured variables that might have influenced our findings despite propensity score matching. Finally, the extent to which these data reflect practice and outcomes outside of the UK is unknown, although some published data do appear comparable.[35, 36]

Future directions of our research may involve the evaluation of better predictors of risk of disease recurrence and treatment benefits in older patients with EBC. While PREDICT was found to be accurate in predicting benefits at five years in those aged ≥65 years,[43] the tool was found to overestimate outcomes and be less accurate at ten years, especially in the context of comorbidities and for patients aged ≥80. The Age Gap Decision tool may overcome these limitations by including data on comorbidities and activities of daily living in the algorithm.[44] Further aspects to investigate may also include the use of chemotherapy regimens with a better safety profile in this population. While capecitabine or weekly docetaxel have been found to be inferior to more standard regimens,[45, 46] taxane-based (and anthracycline-free) regimens remain attractive in older patients to minimise cardiotoxicity risks based on data showing similar efficacy compared with anthracycline-based regimens.[47, 48] Cyclin-dependent kinase 4/6 inhibitors are being investigated in the APPALACHES study (NCT03609047) in an attempt to replace the use of cytotoxic agents in this setting. The integration of gene expression profiling along with measures of fitness may also represent an

additional opportunity to personalise the systemic treatment of older patients with EBC: the results of the ASTER70 study (NCT 01564056) will address this specific question.[49] Finally, an additional area warranting investigation includes patient and clinician education approaches that may be able to increase the use of chemotherapy in older patients with EBC who are most likely to benefit from it.

In summary, this study demonstrates that there are a significant number of older but fit patients with high-risk EBC who are not receiving adjuvant chemotherapy. Some of these patients, particularly those with ER-negative disease, may derive benefit from chemotherapy. Clearly, the benefits need to be discussed in the context of potential side effects and the transient negative impact on QoL. Nonetheless, it is important that individualised treatment decisions and discussions are made to ensure the best outcomes for older adults.

2.6. PROGRESS TO PRESENTATION AND PUBLICATION

This analysis was conducted on behalf of the Bridging The Age Gap study steering group, with specific contribution by statisticians Esther Herbert and Mike Bradburn and by Professor Lynda Wyld (University of Sheffield). I have presented these findings at the 2019 San Antonio Breast Cancer Symposium[50] and I have been awarded the Arti Hurria Award for geriatric oncology (2,000 USD) by the conference scientific committee. I have published this study manuscript in the British Journal of Cancer (impact factor 7.64) as co-first author.[51]

2.7. REFERENCES

1. UK, C.R. Breast cancer incidence (invasive) statistics. [cited 2020 24/05/2020]; Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/incidence-invasive.
2. Statistics, O.f.N., Cancer survival in England: Patients diagnosed between 2010 and 2014 and followed up to 2015. 2016: Newport, UK.
3. Moller, H., G. Flatt, and A. Moran, High cancer mortality rates in the elderly in the UK. Cancer Epidemiol, 2011. 35(5): p. 407-12.
4. Battisti, N.M.L., et al., Is age a barrier to chemotherapy? Rates of treatment in older patients treated with breast, colon and lung cancer in England in 2014: a national registry study. Annals of Oncology, 2018. 29: p. viii562-viii575.
5. Derks, M.G.M., et al., Variation in treatment and survival of older patients with non-metastatic breast cancer in five European countries: a population-based cohort study from the EURECCA Breast Cancer Group. Br J Cancer, 2018. 119(1): p. 121-129.
6. Khan, K., et al., Clinical research to improve outcomes for older cancer patients and conducting clinical trials in cancer patients, in Problem solving in older cancer patients, A. Ring, et al., Editors. 2015, Clinical Publishing: London, UK.
7. Ring, A., et al., The treatment of early breast cancer in women over the age of 70. Br J Cancer, 2011. 105(2): p. 189-93.
8. Charlson, M.E., et al., A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis, 1987. 40(5): p. 373-83.
9. Ottery, F.D., Definition of standardized nutritional assessment and interventional pathways in oncology. Nutrition, 1996. 12(1 Suppl): p. S15-9.
10. Vigano, A.L., et al., The abridged patient-generated subjective global assessment is a useful tool for early detection and characterization of cancer cachexia. J Acad Nutr Diet, 2014. 114(7): p. 1088-98.

11. Mahoney, F.I. and D.W. Barthel, FUNCTIONAL EVALUATION: THE BARTHEL INDEX. Md State Med J, 1965. 14: p. 61-5.
12. Lawton, M.P. and E.M. Brody, Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist, 1969. 9(3): p. 179-86.
13. Folstein, M.F., S.E. Folstein, and P.R. McHugh, "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res, 1975. 12(3): p. 189-98.
14. Aaronson, N.K., et al., The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst, 1993. 85(5): p. 365-76.
15. Sprangers, M.A., et al., The European Organization for Research and Treatment of Cancer breast cancer-specific quality-of-life questionnaire module: first results from a three-country field study. J Clin Oncol, 1996. 14(10): p. 2756-68.
16. Johnson, C., et al., Development of the European Organisation for Research and Treatment of Cancer quality of life questionnaire module for older people with cancer: The EORTC QLQ-ELD15. Eur J Cancer, 2010. 46(12): p. 2242-52.
17. Fayers, P.M., et al., The EORTC QLQ-C30 Scoring Manual (3rd Edition), ed. E.O.f.R.a.T.o. Cancer. 2001.
18. R: A language and environment for statistical computing. R Foundation for Statistical Computing 2020; Available from: https://www.R-project.org/.
19. Galea, M.H., et al., The Nottingham Prognostic Index in primary breast cancer. Breast Cancer Res Treat, 1992. 22(3): p. 207-19.
20. Kunkler, I.H., et al., Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. Lancet Oncol, 2015. 16(3): p. 266-73.
21. (NICE), N.I.f.H.a.C.E., Early and locally advanced breast cancer: diagnosis and management. 2018.

22. Mukesh, M.B., et al., The Cambridge post-mastectomy radiotherapy (C-PMRT) index: a practical tool for patient selection. Radiother Oncol, 2014. 110(3): p. 461-6.
23. Johnson, C., et al., Development of the European Organisation for Research and Treatment of Cancer quality of life questionnaire module for older people with cancer: The EORTC QLQ-ELD15. Eur J Cancer, 2010. 46(12): p. 2242-52.
24. Cocks, K., et al., Evidence-based guidelines for determination of sample size and interpretation of the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. J Clin Oncol, 2011. 29(1): p. 89-96.
25. von Elm, E., et al., The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol, 2008. 61(4): p. 344-9.
26. Peto, R., et al., Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. Lancet, 2012. 379(9814): p. 432-44.
27. Elkin, E.B., et al., Adjuvant chemotherapy and survival in older women with hormone receptor-negative breast cancer: assessing outcome in a population-based, observational cohort. J Clin Oncol, 2006. 24(18): p. 2757-64.
28. Giordano, S.H., et al., Use and outcomes of adjuvant chemotherapy in older women with breast cancer. J Clin Oncol, 2006. 24(18): p. 2750-6.
29. Tamirisa, N., et al., Association of Chemotherapy With Survival in Elderly Patients With Multiple Comorbidities and Estrogen Receptor-Positive, Node-Positive Breast Cancer. JAMA Oncol, 2020. 6(10): p. 1548-1554.
30. Battisti, N.M.L., A. McCartney, and L. Biganzoli, The Conundrum of the Association of Chemotherapy With Survival Outcomes Among Elderly Patients With Curable Luminal Breast Cancer. JAMA Oncol, 2020. 6(10): p. 1535-1537.
31. Fargeot, P., et al., Disease-free survival advantage of weekly epirubicin plus tamoxifen versus tamoxifen alone as adjuvant treatment of

operable, node-positive, elderly breast cancer patients: 6-year follow-up results of the French adjuvant study group 08 trial. J Clin Oncol, 2004. 22(23): p. 4622-30.

32. von Minckwitz, G., T. Reimer, and J. Potenberg, The phase III ICE study: Adjuvant ibandronate with or without capecitabine in elderly patients with moderate or high risk early breast cancer. Abstract S3-04, in 2014 San Antonio Breast Cancer Symposium. 2014.
33. Leonard, R., et al., Adjuvant chemotherapy in older women (ACTION) study - what did we learn from the pilot phase? Br J Cancer, 2011. 105(9): p. 1260-6.
34. Ring, A., et al., Adjuvant chemotherapy in elderly women with breast cancer (AChEW): an observational study identifying MDT perceptions and barriers to decision making. Ann Oncol, 2013. 24(5): p. 1211-9.
35. Bastiaannet, E., et al., Breast cancer in elderly compared to younger patients in the Netherlands: stage at diagnosis, treatment and survival in 127,805 unselected patients. Breast Cancer Res Treat, 2010. 124(3): p. 801-7.
36. Buist, D.S., et al., Referral, receipt, and completion of chemotherapy in patients with early-stage breast cancer older than 65 years and at high risk of breast cancer recurrence. J Clin Oncol, 2009. 27(27): p. 4508-14.
37. Muss, H.B., et al., Adjuvant chemotherapy in older women with early-stage breast cancer. N Engl J Med, 2009. 360(20): p. 2055-65.
38. Crivellari, D., et al., Adjuvant pegylated liposomal doxorubicin for older women with endocrine nonresponsive breast cancer who are NOT suitable for a "standard chemotherapy regimen": the CASA randomized trial. Breast, 2013. 22(2): p. 130-137.
39. Im, S.A., et al., Overall Survival with Ribociclib plus Endocrine Therapy in Breast Cancer. N Engl J Med, 2019. 381(4): p. 307-316.
40. Syed, B.M., et al., Human epidermal growth receptor-2 overexpressing early operable primary breast cancers in older (≥70 years) women: biology and clinical outcome in comparison with younger (<70 years) patients. Ann Oncol, 2014. 25(4): p. 837-842.

41. Adjogatse, D., et al., Febrile neutropaenia and chemotherapy discontinuation in women aged 70 years or older receiving adjuvant chemotherapy for early breast cancer. Clin Oncol (R Coll Radiol), 2014. 26(11): p. 692-6.
42. Todd, A., et al., Age specific recruitment and retention to a large multicentre observational breast cancer trial in older women: The Age Gap Trial. Journal of Geriatric Oncology, 2020.
43. de Glas, N.A., et al., Validity of the online PREDICT tool in older patients with breast cancer: a population-based study. Br J Cancer, 2016. 114(4): p. 395-400.
44. Age Gap Decision Tool. 19/10/2021]; Available from: https://agegap.shef.ac.uk/.
45. Muss, H.B., et al., Randomized Trial of Standard Adjuvant Chemotherapy Regimens Versus Capecitabine in Older Women With Early Breast Cancer: 10-Year Update of the CALGB 49907 Trial. J Clin Oncol, 2019. 37(26): p. 2338-2348.
46. Perrone, F., et al., Weekly docetaxel versus CMF as adjuvant chemotherapy for older women with early breast cancer: final results of the randomized phase III ELDA trial. Ann Oncol, 2015. 26(4): p. 675-682.
47. Caparica, R., et al., Anthracycline and taxane-based chemotherapy versus docetaxel and cyclophosphamide in the adjuvant treatment of HER2-negative breast cancer patients: a systematic review and meta-analysis of randomized controlled trials. Breast Cancer Res Treat, 2019. 174(1): p. 27-37.
48. Jones, S., et al., Docetaxel With Cyclophosphamide Is Associated With an Overall Survival Benefit Compared With Doxorubicin and Cyclophosphamide: 7-Year Follow-Up of US Oncology Research Trial 9735. J Clin Oncol, 2009. 27(8): p. 1177-83.
49. Brain, E., et al., ASTER 70s: Benefit of adjuvant chemotherapy for estrogen receptor-positive HER2-negative breast cancer in women over 70 according to genomic grade—A French GERICO/UCBG UNICANCER multicenter phase III trial. Journal of Clinical Oncology, 2012. 30(15_suppl): p. TPS667-TPS667.

50. Battisti, N.M.L., et al., Use of systemic therapy for early stage breast cancer in older adults: results from the Bridging the Age Gap study (P2-14-08), in San Antonio Breast Cancer Symposium. 2019: San Antonio, TX, USA.
51. Ring, A., et al., Bridging The Age Gap: observational cohort study of effects of chemotherapy and trastuzumab on recurrence, survival and quality of life in older women with early breast cancer. Br J Cancer, 2021.

2.8. TABLES

Table 2.1 – Chemotherapy use and effects analysis: Definition of risk of breast cancer recurrence based on tumour characteristics on diagnostic biopsy or surgical specimen.

Tumour characteristics	Risk of recurrence	
	High*	Low
ER	Negative	Positive
HER2	Positive	Negative
Grade	3	1-2
Nodal involvement	Yes	No
Oncotype DX Recurrence Score	≥25	<25

Abbreviations: ER: oestrogen receptor; HER2: human epidermal growth factor receptor.

* High risk is defined by the presence of ≥1 of the features enlisted.

Table 2.2 – Definition of fitness. Overall scores: Fit: 0-2. Vulnerable: 3-8. Frail: ≥9.

Domain	Range	Score		
		0	1	2
ECOG PS	0-4	0-1	2	3-4
ADL	0-10	20	19	≤18
IADL	0-8	8	7	≤6
Charlson comorbidity index	-	0-1	-	≥2
Prescribed medications (excluding vitamins/minerals)	-	≤3	≥4	-
aPG-SGA		0-3	4-8	≥9
MMSE	0-30	≥24	20-24	<20

Abbreviations: ECOG PS: Eastern Cooperative Oncology Group Performance Status; ADL: activities of daily living; IADL: instrumental activities of daily living; aPG-SGA: abridged patient-generated subjective global assessment; MMSE: Mini Mental State Examination.

Table 2.3 – Radiotherapy use and effects analysis: Definition of risk of breast cancer recurrence based on tumour characteristics on diagnostic biopsy or surgical specimen.

Tumour characteristics	Risk of recurrence	
	High[†]	Low
BREAST-CONSERVING COHORT		
Tumour size	≥3cm	<3cm
ER	Negative	Positive
HER2	Positive	Negative
Grade	3	1
Nodal involvement	Yes	No
MASTECTOMY COHORT		
Tumour size	≥5cm	<5cm
Lymph nodes involved	≥4	<4

Abbreviations: ER: oestrogen receptor; HER2: human epidermal growth factor receptor.

[†] High risk is defined by the presence of ≥1 of the features enlisted.

Table 2.4 – Baseline tumour, patient and treatment characteristics by age.

Variables	Categories	Age group (years)				
		70-74	75-79	80-84	>=85	All
		N = 1,173	N = 899	N = 506	N = 233	N = 2,811
Tumour size (mm)	≤ 20	649 (55.3%)	371 (41.3%)	184 (36.4%)	75 (32.2%)	1,279 (45.5%)
	21-50	439 (37.4%)	439 (48.8%)	271 (53.6%)	136 (58.4%)	1,285 (45.7%)
	> 50	66 (5.6%)	66 (7.3%)	40 (7.9%)	16 (6.9%)	188 (6.7%)
	Unknown	19 (1.6%)	23 (2.6%)	11 (2.2%)	6 (2.6%)	59 (2.1%)
Nodal status	pN0-1mi	867 (73.9%)	573 (63.7%)	326 (64.4%)	147 (63.1%)	1,913 (68.1%)
	pN1	212 (18.1%)	223 (24.8%)	117 (23.1%)	60 (25.8%)	612 (21.8%)
	pN2	46 (3.9%)	54 (6.0%)	36 (7.1%)	11 (4.7%)	147 (5.2%)
	pN3	29 (2.5%)	25 (2.8%)	16 (3.2%)	8 (3.4%)	78 (2.8%)
	pNx	19 (1.6%)	24 (2.7%)	11 (2.2%)	7 (3.0%)	61 (2.2%)
Grade	Grade 1	199 (17.0%)	110 (12.2%)	47 (9.3%)	25 (10.7%)	381 (13.6%)
	Grade 2	635 (54.1%)	482 (53.6%)	255 (50.4%)	113 (48.5%)	1,485 (52.8%)
	Grade 3	311 (26.5%)	278 (30.9%)	190 (37.5%)	86 (36.9%)	865 (30.8%)
	Unknown	28 (2.4%)	29 (3.2%)	14 (2.8%)	9 (3.9%)	80 (2.8%)
ER status	Negative	141 (12.0%)	117 (13.0%)	74 (14.6%)	40 (17.2%)	372 (13.2%)
	Positive	1,002 (85.4%)	753 (83.8%)	414 (81.8%)	185 (79.4%)	2,354 (83.7%)
	Unknown	30 (2.6%)	29 (3.2%)	18 (3.6%)	8 (3.4%)	85 (3.0%)
HER2 status	Negative	981 (83.6%)	724 (80.5%)	375 (74.1%)	192 (82.4%)	2,272 (80.8%)
	Inconclusive	9 (0.8%)	7 (0.8%)	4 (0.8%)	2 (0.9%)	22 (0.8%)
	Positive	136 (11.6%)	115 (12.8%)	63 (12.5%)	18 (7.7%)	332 (11.8%)
	Unknown	47 (4.0%)	53 (5.9%)	64 (12.6%)	21 (9.0%)	185 (6.6%)
Oncotype DX test performed	No	212 (18.1%)	138 (15.4%)	76 (15.0%)	38 (16.3%)	464 (16.5%)
	Yes	26 (2.2%)	13 (1.4%)	2 (0.4%)	0 (0.0%)	41 (1.5%)
	Not applicable	306 (26.1%)	265 (29.5%)	186 (36.8%)	75 (32.2%)	832 (29.6%)

Variables	Categories	Age group (years)				
		70-74	75-79	80-84	>=85	All
		N = 1,173	N = 899	N = 506	N = 233	N = 2,811
	Unknown	629 (53.6%)	483 (53.7%)	242 (47.8%)	120 (51.5%)	1,474 (52.4%)
Charlson comorbidity index (no age)	n	1,133	869	481	224	2,707
	Mean (SD)	0.90 (1.21)	1.10 (1.36)	1.19 (1.37)	1.09 (1.30)	1.03 (1.30)
	Median (IQR)	0.00 (0.00, 2.00)	1.00 (0.00, 2.00)	1.00 (0.00, 2.00)	1.00 (0.00, 2.00)	1.00 (0.00, 2.00)
	Min, Max	0, 6	0, 9	0, 9	0, 6	0, 9
Number of concurrent medications	n	973	801	462	210	2,446
	Mean (SD)	3.85 (2.66)	4.16 (2.63)	4.26 (2.63)	4.21 (2.53)	4.06 (2.64)
	Median (IQR)	3.00 (2.00, 5.00)	4.00 (2.00, 6.00)	4.00 (2.00, 6.00)	4.00 (2.00, 6.00)	4.00 (2.00, 5.75)
	Min, Max	0, 14	0, 18	0, 14	0, 14	0, 18
ADL category	No dependency	924 (78.8%)	623 (69.3%)	331 (65.4%)	126 (54.1%)	2,004 (71.3%)
	Mild dependency	89 (7.6%)	109 (12.1%)	67 (13.2%)	43 (18.5%)	308 (11.0%)
	Moderate/severe dependency	70 (6.0%)	101 (11.2%)	60 (11.9%)	47 (20.2%)	278 (9.9%)
	Unknown	90 (7.7%)	66 (7.3%)	48 (9.5%)	17 (7.3%)	221 (7.9%)
IADL category	No dependency	955 (81.4%)	679 (75.5%)	332 (65.6%)	103 (44.2%)	2,069 (73.6%)
	Mild dependency	54 (4.6%)	78 (8.7%)	70 (13.8%)	47 (20.2%)	249 (8.9%)
	Moderate/severe dependency	67 (5.7%)	70 (7.8%)	55 (10.9%)	66 (28.3%)	258 (9.2%)
	Unknown	97 (8.3%)	72 (8.0%)	49 (9.7%)	17 (7.3%)	235 (8.4%)
MMSE category	Normal function	1,059 (90.3%)	805 (89.5%)	444 (87.7%)	186 (79.8%)	2,494 (88.7%)
	Mild impairment	91 (7.8%)	74 (8.2%)	50 (9.9%)	33 (14.2%)	248 (8.8%)
	Moderate impairment	11 (0.9%)	12 (1.3%)	5 (1.0%)	8 (3.4%)	36 (1.3%)
	Severe	12 (1.0%)	8 (0.9%)	7 (1.4%)	6 (2.6%)	33 (1.2%)
aPG-SGA category	Low	929 (79.2%)	709 (78.9%)	370 (73.1%)	172 (73.8%)	2,180 (77.6%)
	Moderate	111 (9.5%)	88 (9.8%)	62 (12.3%)	27 (11.6%)	288 (10.2%)

Variables	Categories	Age group (years)				
		70-74	75-79	80-84	>=85	All
		N = 1,173	N = 899	N = 506	N = 233	N = 2,811
	High	15 (1.3%)	13 (1.4%)	10 (2.0%)	2 (0.9%)	40 (1.4%)
	Unknown	118 (10.1%)	89 (9.9%)	64 (12.6%)	32 (13.7%)	303 (10.8%)
ECOG PS	0	930 (79.3%)	619 (68.9%)	305 (60.3%)	90 (38.6%)	1,944 (69.2%)
	1	151 (12.9%)	205 (22.8%)	142 (28.1%)	109 (46.8%)	607 (21.6%)
	2	21 (1.8%)	24 (2.7%)	23 (4.5%)	12 (5.2%)	80 (2.8%)
	3	10 (0.9%)	9 (1.0%)	8 (1.6%)	9 (3.9%)	36 (1.3%)
	4	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
	Unknown	60 (5.1%)	42 (4.7%)	28 (5.5%)	13 (5.6%)	143 (5.1%)
Breast surgery	Wide local excision	769 (65.5%)	504 (56.1%)	236 (46.7%)	89 (38.2%)	1,598 (56.8%)
	Therapeutic mammoplasty / breast reshaping after wide local excision	35 (3.0%)	12 (1.3%)	2 (0.4%)	2 (0.9%)	51 (1.8%)
	Mastectomy	316 (26.9%)	346 (38.5%)	251 (49.6%)	136 (58.4%)	1,049 (37.3%)
	Mastectomy and reconstruction	25 (2.1%)	10 (1.1%)	2 (0.4%)	0 (0.0%)	37 (1.3%)
	Other	10 (0.9%)	5 (0.6%)	5 (1.0%)	0 (0.0%)	20 (0.7%)
	Unknown	18 (1.5%)	22 (2.4%)	10 (2.0%)	6 (2.6%)	56 (2.0%)
Axillary surgery	Axillary sample	38 (3.2%)	30 (3.3%)	11 (2.2%)	9 (3.9%)	88 (3.1%)
	Axillary clearance	134 (11.4%)	134 (14.9%)	99 (19.6%)	47 (20.2%)	414 (14.7%)
	Sentinel lymph node biopsy	881 (75.1%)	633 (70.4%)	336 (66.4%)	130 (55.8%)	1,980 (70.4%)
	Internal mammary node biopsy	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
	No axillary surgery	23 (2.0%)	16 (1.8%)	22 (4.3%)	19 (8.2%)	80 (2.8%)
	Unknown	97 (8.3%)	85 (9.5%)	38 (7.5%)	28 (12.0%)	248 (8.8%)

Abbreviations: ER: oestrogen receptor; HER2: human epidermal growth factor receptor; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ADL: activities of daily living; IADL: instrumental activities of daily living; aPG-SGA: abridged patient-generated subjective global assessment; MMSE: Mini Mental State Examination.

Table 2.5 – Baseline patient characteristics by receipt of chemotherapy.

Variables	Categories	No chemotherapy	Chemotherapy
		N = 2,414	N = 397
Age	n	2414	397
	Mean (SD)	76.98 (5.25)	73.62 (3.30)
	Median (IQR)	76.00 (73.00, 80.00)	73.00 (71.00, 76.00)
	Min, Max	69, 95	69, 87
Charlson comorbidity index (no age)	n	2,322	385
	Mean (SD)	1.07 (1.33)	0.81 (1.10)
	Median (IQR)	1.00 (0.00, 2.00)	0.00 (0.00, 2.00)
	Min, Max	0, 9	0, 6
Number of concurrent medications	n	2,116	330
	Mean (SD)	4.13 (2.66)	3.63 (2.49)
	Median (IQR)	4.00 (2.00, 6.00)	3.00 (2.00, 5.00)
	Min, Max	0, 18	0, 14
ADL category	No dependency	1,683 (69.7%)	321 (80.9%)
	Mild dependency	274 (11.4%)	34 (8.6%)
	Moderate/severe dependency	262 (10.9%)	16 (4.0%)
	Unknown	195 (8.1%)	26 (6.5%)
IADL category	No dependency	1737 (72.0%)	332 (83.6%)
	Mild dependency	221 (9.2%)	28 (7.1%)
	Moderate/severe dependency	248 (10.3%)	10 (2.5%)
	Unknown	208 (8.6%)	27 (6.8%)
MMSE category	Normal function	2,133 (88.4%)	361 (90.9%)
	Mild impairment	220 (9.1%)	28 (7.1%)
	Moderate impairment	30 (1.2%)	6 (1.5%)
	Severe	31 (1.3%)	2 (0.5%)

Variables	Categories	No chemotherapy	Chemotherapy
		N = 2,414	N = 397
aPG-SGA category	Low	1,864 (77.2%)	316 (79.6%)
	Moderate	249 (10.3%)	39 (9.8%)
	High	36 (1.5%)	4 (1.0%)
	Unknown	265 (11.0%)	38 (9.6%)
ECOG PS	0	1,632 (67.6%)	312 (78.6%)
	1	544 (22.5%)	63 (15.9%)
	2	77 (3.2%)	3 (0.8%)
	3	34 (1.4%)	2 (0.5%)
	4	1 (0.0%)	0 (0.0%)
	Unknown	126 (5.2%)	17 (4.3%)

Abbreviations: ECOG PS: Eastern Cooperative Oncology Group Performance Status; ADL: activities of daily living; IADL: instrumental activities of daily living; aPG-SGA: abridged patient-generated subjective global assessment; MMSE: Mini Mental State Examination.

Table 2.6 – Postoperative tumour characteristics by receipt of chemotherapy.

Variables	Categories	No chemotherapy	Chemotherapy
		N = 2,414	N = 397
Tumour size (mm)	≤ 20	1,183 (49.0%)	96 (24.2%)
	21-50	1,043 (43.2%)	242 (61.0%)
	> 50	139 (5.8%)	49 (12.3%)
	Unknown	49 (2.0%)	10 (2.5%)
Nodal status	pN0-1mi	1,726 (71.5%)	187 (47.1%)
	pN1	495 (20.5%)	117 (29.5%)
	pN2	95 (3.9%)	52 (13.1%)
	pN3	46 (1.9%)	32 (8.1%)
	pNx	52 (2.2%)	9 (2.3%)
Grade	Grade 1	377 (15.6%)	4 (1.0%)
	Grade 2	1,355 (56.1%)	130 (32.7%)
	Grade 3	618 (25.6%)	247 (62.2%)
	Unknown	64 (2.7%)	16 (4.0%)
ER positive	Negative	240 (9.9%)	132 (33.2%)
	Positive	2,101 (87.0%)	253 (63.7%)
	Unknown	73 (3.0%)	12 (3.0%)
HER2 status	Negative	2,050 (84.9%)	222 (55.9%)
	Inconclusive	19 (0.8%)	3 (0.8%)
	Positive	173 (7.2%)	159 (40.1%)
	Unknown	172 (7.1%)	13 (3.3%)
Oncotype DX test performed	No	428 (17.7%)	36 (9.1%)
	Yes	35 (1.4%)	6 (1.5%)
	Not Applicable	571 (23.7%)	261 (65.7%)
	Unknown	1,380 (57.2%)	94 (23.7%)
Breast surgery	Wide local excision	1,433 (59.4%)	165 (41.5%)

Variables	Categories	No chemotherapy	Chemotherapy
		N = 2,414	N = 397
	Therapeutic mammoplasty / breast reshaping after WLE	33 (1.4%)	18 (4.5%)
	Mastectomy	860 (35.6%)	189 (47.6%)
	Mastectomy and reconstruction	25 (1.0%)	12 (3.0%)
	Other	16 (0.7%)	4 (1.0%)
	Unknown	47 (1.9%)	9 (2.3%)
Axillary surgery	Axillary sample	76 (3.1%)	12 (3.0%)
	Axillary clearance	274 (11.4%)	140 (35.3%)
	Sentinel lymph node biopsy	1,770 (73.3%)	210 (52.9%)
	Internal mammary node biopsy	1 (0.0%)	0 (0.0%)
	No axillary surgery	73 (3.0%)	7 (1.8%)
	Unknown	220 (9.1%)	28 (7.1%)

Abbreviations: ER: oestrogen receptor; HER2: human epidermal growth factor receptor.

Table 2.7 – Relationship between chemotherapy use and patient characteristics: univariate analysis.

Variable	Level	Odds ratio (95% confidence interval)	P-value
Age		0.84 (0.82, 0.87)	<0.001
ADL score		1.07 (1.04, 1.11)	<0.001
IADL score		1.77 (1.43, 2.25)	<0.001
Charlson comorbidity index (no age)		0.84 (0.77, 0.93)	<0.001
aPG-SGA score		0.95 (0.89, 1.01)	0.127
Allred ER score		0.80 (0.78, 0.83)	<0.001
Tumour grade	Grade 1	-	-
	Grade 2	9.04 (3.78, 29.58)	<0.001
	Grade 3	37.67 (15.87, 122.76)	<0.001
ER-positive status		0.22 (0.17, 0.28)	<0.001
HER2 status‡	Negative	-	-
	Positive	8.49 (6.57, 10.97)	<0.001
MMSE category	Normal function	-	-
	Mild impairment	0.75 (0.49, 1.11)	0.172
	Moderate impairment	1.18 (0.44, 2.67)	0.711
	Severe	0.38 (0.06, 1.27)	0.188
Nodal status§	pN0-1mi	-	-
	pN1	2.18 (1.69, 2.80)	<0.001
	pN2	5.05 (3.47, 7.29)	<0.001
	pN3	6.42 (3.96, 10.30)	<0.001

Abbreviations: ER: oestrogen receptor; HER2: human epidermal growth factor receptor; ADL: activities of daily living; IADL: instrumental activities of daily living; aPG-SGA: abridged patient-generated subjective global assessment; MMSE: Mini Mental State Examination.

‡ Tests marked as “Inconclusive” were removed from this analysis.

§ Patients with nodal status pNx were removed from this analysis.

Table 2.8 - Relationship between chemotherapy use and patient characteristics: multivariate analysis.

Variable	Level	Odds ratio (95% confidence interval)	P-value
Age		0.74 (0.71, 0.78)	<0.001
IADL score		1.97 (1.53, 2.63)	<0.001
Charlson comorbidity index (no age)		0.83 (0.73, 0.95)	0.007
Tumour grade	Grade 1	-	-
	Grade 2	8.42 (3.05, 34.90)	<0.001
	Grade 3	29.50 (10.59, 123.00)	<0.001
ER-positive status		0.19 (0.13, 0.28)	<0.001
HER2 status*	Negative	-	-
	Positive	8.94 (6.19, 13.01)	<0.001
Nodal status†	pN0-1mi		
	pN1	4.01 (2.81, 5.75)	<0.001
	pN2	11.24 (6.43, 19.74)	<0.001
	pN3	8.84 (4.31, 18.05)	<0.001

Abbreviations: ER: oestrogen receptor; HER2: human epidermal growth factor receptor; IADL: instrumental activities of daily living.

* Tests marked as “Inconclusive” were removed from this analysis.

† Patients with nodal status pNx were removed from this analysis.

Table 2.9 – Chemotherapy use by risk of breast cancer risk of recurrence.

Risk	Chemotherapy	No chemotherapy	Total
High risk	376 (24.7%)	1,144 (75.3%)	1,520 (100.0%)
Non-high risk	21 (1.6%)	1,270 (98.4%)	1,291 (100.0%)
Total	397 (14.1%)	2,414 (85.9%)	2,811 (100.0%)

Table 2.10 – Chemotherapy use by fitness.

Fitness	Chemotherapy	No chemotherapy	Total
Fit	322 (15.6%)	1,737 (84.4%)	2,059 (100.0%)
Vulnerable	75 (10.0%)	675 (90.0%)	750 (100.0%)
Frail	0 (0.0%)	2 (100.0%)	2 (100.0%)
Total	397 (14.1%)	2,414 (85.9%)	2,811 (100.0%)

Table 2.11 – Chemotherapy use by breast cancer risk of recurrence and fitness.

Fitness	High risk		Non-high risk		Total
	Chemotherapy	No chemotherapy	Chemotherapy	No chemotherapy	
Fit	306 (14.9%)	794 (38.6%)	16 (0.8%)	943 (45.8%)	2,059 (100.0%)
Vulnerable	70 (9.3%)	349 (46.5%)	5 (0.7%)	326 (43.5%)	750 (100.0%)
Frail	0 (0.0%)	1 (50%)	0 (0.0%)	1 (50%)	2 (100.0%)
Total	376 (13.4%)	1,144 (40.7%)	21 (0.7%)	1,270 (45.2%)	2,811 (100.0%)

Table 2.12 – Mortality status for patients with HER2-positive disease and for those with ER-negative disease by chemotherapy use.

		No chemotherapy	Chemotherapy	Total
HER2-positive	n	170	156	326
	Died	45 (26.5%)	19 (12.2%)	64 (19.6%)
	n	169	156	325
	Died of breast cancer	24 (14.2%)	12 (7.7%)	36 (11.1%)
ER-negative	n	237	132	369
	Died	92 (38.8%)	20 (15.2%)	112 (30.4%)
	n	234	131	365
	Died of breast cancer	56 (23.9%)	13 (9.9%)	69 (18.9%)

Abbreviations: ER: oestrogen receptor; HER2: human epidermal growth factor receptor.

Table 2.13 – Adverse event rates according in the overall chemotherapy population and according to level of participation (n = 397).

Adverse event	Participation level			Total
	Consultee	Full	Partial	
	N = 4	N = 322	N = 71	N = 397
Allergic reaction to chemotherapy agents	0 (0%)	21 (7%)	5 (7%)	26 (7%)
Anaemia	2 (50%)	69 (21%)	14 (20%)	85 (21%)
Fatigue	3 (75%)	231 (72%)	49 (69%)	283 (71%)
Hair thinning	2 (50%)	205 (64%)	42 (59%)	249 (63%)
Infection	1 (25%)	103 (32%)	28 (39%)	132 (33%)
Low white cell count	2 (50%)	76 (24%)	19 (27%)	97 (24%)
Nausea	3 (75%)	134 (42%)	30 (42%)	167 (42%)
Thrombocytopenia	3 (75%)	19 (6%)	7 (10%)	29 (7%)

Table 2.14 – Adverse event rates according to CTCAE grading (n = 397).

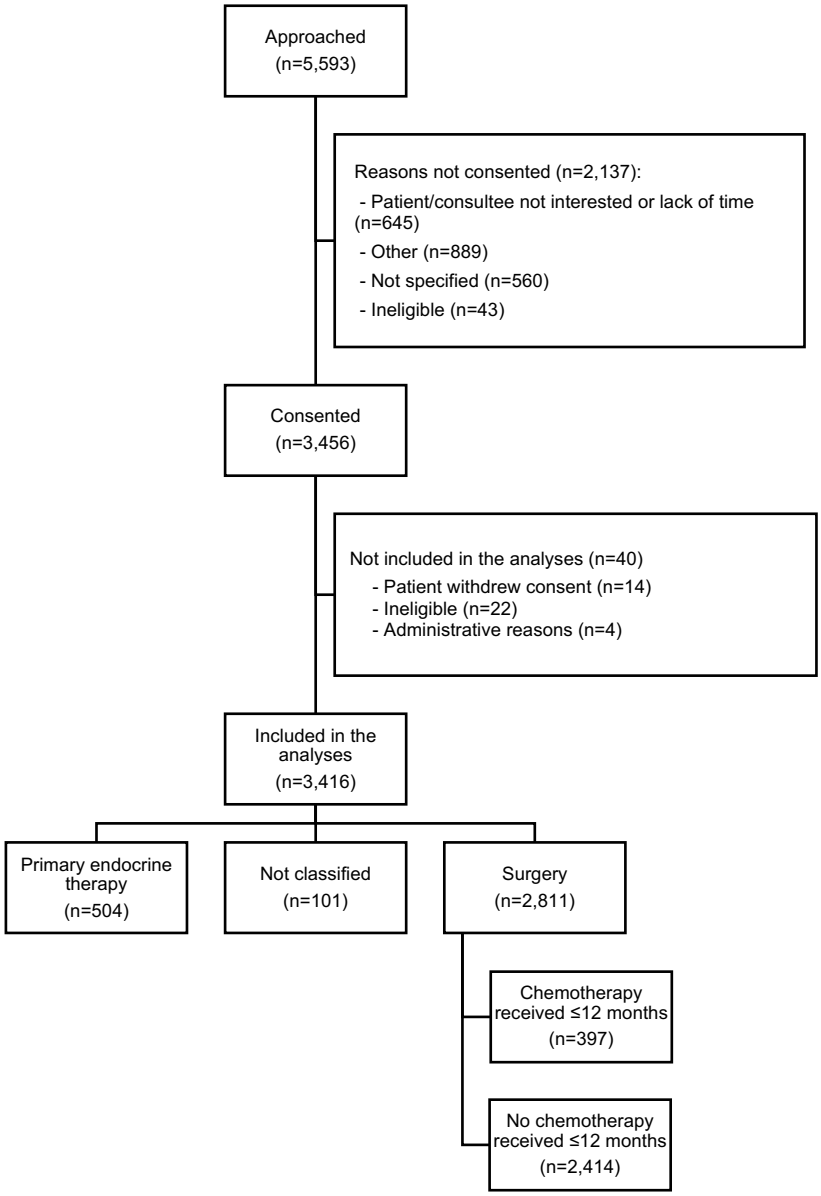
Adverse event	Worse CTCAE grading	Individuals
Allergic reactions	1	7/26 (26.9%)
	2	9/26 (34.6%)
	3	2/26 (7.7%)
	4	1/26 (3.8%)
	Missing	7/26 (26.9%)
Anaemia	1	29/85 (34.1%)
	2	25/85 (29.4%)
	3	2/85 (2.4%)
	4	1/85 (1.2%)
	Missing	28/85 (32.9%)
Fatigue	1	95/283 (33.6%)
	2	75/283 (26.5%)
	3	26/283 (9.2%)
	4	1/283 (0.4%)
	Missing	86/283 (30.4%)
Alopecia	1	60/249 (24.1%)
	2	114/249 (45.8%)
	Missing	75/249 (30.1%)
Infection	2	49/132 (37.1%)
	3	44/132 (33.3%)
	4	6/132 (4.5%)
	Missing	33/132 (25.0%)
Low white cell count	1	16/97 (16.5%)
	2	24/97 (24.7%)
	3	11/97 (11.3%)

Adverse event	Worse CTCAE grading	Individuals
	4	11/97 (11.3%)
	Missing	35/97 (36.1%)
Nausea	1	84/167 (50%)
	2	31/167 (19%)
	3	3/167 (2%)
	Missing	49/167 (29%)
Thrombocytopenia	1	17/29 (59%)
	2	4/29 (14%)
	Missing	8/29 (28%)

Abbreviations: CTCAE: Common Terminology Criteria for Adverse Events.

2.9. FIGURES

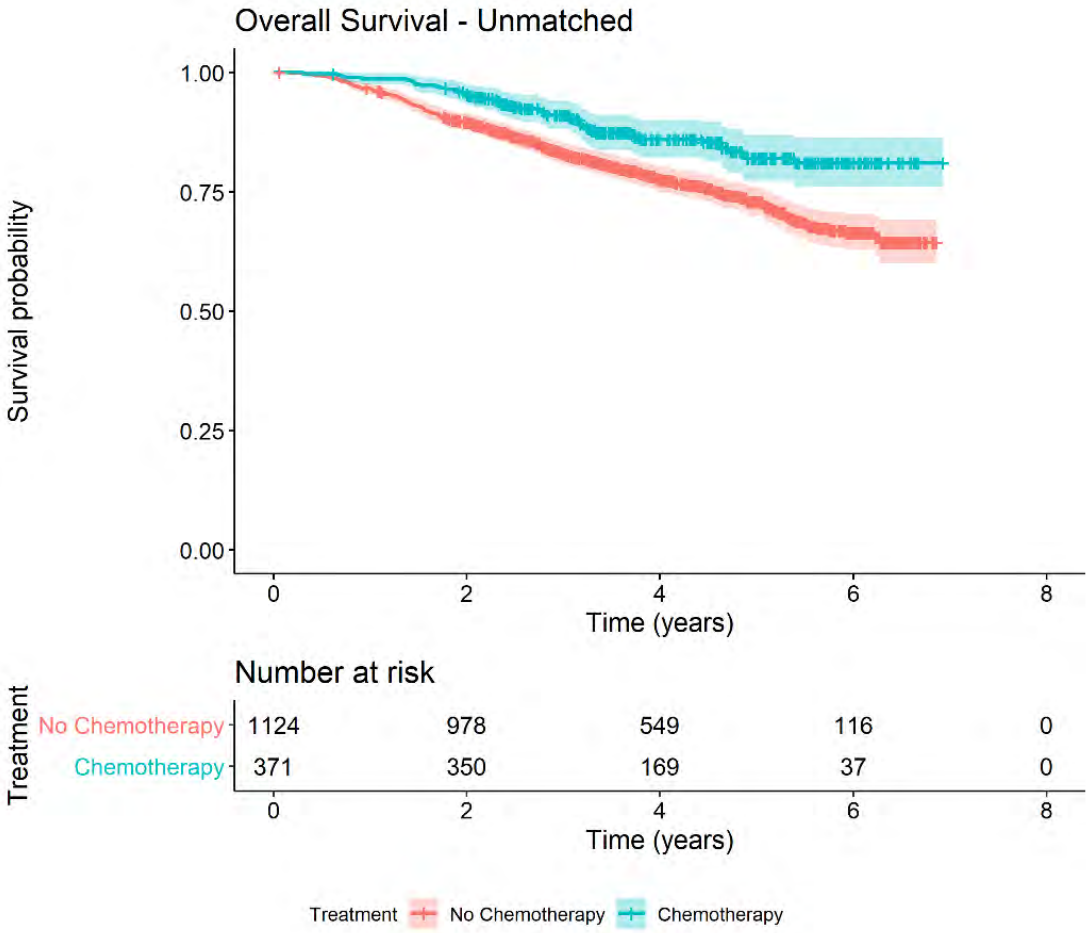
Figure 2.1 – STROBE diagram.[‡‡]



[‡‡] Patients who only received palliative chemotherapy regimens where not counted as having received chemotherapy.

Figure 2.2 – Kaplan-Meier plot of overall survival in unmatched high-risk patients (n = 1,495).

Adjusted HR 0.87 (95% CI 0.58–1.28, p = 0.47).



Abbreviations: HR: hazard ratio; CI: confidence interval.

Figure 2.3 – Propensity score overlap and number of observations for matched groups with differing ratios (y-axis) and callipers (x-axis): chemotherapy versus no chemotherapy.

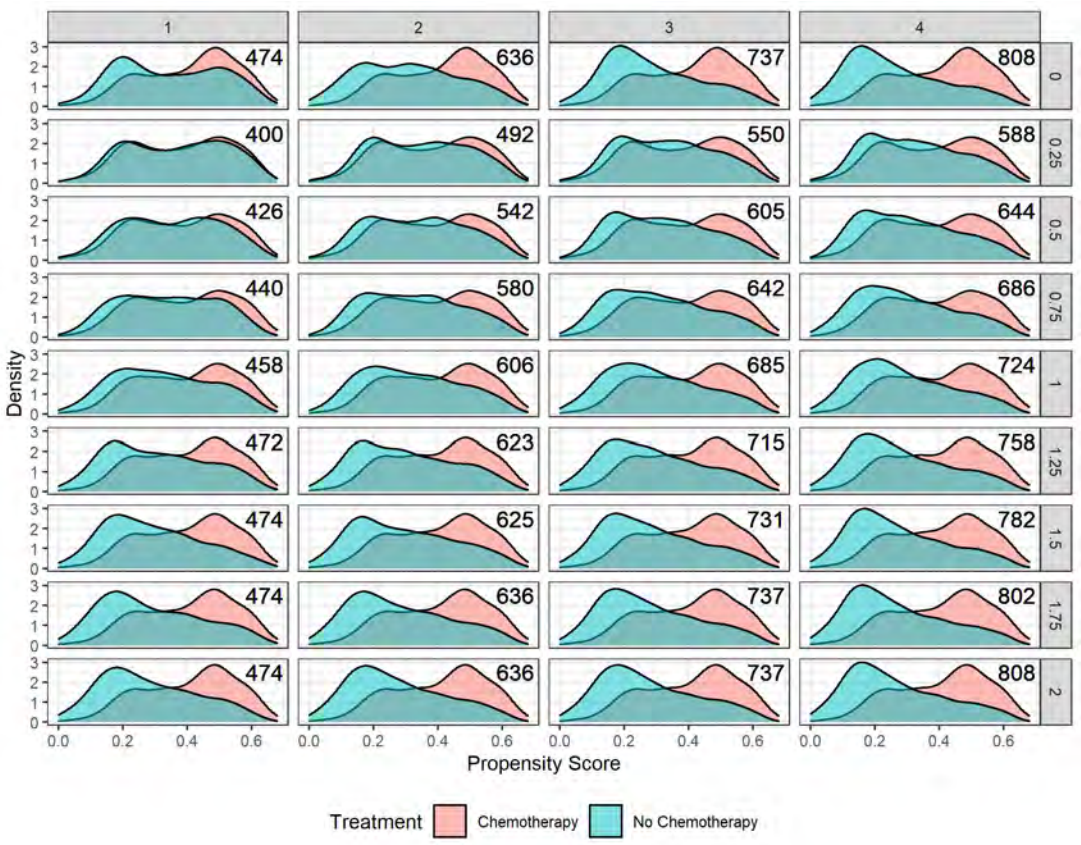
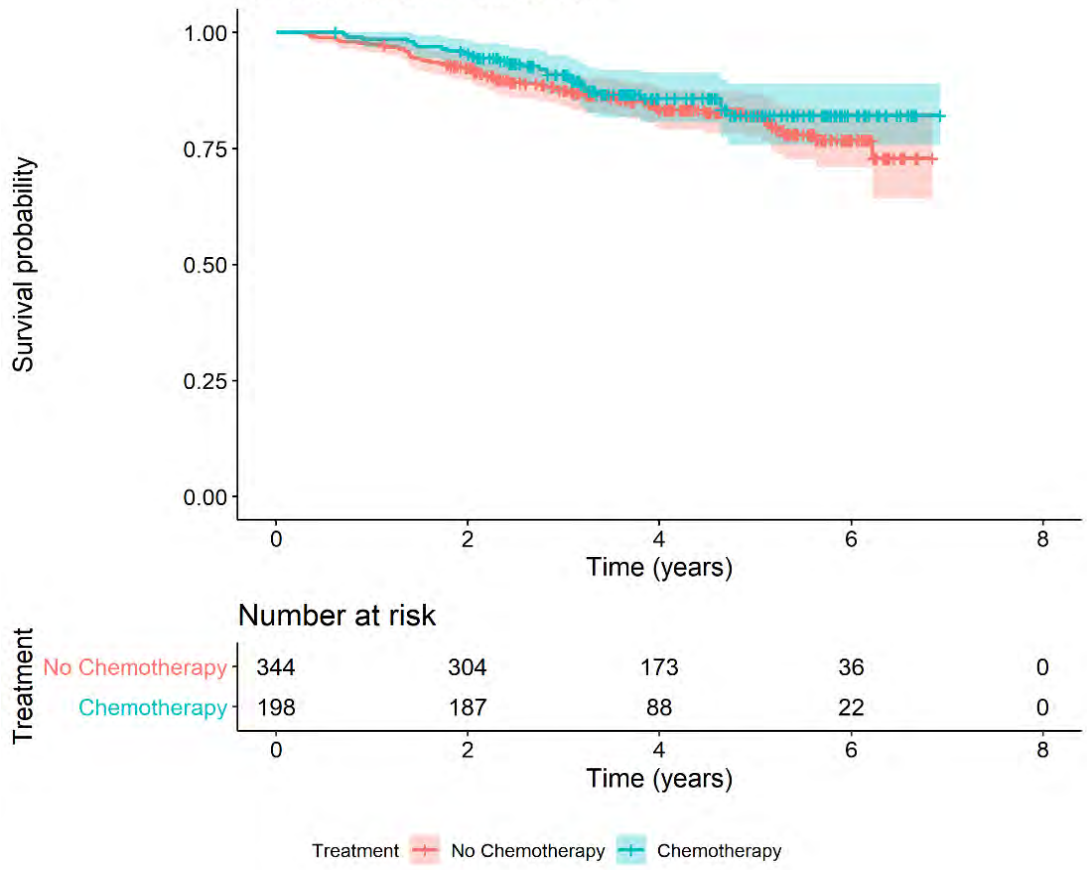


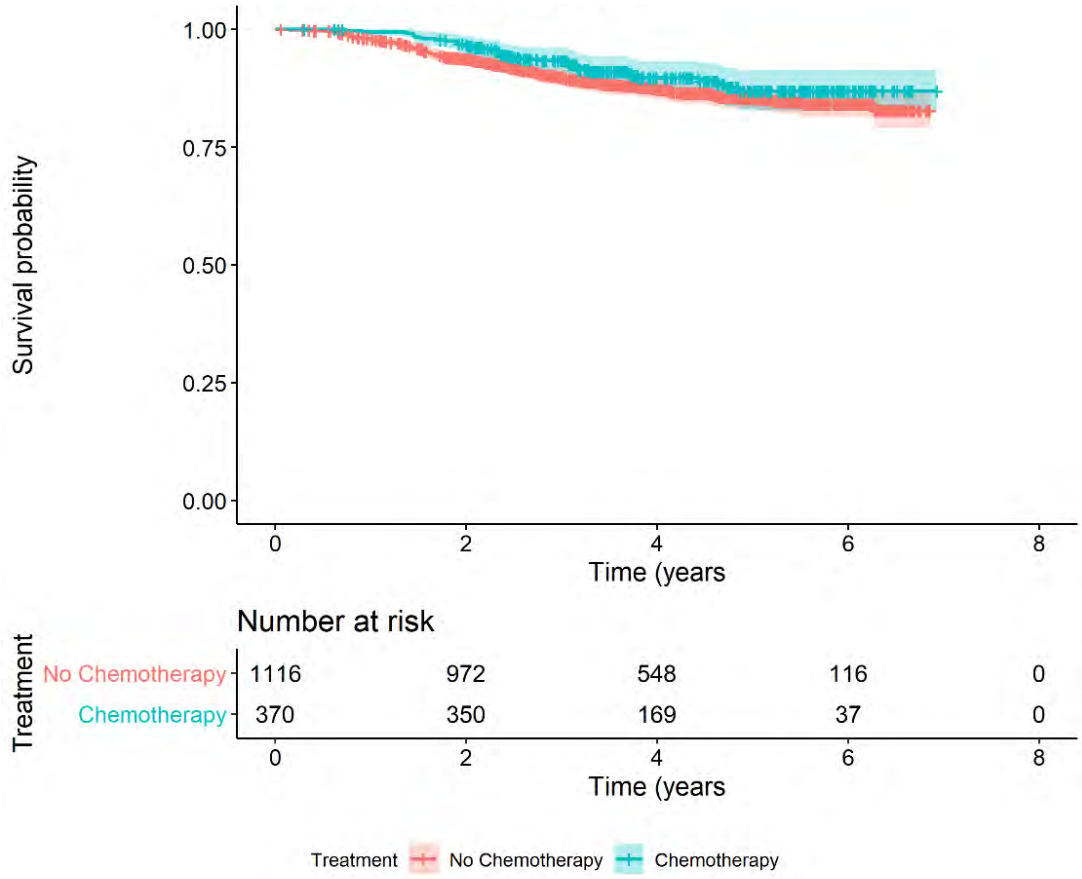
Figure 2.4 – Kaplan-Meier plot of overall survival in matched high-risk patients (n= 542). Adjusted HR 0.79 (95% CI: 0.50–1.26, p=0.32).



Abbreviations: HR: hazard ratio; CI: confidence interval.

Figure 2.5 – Kaplan-Meier plot of breast cancer-specific survival in unmatched high-risk patients (n= 1,486).

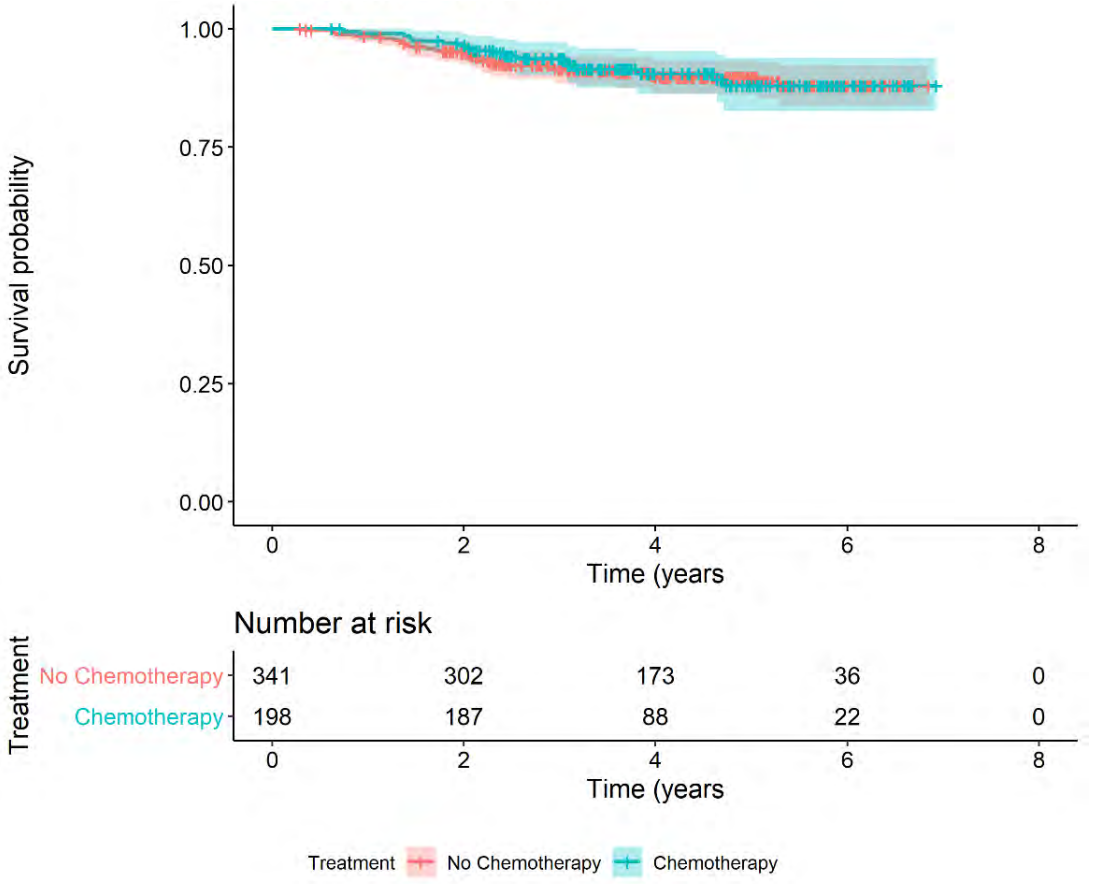
Adjusted HR 0.92 (95% CI: 0.56–1.53, p = 0.76).



Abbreviations: HR: hazard ratio; CI: confidence interval.

Figure 2.6 – Kaplan-Meier plot of breast cancer-specific survival in matched high-risk patients (n = 539).

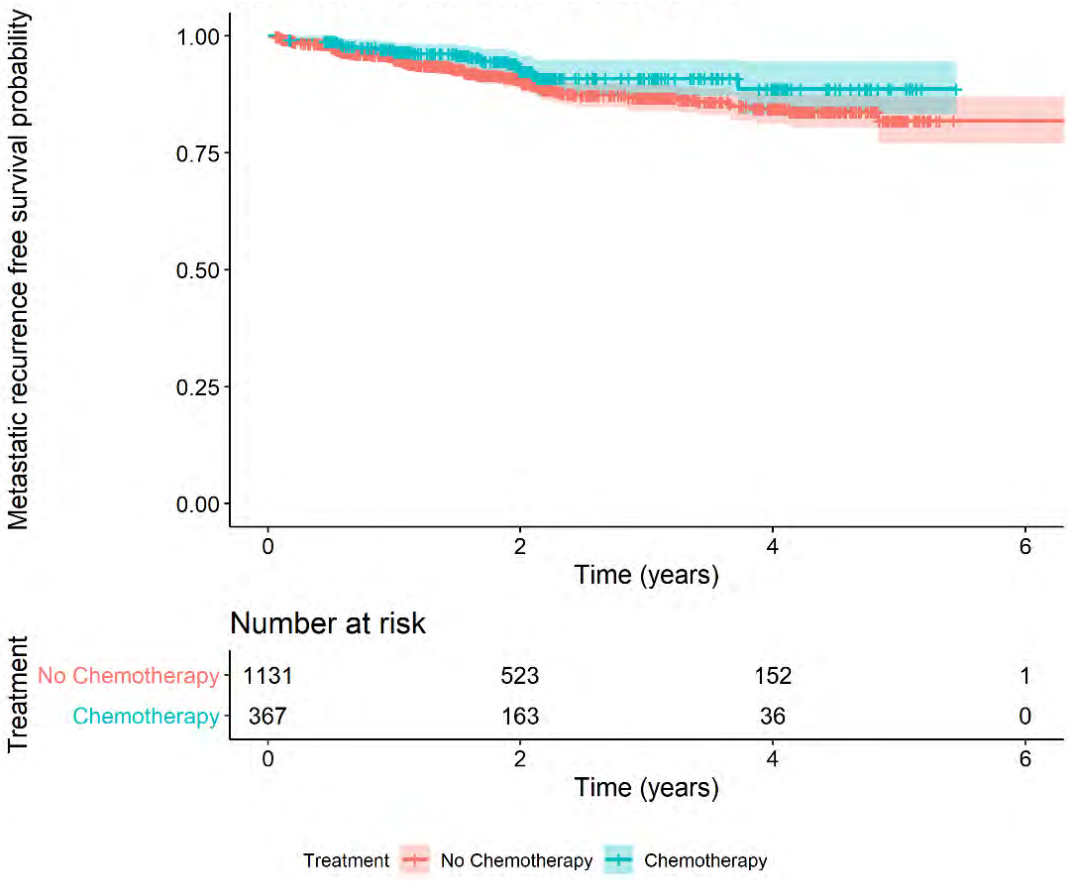
Adjusted HR 0.93 (95% CI: 0.52–1.66, p = 0.80).



Abbreviations: HR: hazard ratio; CI: confidence interval.

Figure 2.7 – Kaplan-Meier plot of metastatic recurrence in unmatched high-risk patients (n = 1,498).

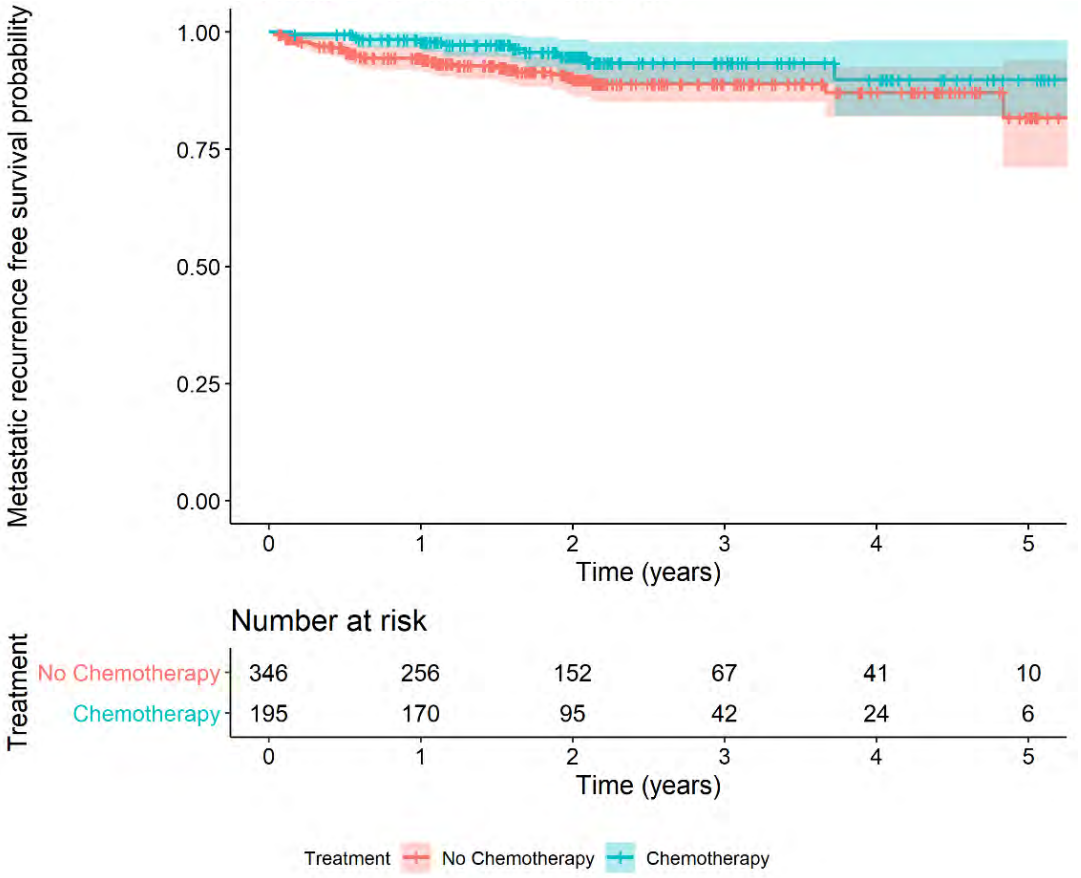
Adjusted HR 0.36 (95% CI: 0.19–0.68, p = 0.002).



Abbreviations: HR: hazard ratio; CI: confidence interval.

Figure 2.8 – Kaplan-Meier plot of metastatic recurrence in matched high-risk patients (n = 541).

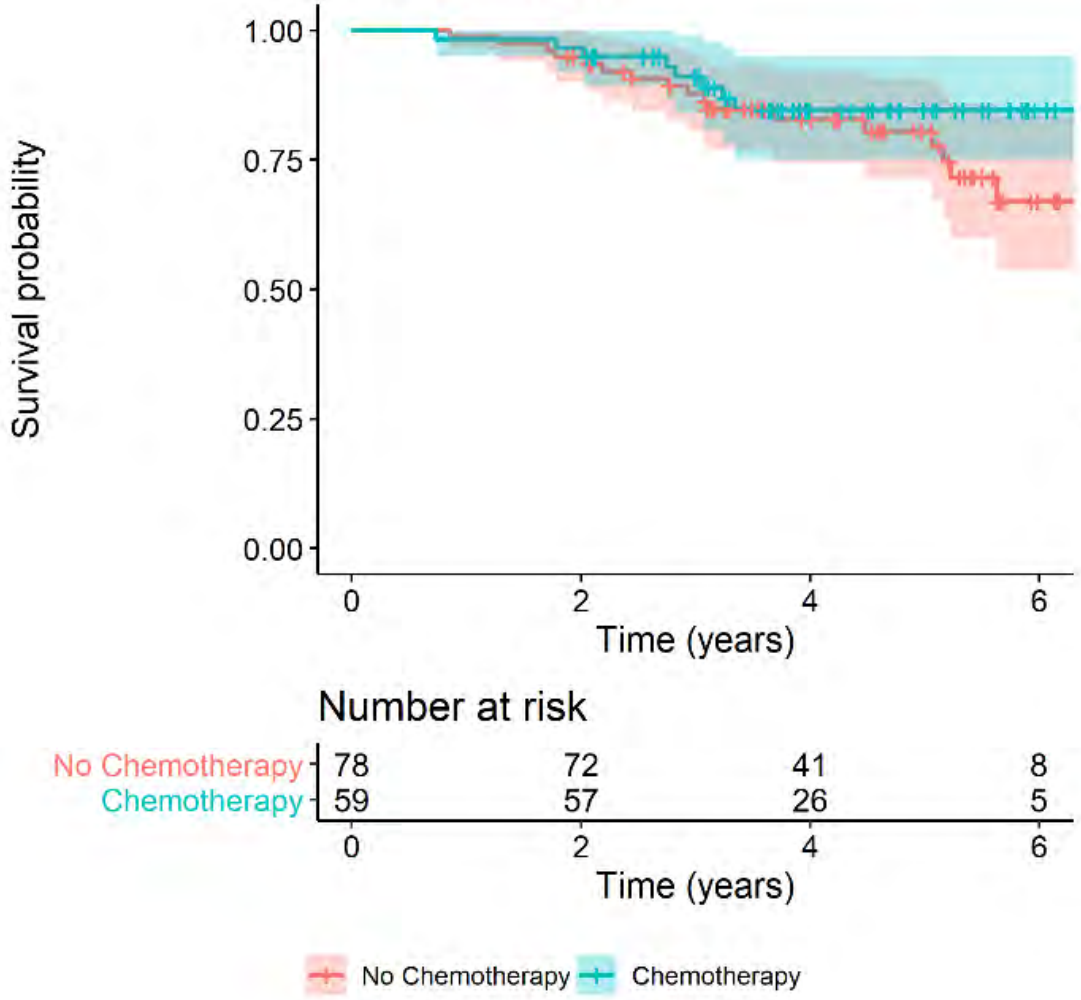
Adjusted HR 0.53 (95% CI: 0.26–1.07, p = 0.08).



Abbreviations: HR: hazard ratio; CI: confidence interval.

Figure 2.9 – Kaplan-Meier plot of overall survival in matched patients with HER2-positive breast cancer (n = 137).

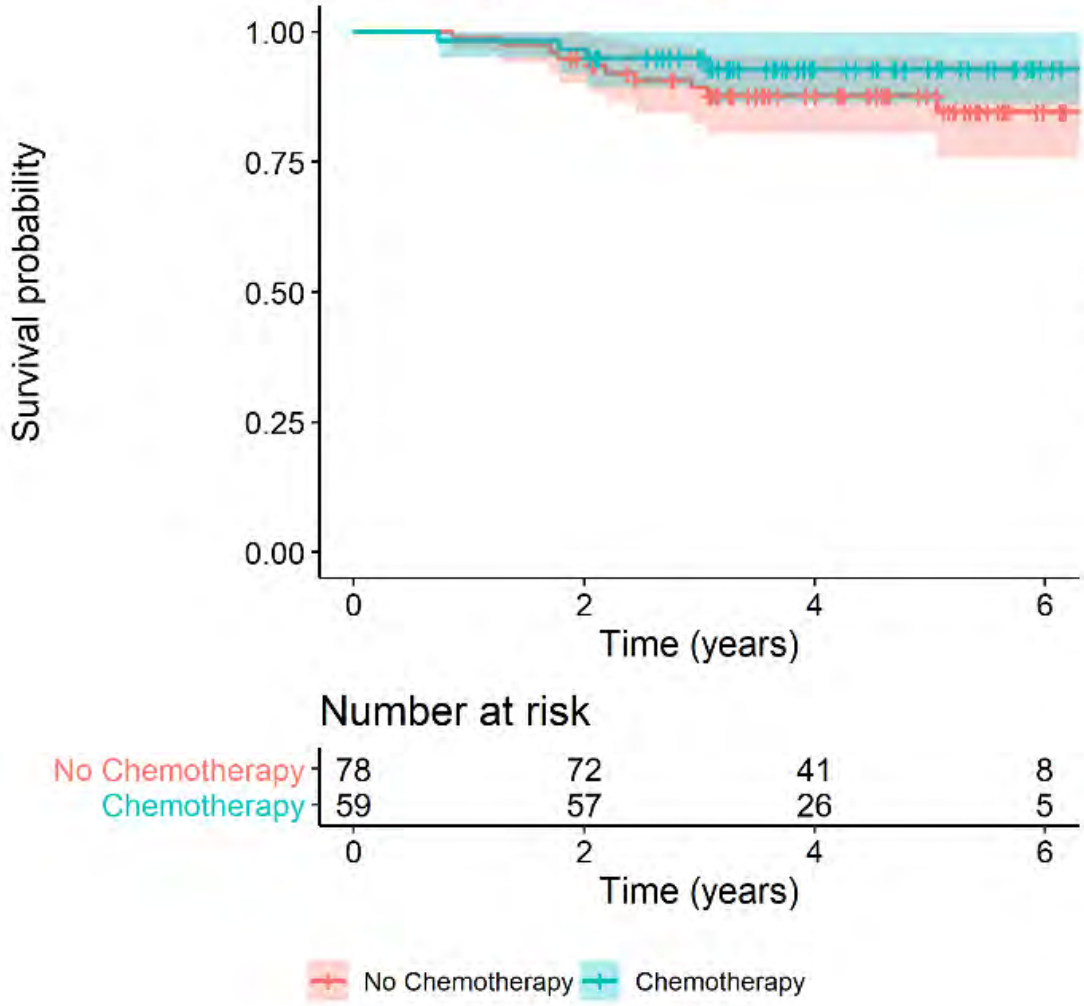
HR 0.63 (95% CI 0.27–1.48)



Abbreviations: HR: hazard ratio; CI: confidence interval.

Figure 2.10 – Kaplan-Meier plot of breast cancer-specific survival in matched patients with HER2-positive breast cancer (n = 137).

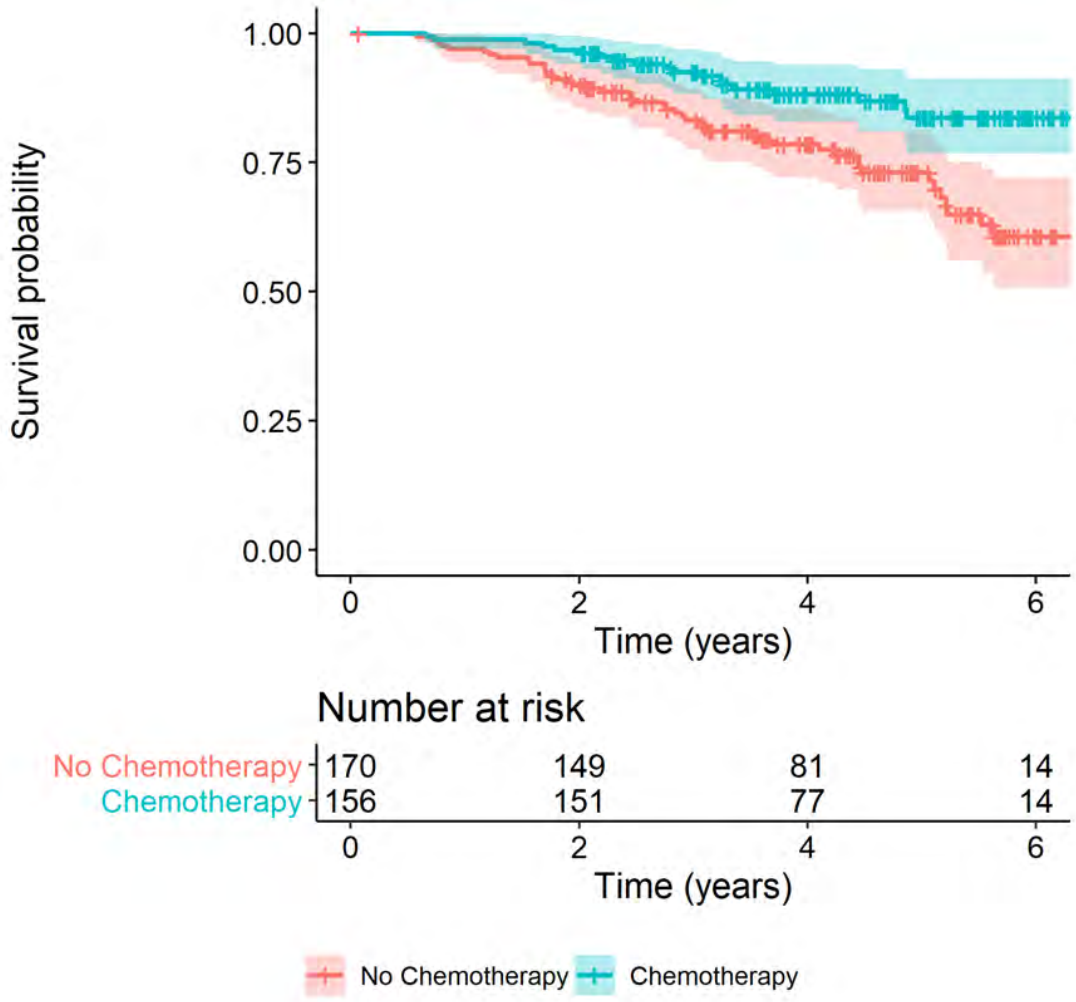
HR 0.50 (95% CI 0.16–1.63).



Abbreviations: HR: hazard ratio; CI: confidence interval.

Figure 2.11 – Kaplan-Meier plot of overall survival in unmatched patients with HER2-positive breast cancer (n = 326).

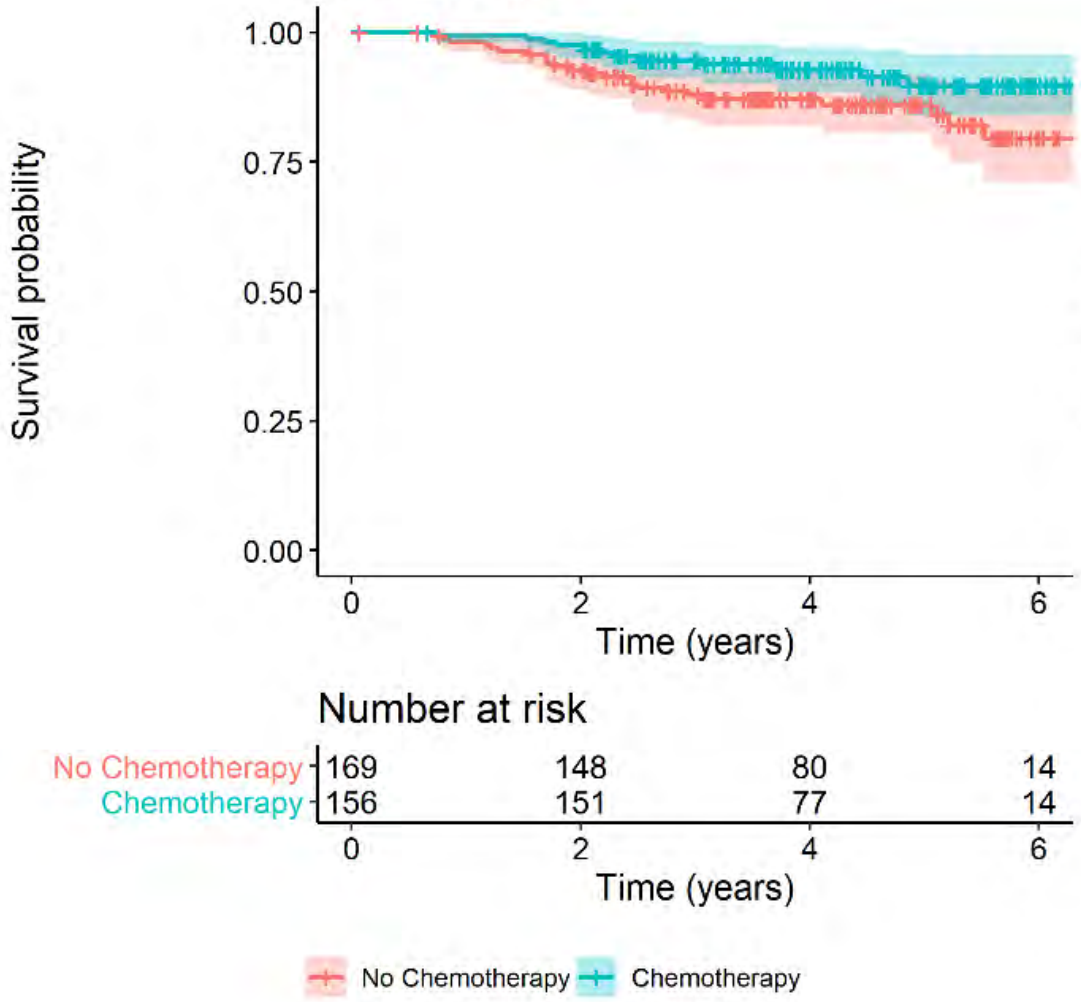
HR 0.64 (95% CI 0.23–1.51).



Abbreviations: HR: hazard ratio; CI: confidence interval.

Figure 2.12 – Kaplan-Meier plot of breast cancer-specific survival in unmatched patients with HER2-positive breast cancer (n = 325).

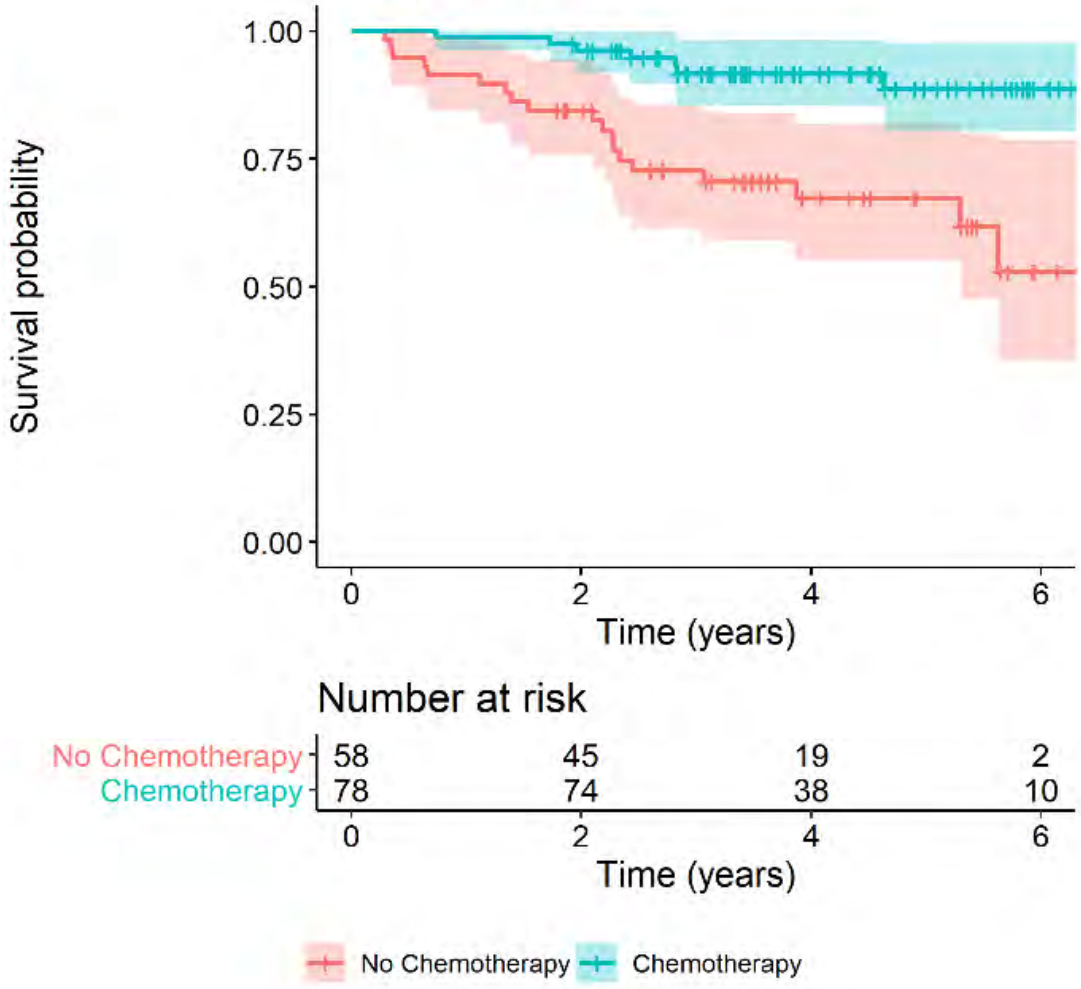
HR 0.52 (95% CI 0.18–1.62).



Abbreviations: HR: hazard ratio; CI: confidence interval.

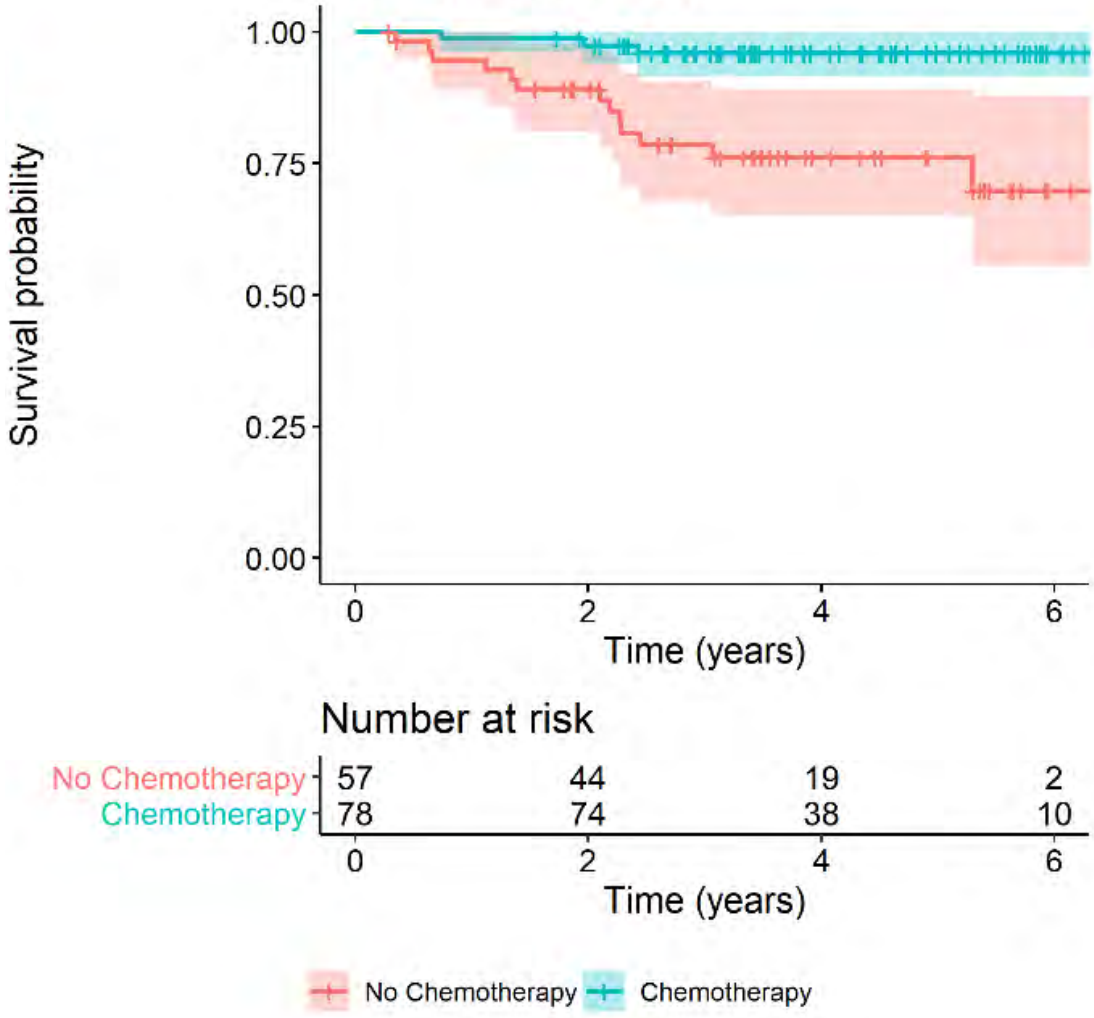
Figure 2.13 – Kaplan-Meier plot of overall survival in matched patients with ER-negative breast cancer (n = 136).

HR 0.20 (95% CI 0.08–0.49).



Abbreviations: HR: hazard ratio; CI: confidence interval.

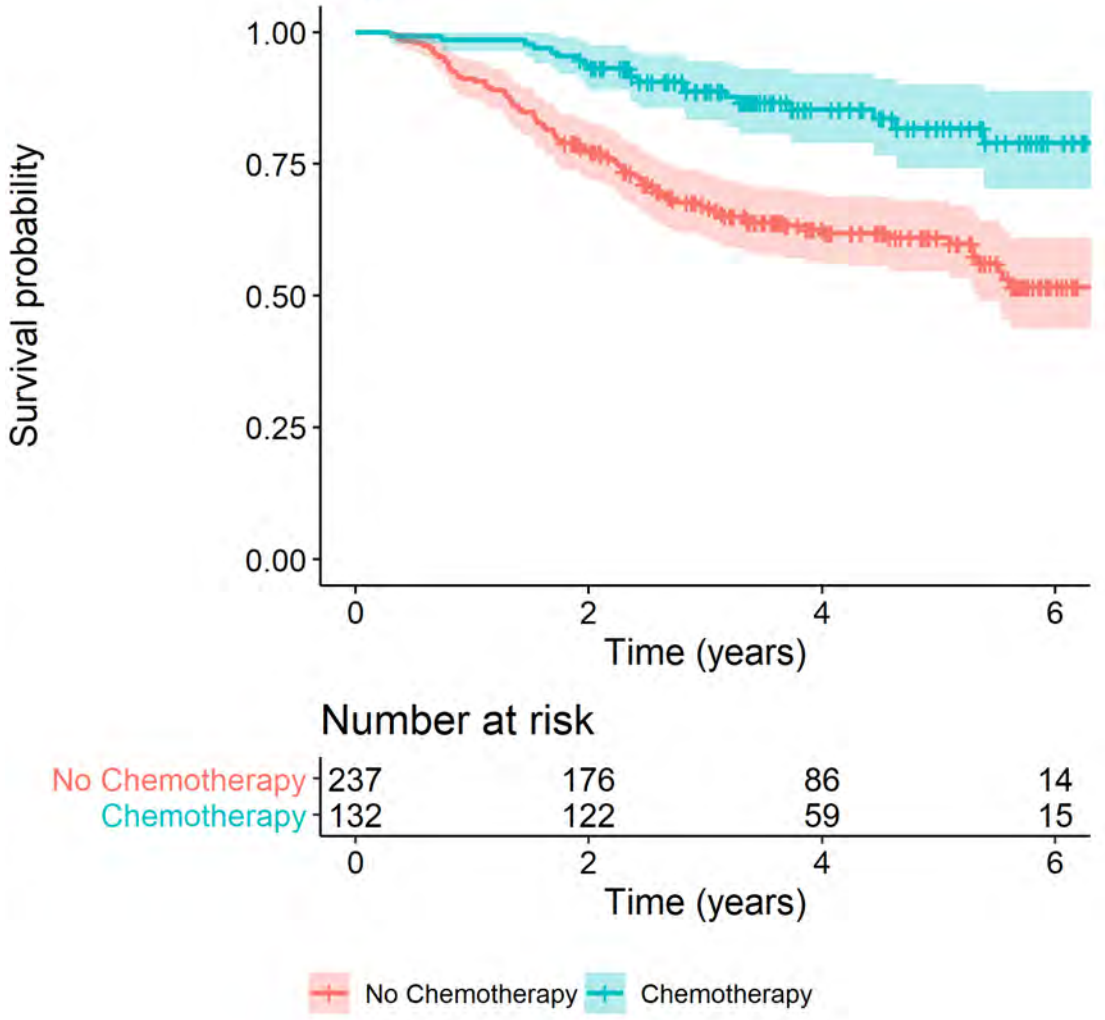
Figure 2.14 – Kaplan-Meier plot of breast cancer-specific survival in matched patients with ER-negative breast cancer (n = 135).
HR 0.12 (95% CI 0.03–0.44).



Abbreviations: HR: hazard ratio; CI: confidence interval.

Figure 2.15 – Kaplan-Meier plot of overall survival in unmatched patients with ER-negative breast cancer (n = 369).

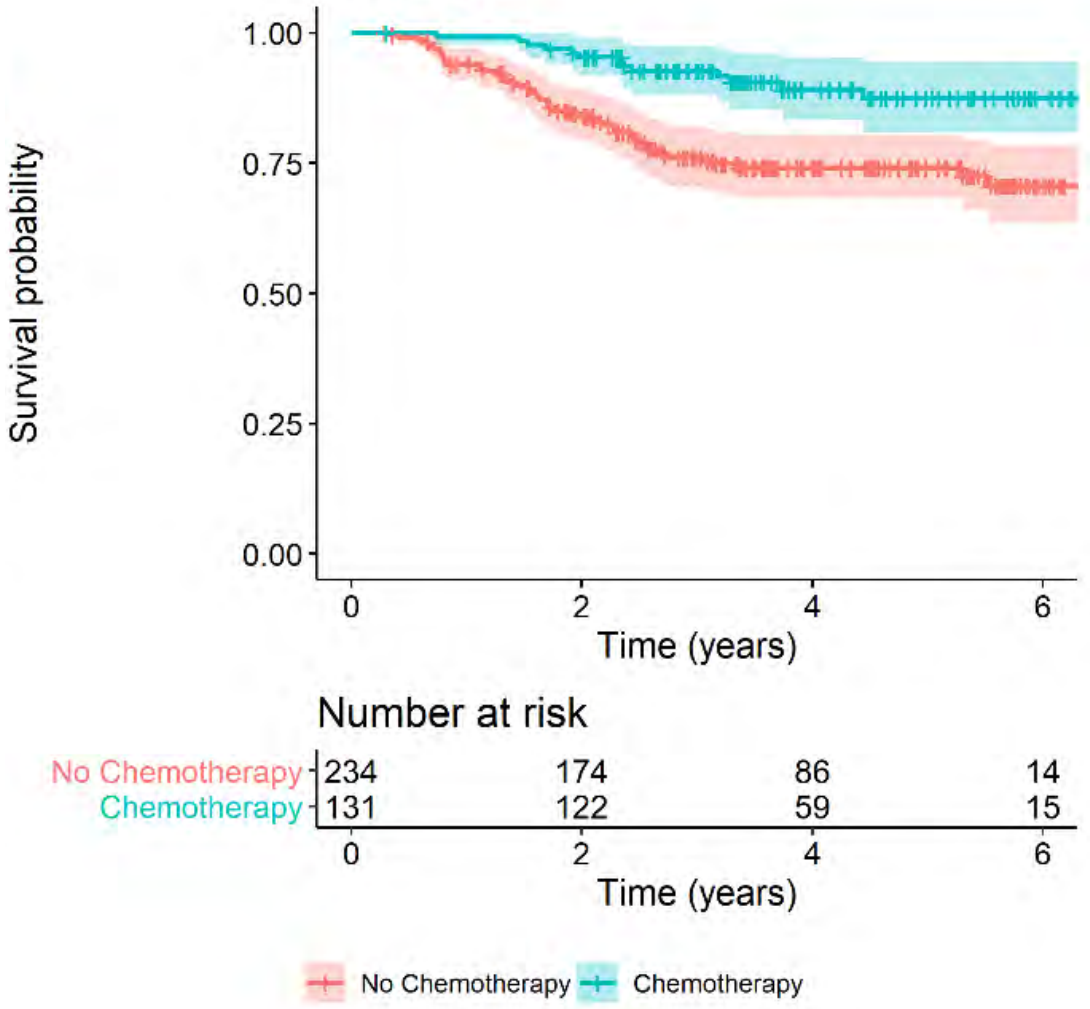
HR 0.21 (95% CI 0.09–0.53).



Abbreviations: HR: hazard ratio; CI: confidence interval.

Figure 2.16 – Kaplan-Meier plot of breast cancer-specific survival in unmatched patients with ER-negative breast cancer (n = 365).

HR 0.31 (95% CI 0.13–0.68).



Abbreviations: HR: hazard ratio; CI: confidence interval.

CHAPTER 3. IMPACT OF CHEMOTHERAPY ON QUALITY OF LIFE IN OLDER WOMEN WITH EARLY BREAST CANCER

3.1. ABSTRACT

Older patients with early breast cancer (EBC) derive modest survival benefit from chemotherapy but have increased toxicity risk. Data on the impact of chemotherapy for EBC on quality of life (QoL) in older patients are limited, but this is a key determinant of treatment acceptance. We aimed to investigate its effect on QoL in older patients enrolled in the Bridging the Age Gap study.

A prospective, multicentre, observational study of EBC patients ≥70 years old was conducted in 2013-2018 at 56 UK hospitals. Demographics, patient, tumour characteristics, treatments and adverse events were recorded. QoL was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaires (QLQ)-C30, BR23 and ELD 15 plus the 5-level Euroqol-5D (EQ-5D-5L) over 24 months and analysed at each time point using baseline adjusted linear regression analysis and propensity score-matching.

3,416 patients were enrolled in the study; 1,520 patients undergoing surgery and who had high-risk EBC were included in this analysis. 376/1,520 (24.7%) received chemotherapy. At 6 months, chemotherapy had a significant negative impact in several EORTC-QLQ-C30 domains, including global health score, physical, role, social functioning, cognition, fatigue, nausea/vomiting, dyspnoea, appetite loss, diarrhoea and constipation. Similar trends were documented on other scales (EORTC-QLQ-BR23, EORTC-QLQ-ELD15 and EQ-5D-5L). Its impact was no longer significant at 18-24 months in unmatched and matched cohorts.

The negative impact of chemotherapy on QoL is clinically and statistically significant at 6 months but resolves by 18 months, which is crucial to inform decision-making for older patients contemplating chemotherapy.

3.2. INTRODUCTION

Almost half of all breast cancer cases are diagnosed in patients aged ≥65 years.[1] Nonetheless, older adults are under-represented in clinical trials.[2] Moreover, standard trial endpoints may not be appropriate for older individuals and quality of life (QoL), functional status and cognition may be as important as chance of cure.[3] These knowledge gaps contribute to considerable variation in treatment in this age group.[4]

In Chapter 2, the evidence base surrounding the benefits of (neo)adjuvant chemotherapy use for early breast cancer (EBC) in older patients were discussed. Based on that discussion and the findings presented on that analysis, the benefits associated with the use of chemotherapy are likely to be limited only to a subgroup of older patients with EBC. This includes those with oestrogen receptor (ER)-negative and/or human epidermal growth factor receptor 2 (HER2)-positive breast cancer.[5, 6] However, even in those for whom chemotherapy may be beneficial and associated with a reduction in the risks of disease recurrence or death, clinicians and patients may have concerns about the risk of side effects and impacts on QoL. Older adults have higher risk of treatment toxicities due to comorbidities and reduced organ function, while benefits are mitigated by competing risks.[7] The impact of chemotherapy on QoL may influence clinicians' and patients' perspectives.[8]

Therefore, the effect of anticancer treatments on QoL is essential to inform treatment decisions in this cohort. The Cancer and Leukemia Group B (CALGB) 49907 study documented better QoL for patients aged ≥65 receiving capecitabine versus standard regimens but no QoL differences persisted at 1 year.[9] Patients receiving chemotherapy within clinical trials had better QoL improvements compared with those treated off study.[10] Nonetheless, prospective data on QoL for older patients with EBC receiving standard chemotherapy are lacking.

The nature of QoL assessments is that they depend on patient-reporting of symptoms. Comorbidities, literacy, symptoms and compliance may influence

patient-reported outcomes.[11] While available evidence does not support the use of one specific QoL questionnaire over others in clinical research,[12] important differences exist between the scale structure, social domains and tone that may be relevant for any particular study. The European Organisation for Research and Treatment of Cancer (EORTC) questionnaires have been validated to evaluate QoL generically in cancer patients,[13] and specifically in older individuals[14] and in those diagnosed with breast cancer.[15] The EORTC Quality of Life Questionnaires (QLQ)-C30, BR23 and ELD15 are designed to evaluate physical well-being, social well-being, emotional well-being, functional well-being and breast cancer concerns. The EORTC QLQ-C30 comprises 30 questions related to general well-being, and the BR23 adds 23 specific questions related to breast cancer. These questionnaires are widely used in breast cancer trials and, unlike other QoL scales, differentiate symptoms and concerns. The EORTC QLQ-ELD15 has 15 domains each scored on a 0 to 100 scale. The ELD15 is a module specific to older patients and their QoL.

We aimed to investigate the impact of chemotherapy on QoL in real-world EBC patients aged ≥70 recruited to the Bridging the Age Gap study.[16] Matching survival outcomes for the cohort are reported separately.[17] The study methods are presented in Chapter 2.

The Bridging the Age Gap study had completed recruitment by the time of registration of my research degree. Within this study, I have been responsible for the cleaning of the study database, the statistical analysis in conjunction with the trial statistician and the formulation of specific research questions to be investigated in the study cohort.

3.3. RESULTS

Between January 2013 and June 2018, 3,456 women were recruited from 56 hospitals in England and Wales (Supplementary table 2.1) and 3,416 included in the analysis. 2,811/3,416 (82.3%) underwent surgery within 6 months of diagnosis, 1,520/2,811 (54.1%) had high-risk EBC and 376/1,520 (24.7%) received chemotherapy (Figure 3.1)[18]. The time frames for treatments received in each cohort are shown in Figure 3.2 wherein the slight offset in timing of endocrine therapy and radiotherapy between the chemotherapy and no chemotherapy groups can be seen and should be considered when interpreting the findings.

Patients had a median age of 76.9 years, Charlson comorbidity index (CCI) of 1 (range 0-9) and took a median of 4 medications (0-18); 1,063 (69.9%) were independent in their activities of daily living (ADLs) and 1,091 (71.8%) in their instrumental activities of daily living (IADLs), 1,346 (88.6%) had normal Mini Mental State Examination (MMSE), 1,168 (76.8%) had a low Abridged Patient Generated Subjective Global Assessment (aPG-SGA) score and 1,379 (90.7%) had Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0-1 (Table 3.1). Detailed findings on tumour and patient characteristics are presented in Supplementary Table 3.1.

Chemotherapy data were available for 360 patients: 124 (34.4%) received anthracycline and taxanes, 119 (33.1%) a taxane alone, and 116 (32.2%) an anthracycline alone; one patient received cyclophosphamide, methotrexate, fluorouracil (CMF). 332 patients (21.8%) had HER2-positive disease: 150 (45.2%) received chemotherapy plus trastuzumab, 13 (3.9%) received trastuzumab alone, and 9 (2.7%) chemotherapy alone. EBC was ER-positive in 1134 patients (75.3%), with 1079 (95.1%) receiving endocrine therapy (Figure 3.2).

Of these high-risk patients, 1,120 (73.7%) enrolled with full participation in the protocol (necessary for completion of QoL questionnaires) and 304/1,120

(27.1%) had chemotherapy. Figures 3.3, 3.4 and 3.5 and Supplementary tables 3.2, 3.3 and 3.4 show completion rates of QoL questionnaires.

3.3.1. Impact on quality of life domains (EORTC QLQ-C30)

The impacts of chemotherapy on QoL are summarised in Figure 3.6. 1,049/1,120 patients (93.7%) completed the global health status questions included in the EORTC QLQ-C30 questionnaire at baseline (Supplementary table 3.5; Figure 3.7). Following adjustment for baseline scores, at 6 weeks the differences in the mean scores on some EORTC QLQ-C30 domains were statistically significant between patients undergoing chemotherapy compared to those not receiving it, including global health (adjusted mean difference -2.81, 95% confidence intervals [CI] -5.17 to -0.44, p=0.020), social functioning (-3.57, CI -6.71 to -0.43, p=0.026) and constipation (3.43, CI 0.23 to 6.62, p=0.035). The impact of chemotherapy remained significant on most domains at 6 months, including global health which was both statistically and clinically significant but small (-9.20, CI -11.95 to -6.44, p <0.001), physical functioning (medium difference: -8.05, CI -10.21 to -5.89, p<0.001), role functioning (small difference: -17.59, CI -21.24 to -13.95, p<0.001), cognitive functioning (small difference: -5.55, CI -7.97 to -3.13, p<0.001), social functioning (large difference: -18.72, CI -22.17 to -15.27, p<0.001), and financial problems (small difference: 3.28, CI 1.16 to 5.39, p=0.002). At 12 months statistically significant differences persisted in physical functioning (trivial difference: -2.76, CI -4.95 to -0.57, p=0.014), role functioning (trivial difference: -4.41, CI -8.17 to -0.64, p=0.022), social functioning (trivial difference: -3.78, CI -7.00 to -0.56, p=0.022), diarrhoea (small difference: 4.15, CI 1.62 to 6.68, p=0.001) and financial problems (trivial difference: 2.50, CI 0.27 to 4.73, p=0.028). Chemotherapy was no longer impactful in any of these domains at 18 and 24 months.

The analyses were repeated on a propensity score-matched subgroup of 410 patients (150 chemotherapy, 260 no chemotherapy) with similar findings (Figure 3.8, 3.9 and 3.10; Supplementary table 3.6).

3.3.2. Impact on breast cancer-specific quality of life domains (EORTC QLQ-BR23)

1,054/1,120 patients (94.1%) completed some or all of the EORTC QLQ-BR23 questionnaire at baseline (Supplementary table 3.7; Figure 3.11). After adjustment for baseline measurements patients given chemotherapy experienced a significant decline of some EORTC QLQ-BR23 mean scores at 6 weeks compared with those not receiving it in future perspective (adjusted mean difference -7.20, 95% CI -10.72 to -3.68, p<0.001) and systemic therapy side-effects (3.04, CI 1.47 to 4.61, p<0.001). At 6 months, mean scores were significantly different in future perspectives (-7.54, CI -11.28 to -3.80, p<0.001) and systemic therapy side-effects (16.97, CI 15.00 to 18.94, p<0.001). At 12 months, the mean scores between the two groups differed in future perspectives (-4.96, CI -8.89 to -1.03, p=0.013), systemic therapy side-effects (3.32, CI 1.41 to 5.22, p=0.001) and the effect of chemotherapy became significant in arm symptoms (4.94, CI 2.18 to 7.69, p<0.001). At 18 months, the differences remained significant in future perspective (-4.97, CI -9.37 to -0.57, p=0.027) and arm symptoms (3.27, CI 0.01 to 6.54, p=0.049), and at 24 months only in arm symptoms (4.02, CI 0.13 to 7.90, p=0.043).

3.3.3. Impact on older adults-specific quality of life domains (EORTC QLQ-ELD15)

Some or all of the EORTC QLQ-ELD15 questionnaire was completed at baseline by 1,048/1,120 (Supplementary table 3.8; Figure 3.12). At 6 weeks scores were significantly different between patients given chemotherapy and those not treated in worries about others (adjusted mean difference 5.31, 95% CI 1.55 to 9.07, p=0.006), worries (4.09, CI 0.92 to 7.27, p=0.011) and burden of illness (4.68, CI 1.25 to 8.11, p=0.007). These differences persisted at 6 months (worries about others [6.19, CI 2.44 to 9.95, p=0.001]; worries [4.18, CI 0.89 to 7.46, p=0.013]; burden of illness [21.60, CI 17.82 to 25.39, p<0.001]); the impact on mobility also became significant (9.82, CI 6.87 to 12.78, p<0.001). At 12 months, changes remained significant regarding worries about others (4.47, CI 0.42 to 8.52, p=0.031) and burden of illness (15.21, CI 11.30 to 19.12, p<0.001), which was the only domain significantly

influenced also at 18 months (12.99, CI 8.81 to 17.17, p<0.001) and 24 months (8.80, CI 3.93 to 13.66, p<0.001).

Maintaining purpose did not differ throughout the follow-up period, whereas chemotherapy had a positive impact on family support mean scores at 6 weeks (6.21, CI 2.26 to 10.17, p=0.002), at 6 months (4.91, CI 0.26 to 9.56, p=0.038) and at 12 months (5.43, CI 0.39 to 10.46, p=0.035).

3.3.4. Impact on EQ-5D-5L score and questions

Among the high-risk patients, an EQ-5D-5L score was calculated in 1,315 patients (86.5%) at baseline. Health utilities were similar with estimated mean differences less than 0.02 units (p>0.1), whereas the visual analogue scale (VAS) measures were significantly worse at 6 months in patients receiving chemotherapy versus not (adjusted mean difference -6.57, 95% CI -8.74 to -4.40, p<0.001). Changes were subsequently no longer significant (Supplementary table 3.9; Figure 3.13).

A similar pattern on EQ-5D-5L usual activities score was seen in 520 (118 chemotherapy, 332 no chemotherapy) propensity score-matched patients (Figure 3.14).

3.4. DISCUSSION

This study demonstrates that chemotherapy has a both a clinically and statistically significantly negative impact at 6-12 months on several QoL domains (physical, role, cognitive and social functioning, financial problems), symptoms (fatigue, nausea, dyspnoea, appetite loss, constipation, diarrhoea), and perceived global health. These changes are clinically meaningful and involve key domains for this population[19] for whom even low-grade toxicities may be challenging.[20]

Reassuringly, this effect resolves for most items over 18-24 months. This is consistent with previous QoL data reported in younger cohorts: for example, in 280 EBC patients many domains improved within 12 months after diagnosis, with the exception of cognitive function and financial problems[21] and similar improvements in role functioning were seen in a study of 817 EBC patients.[22] A registry-based analysis documented better physical functioning, role-physical, role-emotional and fatigue scales at 15 years in EBC patients including 46.9% aged ≥65.[23] Similarly, 588 EBC patients enrolled in the Moving Beyond Cancer study had improved physical and psychosocial functioning after radical treatment regardless of chemotherapy use.[22] Neuropsychological analyses also confirmed improving cognitive function during the first four years after radical therapy for EBC,[24, 25] although data on financial impact are limited.[21] The CANTO study confirmed the transient nature of the impact of chemotherapy on QoL in a large population.[26] Nonetheless, these analyses have either focused on younger patients, where the risk/benefit is different, or addressed the impact of breast cancer treatments (and not specifically of chemotherapy) on QoL in this age group. Our findings are consistent with a previous study in 109 patients aged 70 or older, of whom 57 received adjuvant docetaxel/cyclophosphamide chemotherapy.[27]

To our knowledge, this is the largest study to evaluate the impact of contemporary chemotherapy regimens in older adults with EBC in real-world

patients. QoL is a meaningful endpoint for older patients, who typically derive less survival benefit and increased toxicities on systemic anticancer therapy (SACT).[28, 29] These benefits need to be carefully balanced with the detrimental impact on QoL and treatment side-effects.[30]

Our analysis included baseline geriatric assessments characterizing patients in relevant health domains for this age group, such as functional status, comorbidity, cognition, nutrition and concurrent medications which may impact QoL. A comprehensive geriatric assessment (CGA) can help achieve the required balance between treatment benefits and side-effects and is recommended by guidelines from the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), and the International Society for Geriatric Oncology (SIOG).[19, 31] In a randomized study, integrated oncogeriatric care has recently been shown to improve QoL in older patients with cancer being considered for SACT.[32] Of particular interest was our finding that in patients ≥80 the negative impact on QoL does not resolve, which suggests a lack of resilience in this cohort.

The study has several limitations. Selection bias may have influenced our findings despite its inclusive entry criteria and the different levels of participation. The recruited population was slightly skewed towards younger individuals compared with the general UK EBC patient population.[33] Moreover, we did not include socio-economic factors that might influence frailty nor the effect of endocrine therapy or radiotherapy on QoL, owing to multiple confounders to such an analysis. We did not capture the impact of chemotherapy on QoL outcomes beyond 24 months and missing data on longitudinal QoL assessments may have influenced findings. Other factors not measured by our analysis may also impact on chemotherapy decisions; therefore, the propensity score matching does not adjust for all differences between the groups. Furthermore, some effects of chemotherapy on QoL documented in our analysis might be statistically significant but not clinically relevant. Moreover, some statistically significant effects may be attributed to other factors: for example, the effect of chemotherapy on arm symptoms might simply be attributed to the fact that patients who were offered chemotherapy

may have more frequent nodal involvement, which typically requires a more extensive locoregional management. However, for the majority of domains clinically meaningful changes are seen at the six-month timepoint, which represents the time when most women would have been on chemotherapy. Finally, it was not possible to categorise chemotherapy effects on QoL measured on BR23, ELD15 and EQ-5D-5L domains as thresholds have not been established for these specific tools and the latter is a utility scale.

Our research has key implications. For individual patients, it provides evidence on the transient impact of chemotherapy on QoL in older individuals with curable breast cancer. These findings may be useful for clinicians and patients to enhance discussions around a crucial ageing-related concern and to expand opportunities for shared decision-making in this specific population. The impact of chemotherapy on QoL persisted also following propensity score-matching based on geriatric assessments: this suggests that the effect of cytotoxic therapy on QoL is not necessarily influenced by baseline overall health in this population. By expanding the available evidence on its impact on QoL, these findings may contribute to reduce the variation in the use of chemotherapy which is well-documented in this group of patients.[4] For investigators, this study confirms the feasibility of embedding geriatric assessments in the design of trials addressing meaningful endpoints for older adults with cancer.

The future direction of our research may involve several additional aspects. While a differential impact of endocrine therapy and chemotherapy on QoL has been documented in a broader (and younger) population of patients with EBC,[26] it is unclear whether similar findings are relevant also to older individuals. Moreover, although integrated geriatric assessment-driven interventions have a positive impact on QoL in older patients with cancer initiating a new line of SACT,[32] their effect is not known specifically in those receiving chemotherapy for EBC. Finally, developing prediction models of the effect of SACT on QoL is attractive in the context of more limited survival benefits: while initial data have been generated in younger patient populations,[34] evidence is more sparce in the older group where they would

represent a key tool to support decision-making and communication alongside established benefit prediction models.

In conclusion, our analysis shows that chemotherapy has an impact on several QoL domains in older EBC patients compared to a matched cohort who did not receive cytotoxics. Nonetheless, these effects are temporary and largely resolve within two years; these findings are consistent with the transient impact of chemotherapy on QoL documented also in younger cohorts.[26] This is essential information for older women to use in decision-making, since individualised decisions on treatment options should be based on their values.

3.5. PROGRESS TO PRESENTATION AND PUBLICATION

This analysis was conducted on behalf of the Bridging The Age Gap study steering group, with specific contribution by statisticians Esther Herbert and Mike Bradburn and by Professor Lynda Wyld (University of Sheffield). I have presented these findings at the 2020 European Society for Medical Oncology (ESMO) Congress.[35] I have published this study manuscript in the European Journal of Cancer (impact factor 9.162) as first author.[36]

3.6. REFERENCES

1. Ferlay, J., et al. Global Cancer Observatory: Cancer Today. 2018 06/06/2020]; Available from: https://gco.iarc.fr/today.
2. Hurria, A., et al., Improving the Evidence Base for Treating Older Adults With Cancer: American Society of Clinical Oncology Statement. J Clin Oncol, 2015. 33(32): p. 3826-33.
3. Wildiers, H., et al., End points and trial design in geriatric oncology research: a joint European organisation for research and treatment of cancer--Alliance for Clinical Trials in Oncology--International Society Of Geriatric Oncology position article. J Clin Oncol, 2013. 31(29): p. 3711-8.
4. Battisti, N.M.L., et al., Is age a barrier to chemotherapy? Rates of treatment in older patients treated with breast, colon and lung cancer in England in 2014: a national registry study. Annals of Oncology, 2018. 29: p. viii562-viii575.
5. Giordano, S.H., et al., Use and outcomes of adjuvant chemotherapy in older women with breast cancer. J Clin Oncol, 2006. 24(18): p. 2750-6.
6. Biganzoli, L., et al., Management of elderly patients with breast cancer: updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA). Lancet Oncol, 2012. 13(4): p. e148-60.
7. Kim, J. and A. Hurria, Determining chemotherapy tolerance in older patients with cancer. J Natl Compr Canc Netw, 2013. 11(12): p. 1494-502.
8. Ring, A., et al., Adjuvant chemotherapy in elderly women with breast cancer (AChEW): an observational study identifying MDT perceptions and barriers to decision making. Ann Oncol, 2013. 24(5): p. 1211-9.
9. Kornblith, A.B., et al., Quality of life of older patients with early-stage breast cancer receiving adjuvant chemotherapy: a companion study to cancer and leukemia group B 49907. J Clin Oncol, 2011. 29(8): p. 1022-8.
10. Mandelblatt, J.S., et al., A planned, prospective comparison of short-term quality of life outcomes among older patients with breast cancer

treated with standard chemotherapy in a randomized clinical trial vs. an observational study: CALGB #49907 and #369901. J Geriatr Oncol, 2013. 4(4): p. 353-61.

11. Scotté, F., et al., Addressing the quality of life needs of older patients with cancer: a SIOG consensus paper and practical guide. Ann Oncol, 2018. 29(8): p. 1718-1726.
12. Luckett, T., et al., Choosing between the EORTC QLQ-C30 and FACT-G for measuring health-related quality of life in cancer clinical research: issues, evidence and recommendations. Annals of Oncology, 2011. 22(10): p. 2179-2190.
13. Aaronson, N.K., et al., The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst, 1993. 85(5): p. 365-76.
14. Johnson, C., et al., Development of the European Organisation for Research and Treatment of Cancer quality of life questionnaire module for older people with cancer: The EORTC QLQ-ELD15. Eur J Cancer, 2010. 46(12): p. 2242-52.
15. Sprangers, M.A., et al., The European Organization for Research and Treatment of Cancer breast cancer-specific quality-of-life questionnaire module: first results from a three-country field study. J Clin Oncol, 1996. 14(10): p. 2756-68.
16. Collins, K., et al., Bridging the age gap in breast cancer: evaluation of decision support interventions for older women with operable breast cancer: protocol for a cluster randomised controlled trial. BMJ Open, 2017. 7(7): p. e015133.
17. Ring, A., et al., Bridging The Age Gap: observational cohort study of effects of chemotherapy and trastuzumab on recurrence, survival and quality of life in older women with early breast cancer. Br J Cancer, 2021.
18. von Elm, E., et al., The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol, 2008. 61(4): p. 344-9.

19. Mohile, S.G., et al., Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Chemotherapy: ASCO Guideline for Geriatric Oncology Summary. J Oncol Pract, 2018. 14(7): p. 442-446.
20. Kalsi, T., et al., The impact of low-grade toxicity in older people with cancer undergoing chemotherapy. Br J Cancer, 2014. 111(12): p. 2224-8.
21. Hsu, T., et al., Quality of life in long-term breast cancer survivors. J Clin Oncol, 2013. 31(28): p. 3540-8.
22. Ganz, P.A., et al., Physical and psychosocial recovery in the year after primary treatment of breast cancer. J Clin Oncol, 2011. 29(9): p. 1101-9.
23. Klein, D., et al., Long-term quality of life after breast cancer: a French registry-based controlled study. Breast Cancer Res Treat, 2011. 129(1): p. 125-34.
24. Schagen, S.B., et al., Late effects of adjuvant chemotherapy on cognitive function: a follow-up study in breast cancer patients. Ann Oncol, 2002. 13(9): p. 1387-97.
25. Ahles, T.A., et al., Longitudinal assessment of cognitive changes associated with adjuvant treatment for breast cancer: impact of age and cognitive reserve. J Clin Oncol, 2010. 28(29): p. 4434-40.
26. Ferreira, A.R., et al., Differential impact of endocrine therapy and chemotherapy on quality of life of breast cancer survivors: a prospective patient-reported outcomes analysis. Ann Oncol, 2019. 30(11): p. 1784-1795.
27. Quinten, C., et al., The effect of adjuvant chemotherapy on symptom burden and quality of life over time; a preliminary prospective observational study using individual data of patients aged ≥70 with early stage invasive breast cancer. J Geriatr Oncol, 2018. 9(2): p. 152-162.
28. Extermann, M., et al., Predicting the risk of chemotherapy toxicity in older patients: the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score. Cancer, 2012. 118(13): p. 3377-86.

29. Hurria, A., et al., Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. J Clin Oncol, 2011. 29(25): p. 3457-65.
30. Wu, H.S. and J.K. Harden, Symptom burden and quality of life in survivorship: a review of the literature. Cancer Nurs, 2015. 38(1): p. E29-54.
31. Wildiers, H., et al., International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. J Clin Oncol, 2014. 32(24): p. 2595-603.
32. Soo, W.-K., et al., Integrated geriatric assessment and treatment (INTEGERATE) in older people with cancer planned for systemic anticancer therapy. Journal of Clinical Oncology, 2020. 38(15_suppl): p. 12011-12011.
33. Todd, A., et al., Age specific recruitment and retention to a large multicentre observational breast cancer trial in older women: The Age Gap Trial. Journal of Geriatric Oncology, 2020.
34. Carmona-Bayonas, A., et al., Prediction of quality of life in early breast cancer upon completion of adjuvant chemotherapy. npj Breast Cancer, 2021. 7(1): p. 92.
35. Battisti, N.M.L., et al., Impact of chemotherapy for early stage breast cancer on quality of life in older adults: results from 2811 women enrolled in the Bridging the Age Gap study (#2586), in European Society for Medical Oncology (ESMO) Virtual Congress. 2020.
36. Battisti, N.M.L., et al., Bridging the Age Gap in breast cancer: Impact of chemotherapy on quality of life in older women with early breast cancer. Eur J Cancer, 2021. 144: p. 269-280.

3.7. TABLES

Table 3.1 – Baseline postoperative tumour and patient characteristics by chemotherapy receipt.

Variables	Categories	Chemotherapy	No chemotherapy	Total
		N = 376	N = 1,144	N = 1,520
Tumour size (mm)	≤ 20	93 (24.7%)	399 (34.9%)	492 (32.4%)
	21-50	233 (62.0%)	644 (56.3%)	877 (57.7%)
	> 50	49 (13.0%)	100 (8.7%)	149 (9.8%)
	Unknown	1 (0.3%)	1 (0.1%)	2 (0.1%)
Grade	Grade 1	2 (0.5%)	77 (6.7%)	79 (5.2%)
	Grade 2	122 (32.4%)	447 (39.1%)	569 (37.4%)
	Grade 3	247 (65.7%)	617 (53.9%)	864 (56.8%)
	Unknown	5 (1.3%)	3 (0.3%)	8 (0.5%)
ER status	Negative	132 (35.1%)	240 (21.0%)	372 (24.5%)
	Positive	241 (64.1%)	893 (78.1%)	1,134 (74.6%)
	Unknown	3 (0.8%)	11 (1.0%)	14 (0.9%)
HER2 status	Negative	210 (55.9%)	908 (79.4%)	1,118 (73.6%)
	Inconclusive	3 (0.8%)	7 (0.6%)	10 (0.7%)
	Positive	159 (42.3%)	173 (15.1%)	332 (21.8%)
	Unknown	4 (1.1%)	56 (4.9%)	60 (3.9%)
Oncotype DX test performed	No	35 (9.3%)	150 (13.1%)	185 (12.2%)
	Yes	5 (1.3%)	16 (1.4%)	21 (1.4%)
	Not applicable	252 (67.0%)	434 (37.9%)	686 (45.1%)
	Unknown	84 (22.3%)	544 (47.6%)	628 (41.3%)
Breast surgery	Wide local excision (non wire localised)	113 (30.1%)	412 (36.0%)	525 (34.5%)
	Wire localised wide local excision	43 (11.4%)	150 (13.1%)	193 (12.7%)

Variables	Categories	Chemotherapy	No chemotherapy	Total
		N = 376	N = 1,144	N = 1,520
	Therapeutic mammoplasty / breast reshaping after wide local excision	18 (4.8%)	14 (1.2%)	32 (2.1%)
	Mastectomy	186 (49.5%)	549 (48.0%)	735 (48.4%)
	Mastectomy and reconstruction	12 (3.2%)	11 (1.0%)	23 (1.5%)
	Other	4 (1.1%)	8 (0.7%)	12 (0.8%)
Axillary surgery	Axillary sample	11 (2.9%)	38 (3.3%)	49 (3.2%)
	Axillary clearance	136 (36.2%)	247 (21.6%)	383 (25.2%)
	Sentinel lymph node biopsy	200 (53.2%)	725 (63.4%)	925 (60.9%)
	Internal mammary node biopsy	0 (0.0%)	1 (0.1%)	1 (0.1%)
	No axillary surgery	7 (1.9%)	27 (2.4%)	34 (2.2%)
	Unknown	22 (5.9%)	106 (9.3%)	128 (8.4%)
Nodal status	pN0-1mi	175 (46.5%)	508 (44.4%)	683 (44.9%)
	pN1	117 (31.1%)	494 (43.2%)	611 (40.2%)
	pN2	52 (13.8%)	95 (8.3%)	147 (9.7%)
	pN3	32 (8.5%)	46 (4.0%)	78 (5.1%)
	pNx	0 (0.0%)	1 (0.1%)	1 (0.1%)
Nottingham Prognostic Index	n	371	1139	1510
	Mean (SD)	5.1 (1.0)	4.7 (0.9)	4.8 (1.0)
	Median (IQR)	4.9 (4.4, 5.7)	4.5 (4.3, 5.3)	4.6 (4.3, 5.4)
	Min, Max	2.4, 10.2	2.1, 8.1	2.1, 10.2
Age	n	376	1144	1520
	Mean (SD)	73.65 (3.33)	77.97 (5.19)	76.90 (5.14)
	Median (IQR)	73.00 (71.00, 76.00)	78.00 (74.00, 81.00)	76.00 (72.00, 80.00)
	Min, Max	69, 87	69, 95	69, 95
	n	365	1,103	1,468

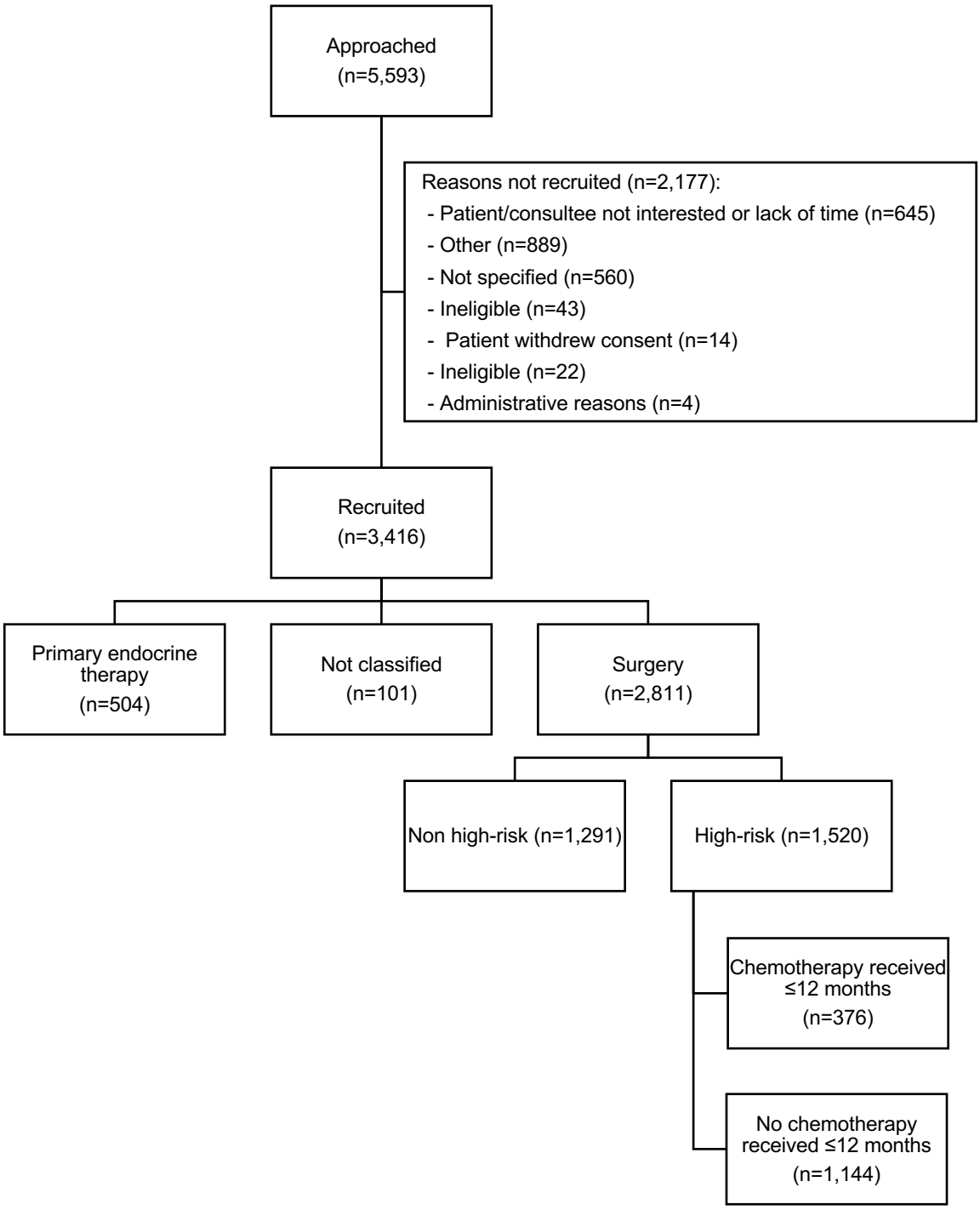
Variables	Categories	Chemotherapy	No chemotherapy	Total
		N = 376	N = 1,144	N = 1,520
Charlson comorbidity index (no age)	Mean (SD)	0.79 (1.08)	1.11 (1.38)	1.03 (1.32)
	Median (IQR)	0.00 (0.00, 2.00)	1.00 (0.00, 2.00)	1.00 (0.00, 2.00)
	Min, Max	0, 6	0, 9	0, 9
Number of concurrent medications	n	314	1,021	1,335
	Mean (SD)	3.66 (2.51)	4.30 (2.69)	4.15 (2.66)
	Median (IQR)	3.00 (2.00, 5.00)	4.00 (2.00, 6.00)	4.00 (2.00, 6.00)
	Min, Max	0, 14	0, 18	0, 18
ADL category	No dependency	303 (80.6%)	760 (66.4%)	1,063 (69.9%)
	Mild dependency	33 (8.8%)	146 (12.8%)	179 (11.8%)
	Moderate/severe dependency	16 (4.3%)	136 (11.9%)	152 (10.0%)
	Unknown	24 (6.4%)	102 (8.9%)	126 (8.3%)
IADL category	No dependency	315 (83.8%)	776 (67.8%)	1,091 (71.8%)
	Mild dependency	26 (6.9%)	124 (10.8%)	150 (9.9%)
	Moderate/severe dependency	10 (2.7%)	136 (11.9%)	146 (9.6%)
	Unknown	25 (6.6%)	108 (9.4%)	133 (8.7%)
MMSE category	Normal function	342 (91.0%)	1,004 (87.8%)	1,346 (88.6%)
	Mild impairment	28 (7.4%)	111 (9.7%)	139 (9.1%)
	Moderate impairment	4 (1.1%)	14 (1.2%)	18 (1.2%)
	Severe	2 (0.5%)	15 (1.3%)	17 (1.1%)
aPG-SGA category	Low	299 (79.5%)	869 (76.0%)	1,168 (76.8%)
	Moderate	38 (10.1%)	125 (10.9%)	163 (10.7%)
	High	4 (1.1%)	19 (1.7%)	23 (1.5%)
	Unknown	35 (9.3%)	131 (11.5%)	166 (10.9%)
ECOG PS	0	296 (78.7%)	740 (64.7%)	1,036 (68.2%)
	1	59 (15.7%)	284 (24.8%)	343 (22.6%)

Variables	Categories	Chemotherapy	No chemotherapy	Total
		N = 376	N = 1,144	N = 1,520
	2	3 (0.8%)	43 (3.8%)	46 (3.0%)
	3	2 (0.5%)	18 (1.6%)	20 (1.3%)
	Unknown	16 (4.3%)	59 (5.2%)	75 (4.9%)

Abbreviations: ER: oestrogen receptor; HER2: human epidermal growth factor receptor; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ADL: activities of daily living; IADL: instrumental activities of daily living; aPG-SGA: abridged patient-generated subjective global assessment; MMSE: Mini Mental State Examination.

3.8. FIGURES

Figure 3.1 – STROBE diagram.[8]



[88] Patients who only received palliative chemotherapy regimens where not counted as having received chemotherapy.

Figure 3.2 – Patients receiving surgery, endocrine therapy, radiotherapy and chemotherapy at each assessment.

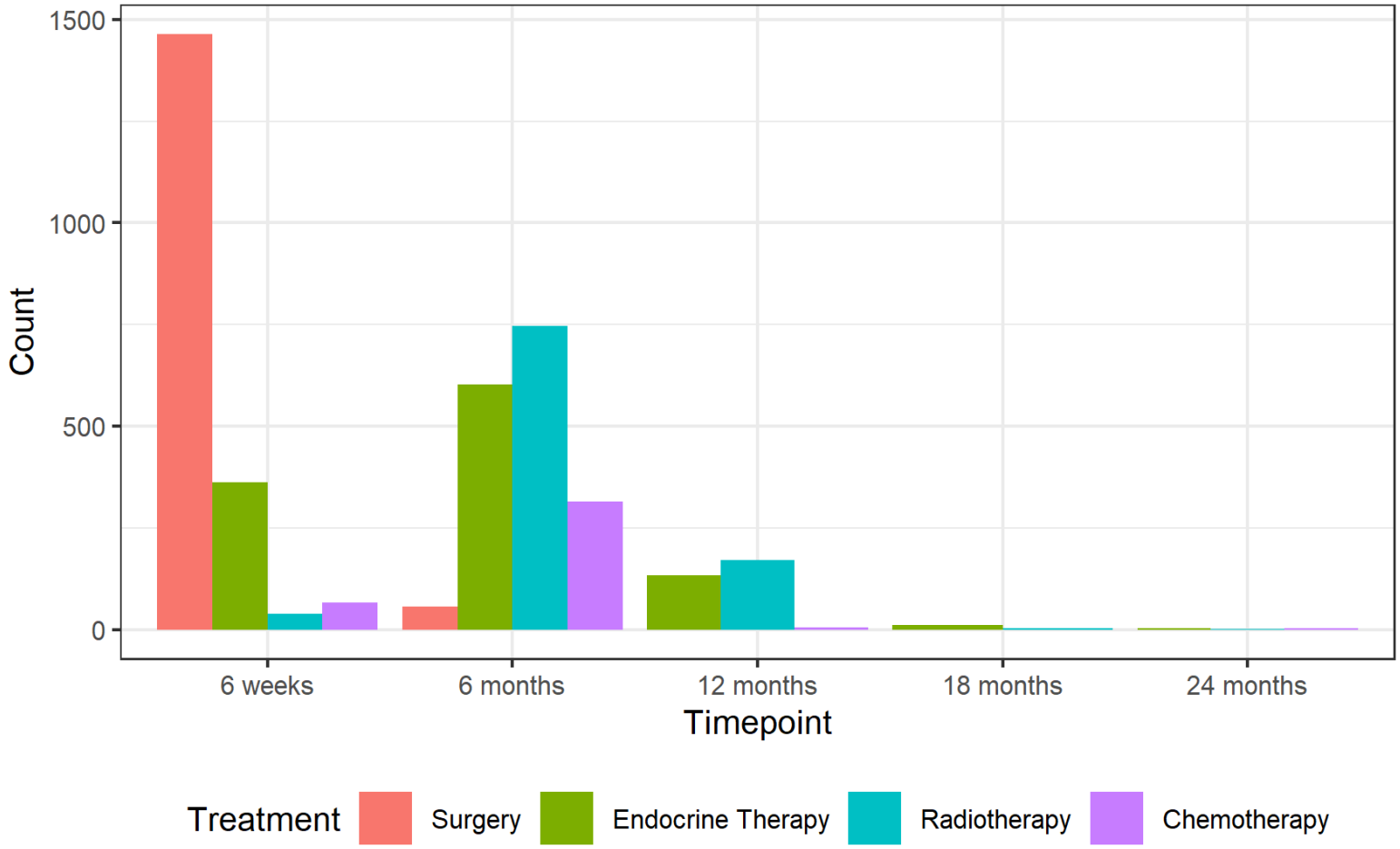


Figure 3.3 – Completion of the EORTC-QLQ-C30 at each time point.

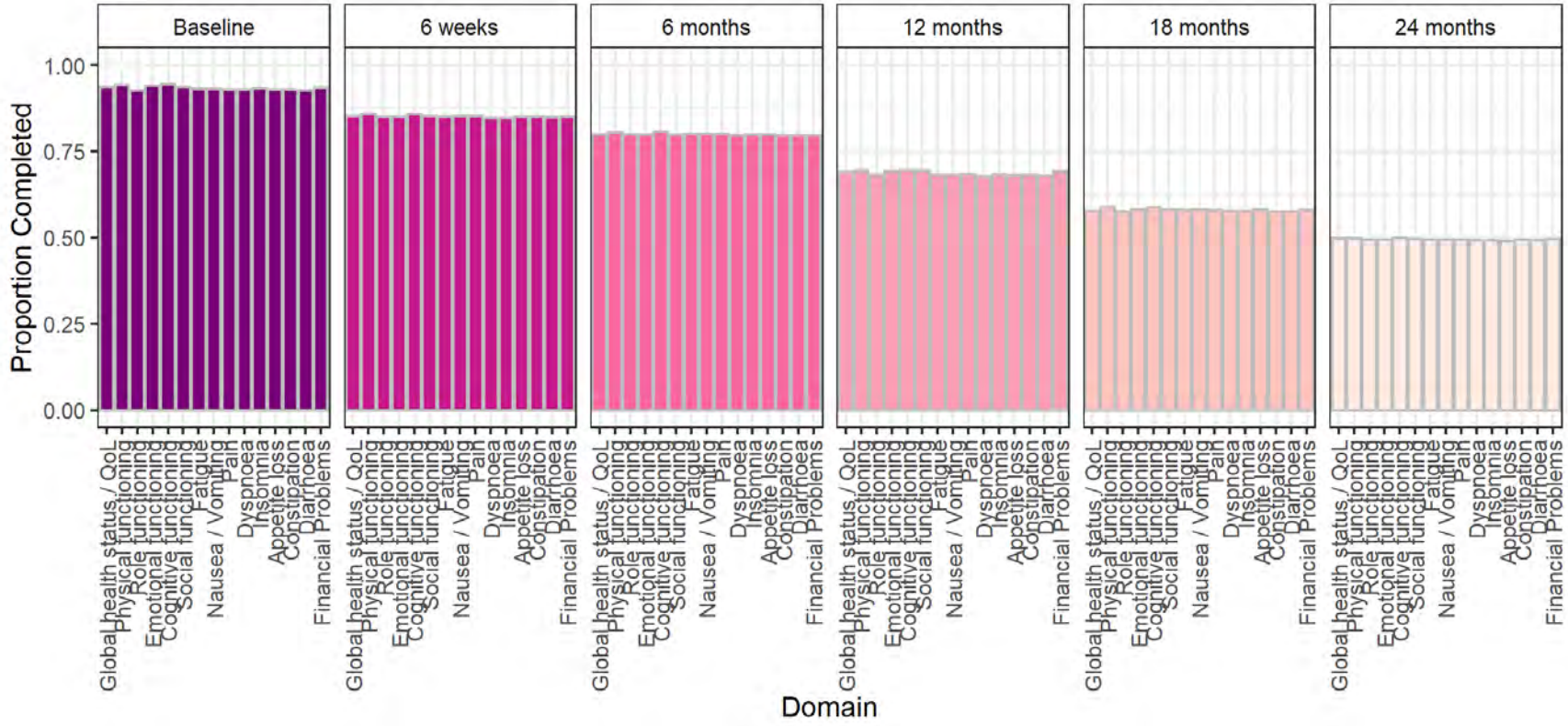


Figure 3.4 – Completion of the EORTC-QLQ-BR23 at each time point.

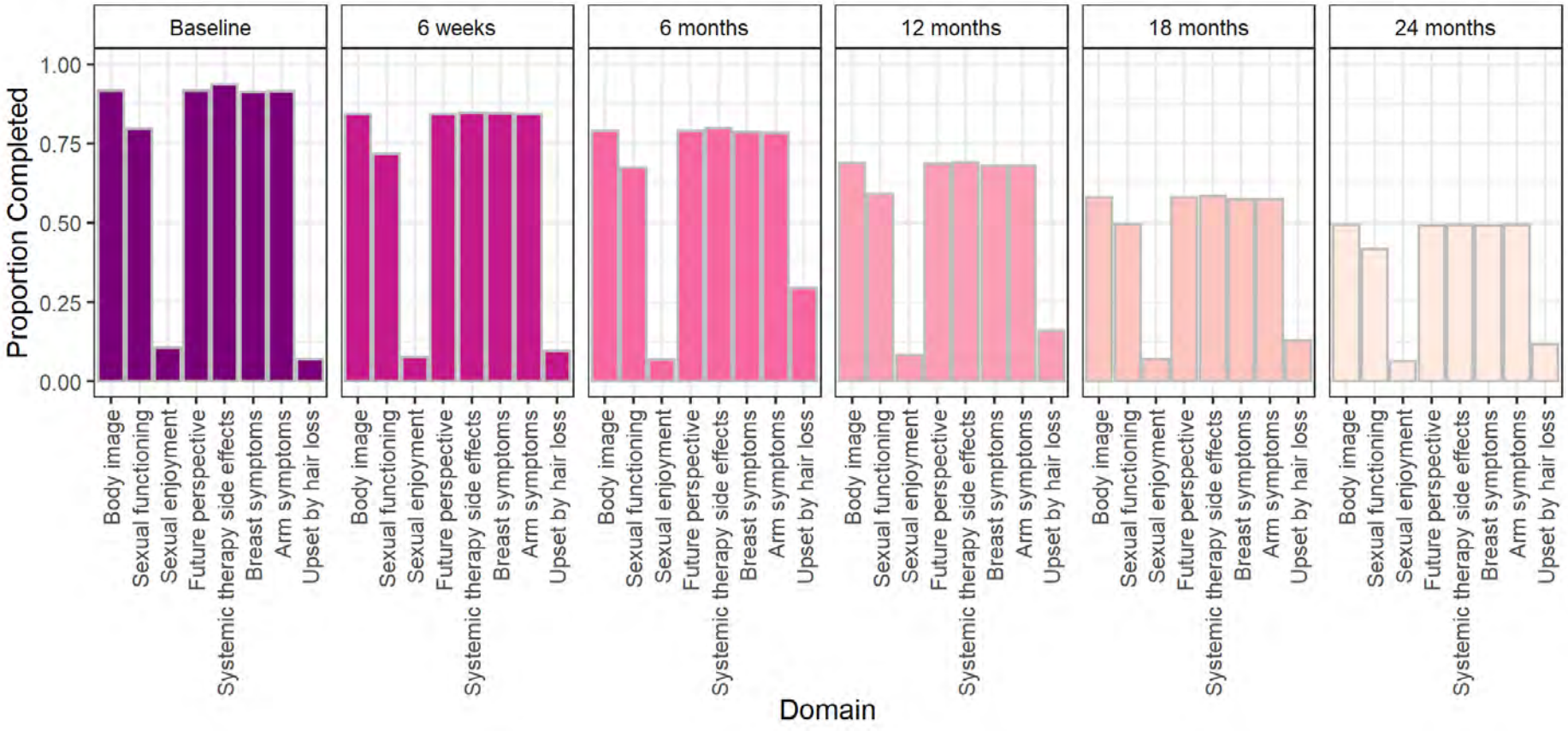


Figure 3.5 – Completion of the EORTC-QLQ-ELD15 at each time point.

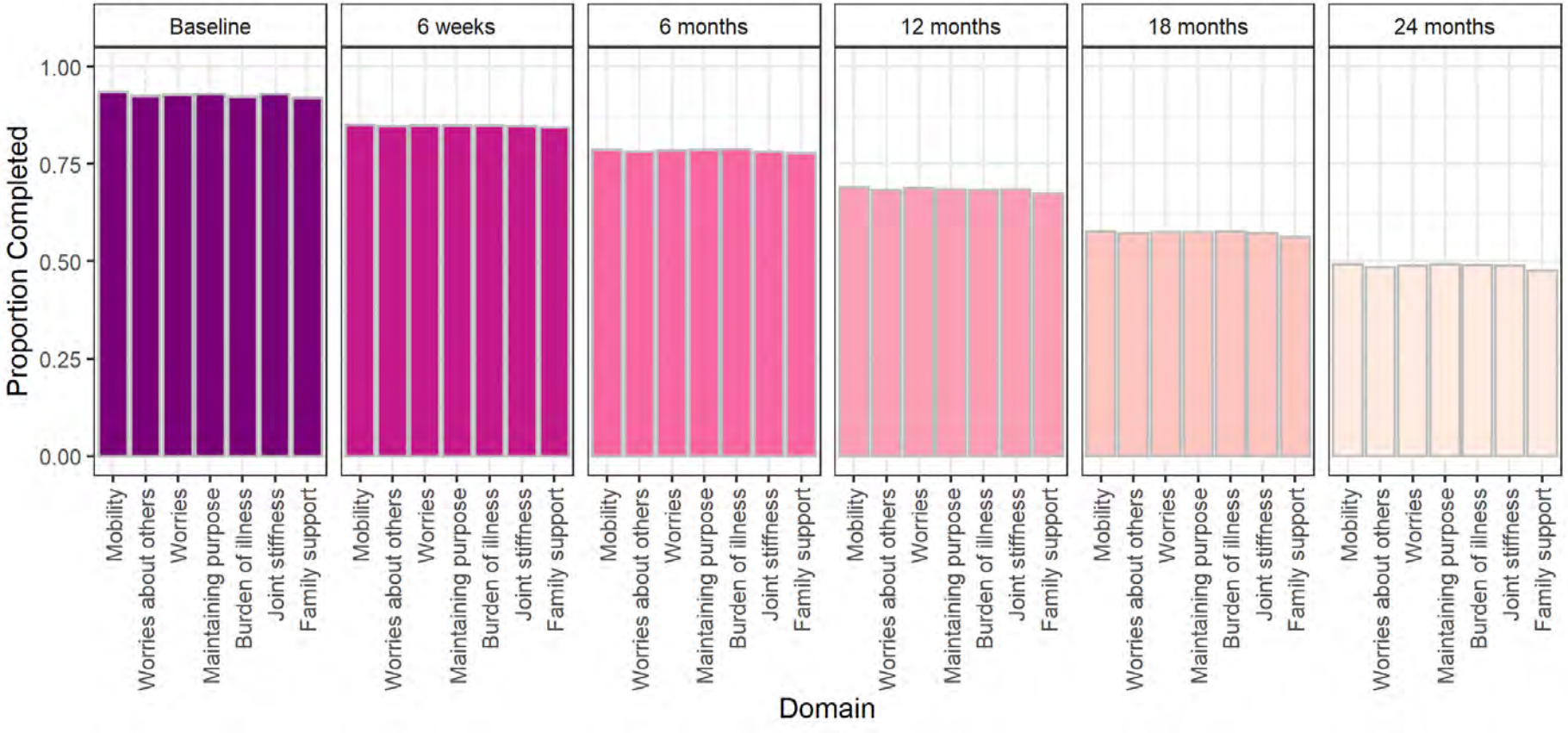
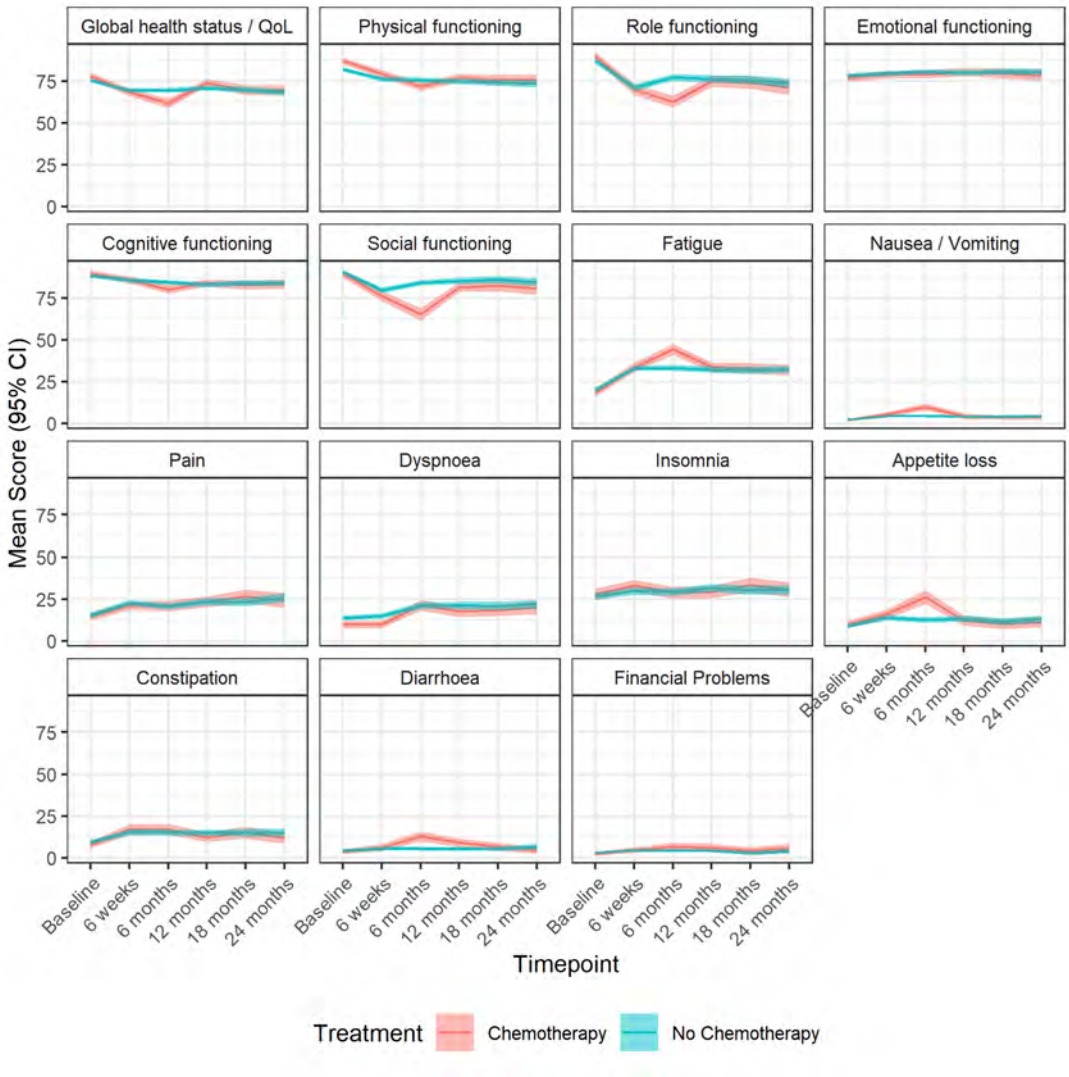


Figure 3.6 – Impacts of chemotherapy on quality of life over time.

Figure 3.7 – Mean (95% CI) scores over time points for the chemotherapy versus no chemotherapy population measured on the EORTC-QLQ-C30 scale.



Abbreviations: CI: confidence interval.

Figure 3.8 – Mean (95% confidence interval) EORTC-QLQ-C30 global health status/quality of life score over timepoints for the matched chemotherapy versus no chemotherapy population.

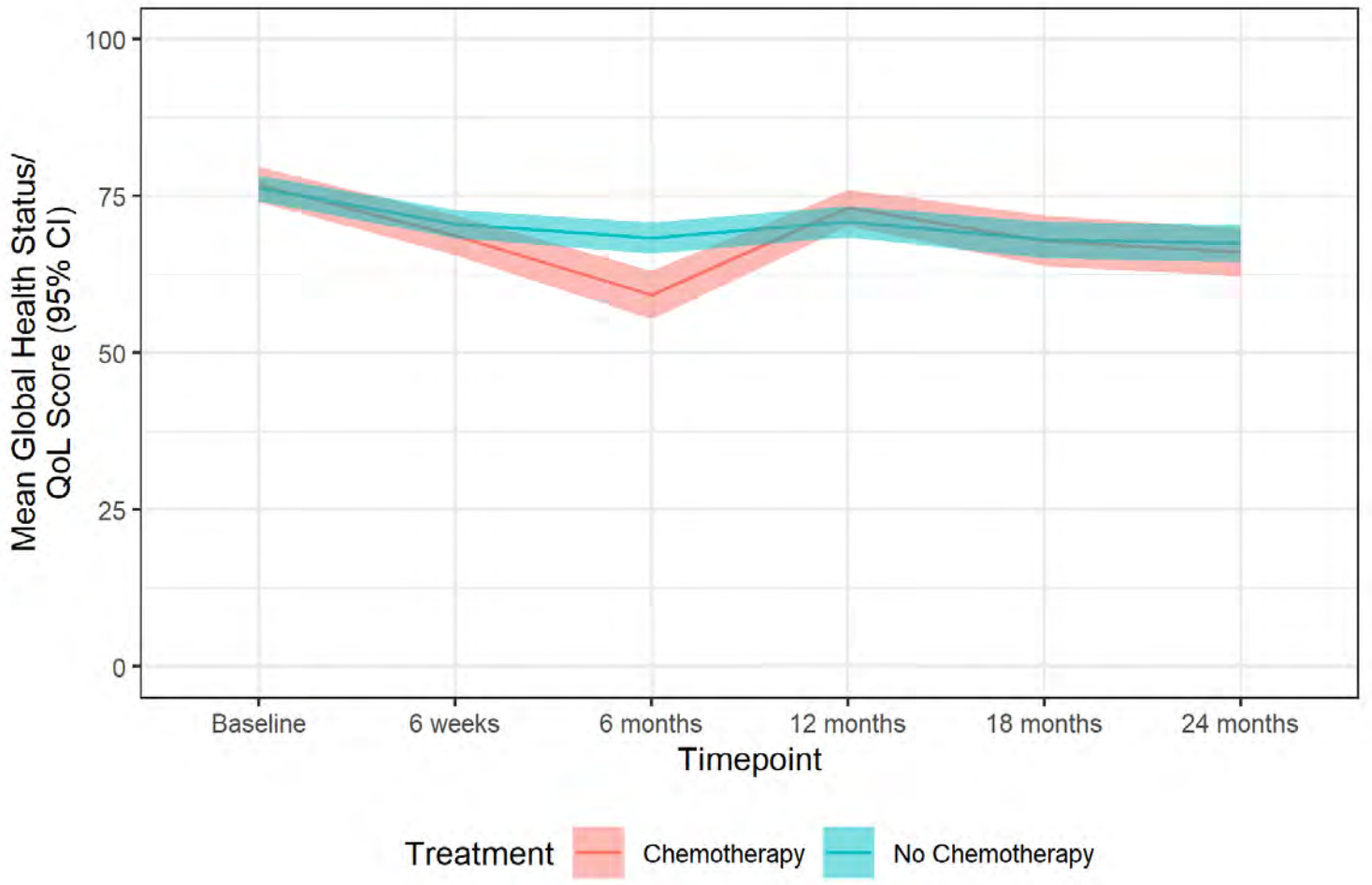


Figure 3.9 – Estimated marginal mean global health score (95% confidence interval) included in the EORTC-QLQ-C30 score for chemotherapy and no chemotherapy from the matched longitudinal modelling.

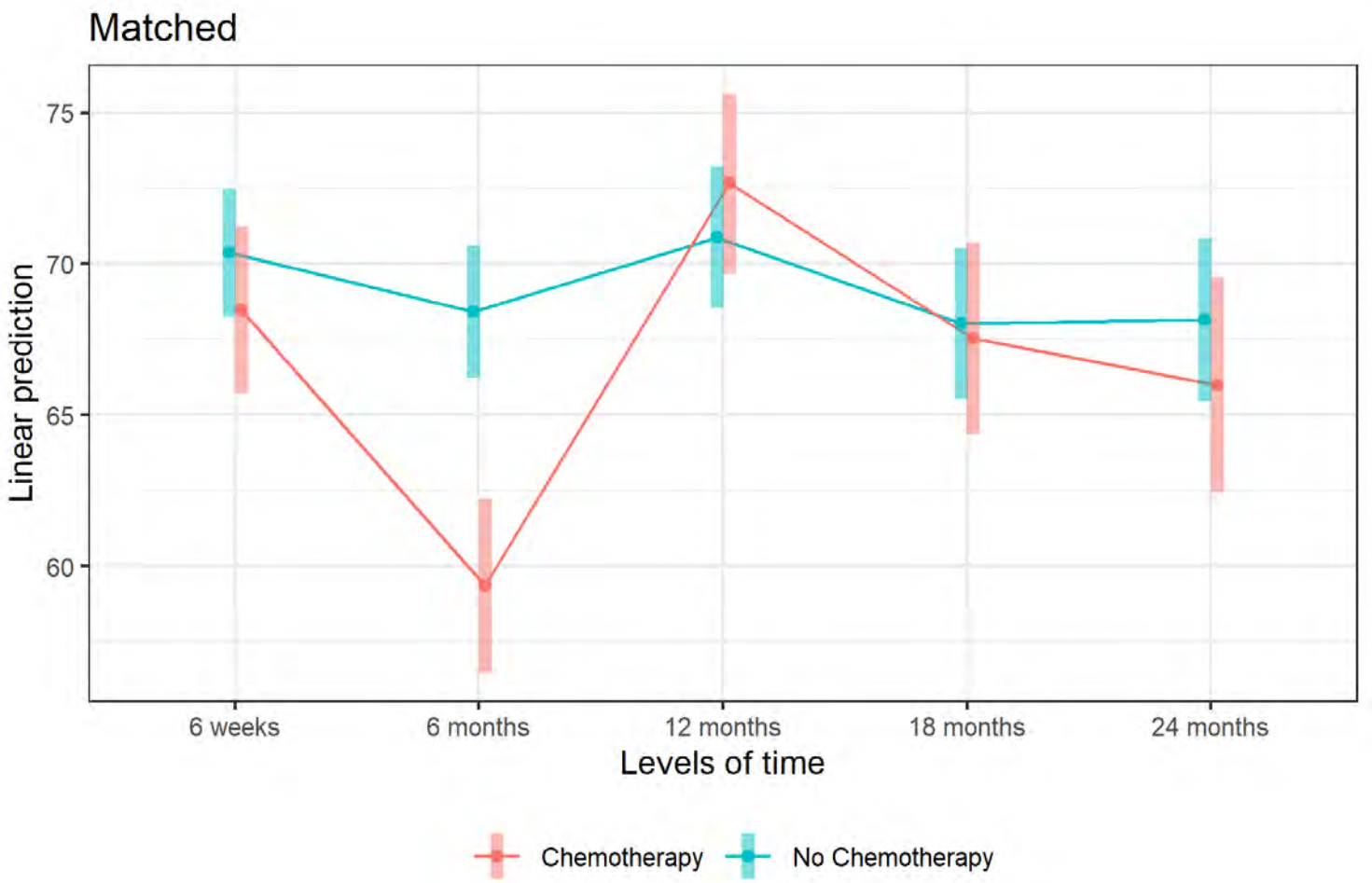


Figure 3.10 – Mean (95% confidence interval) EORC-QLQ-C30 global health status scores over time points for the chemotherapy versus no chemotherapy population by age group.

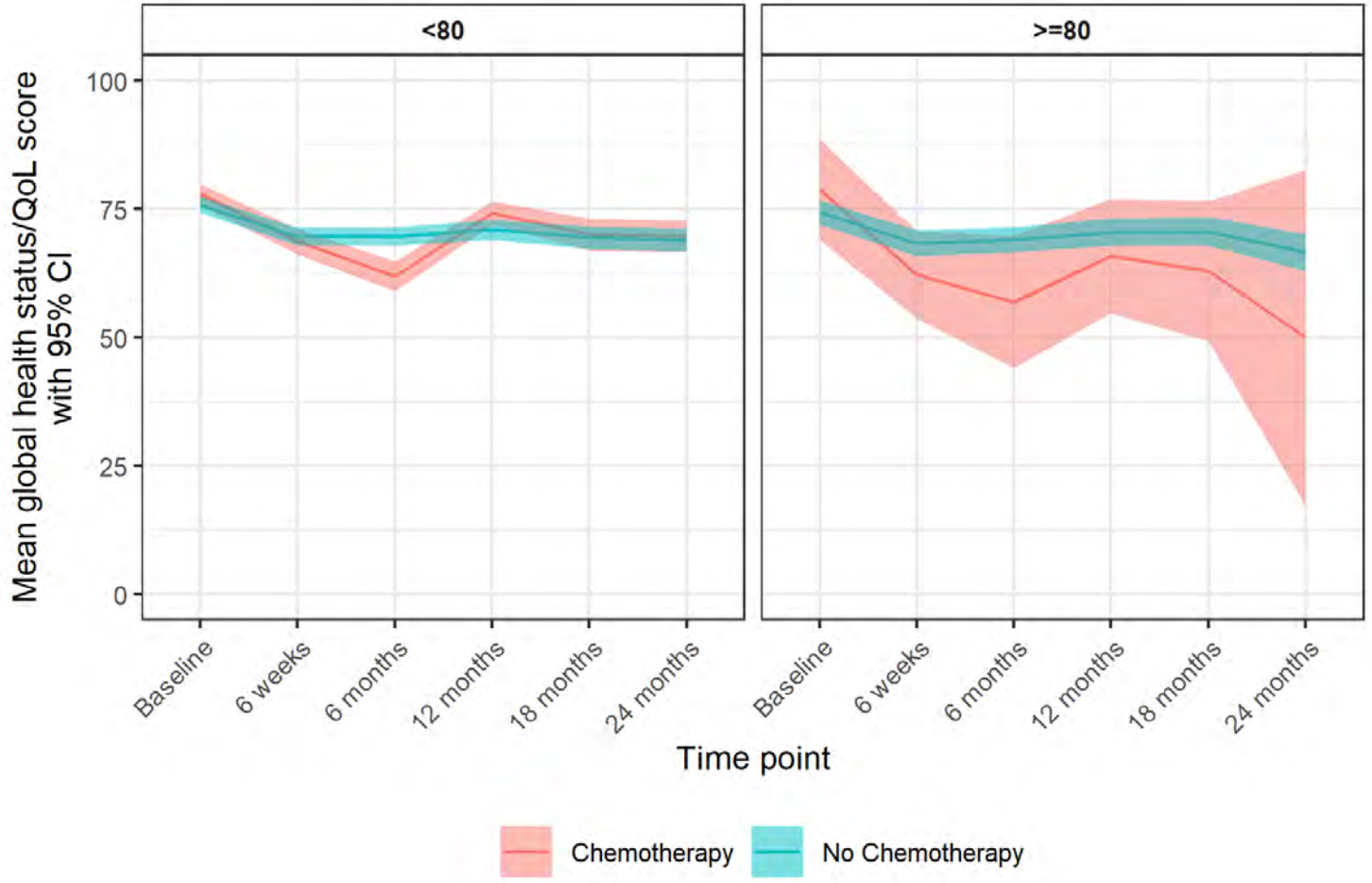


Figure 3.11 – Mean (95% confidence interval) scores over time points for the chemotherapy versus no chemotherapy population measured on the EORTC-QLQ-B23 scale.

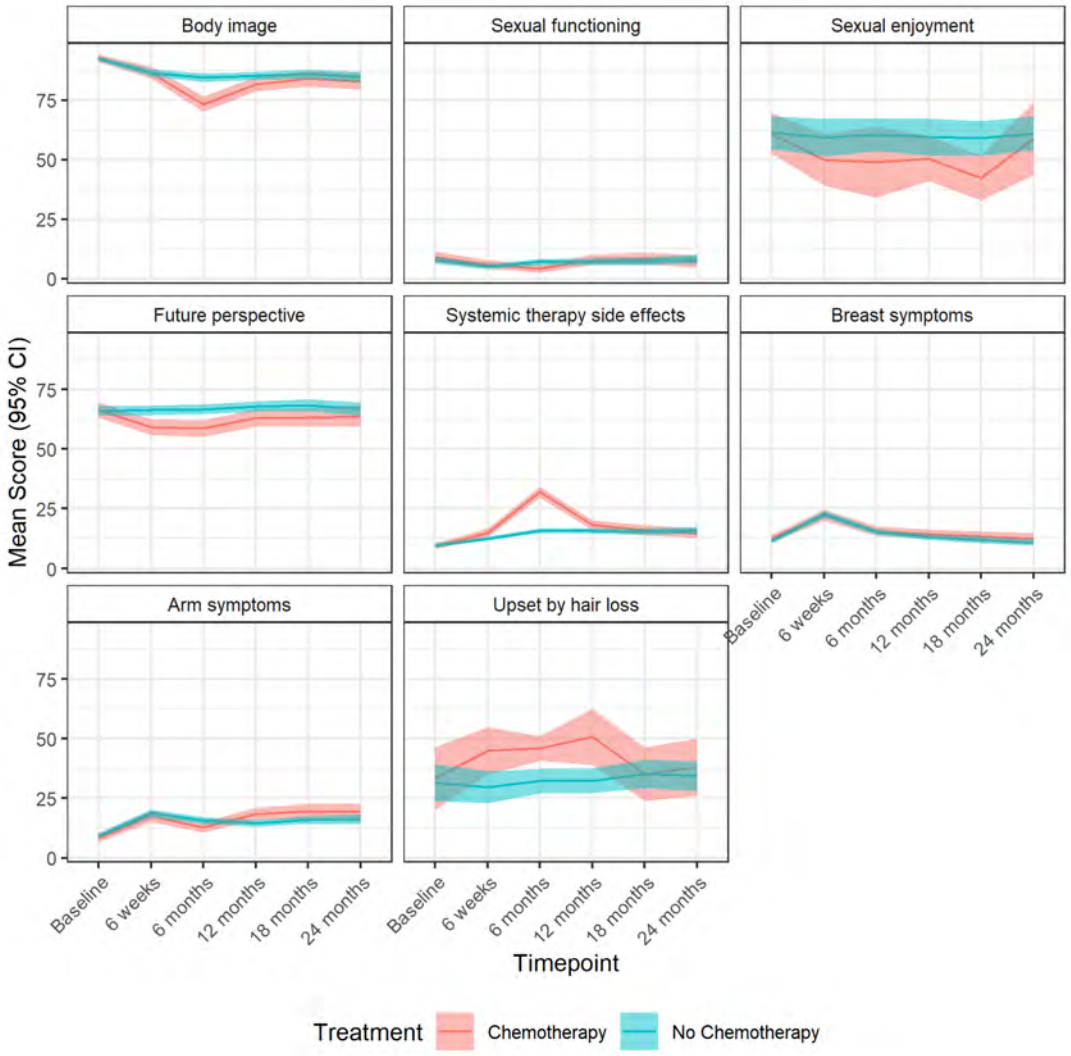


Figure 3.12 – Mean (95% confidence interval) scores over time points for the chemotherapy versus no chemotherapy population measured on the EORTC-QLQ-ELD15 scale.

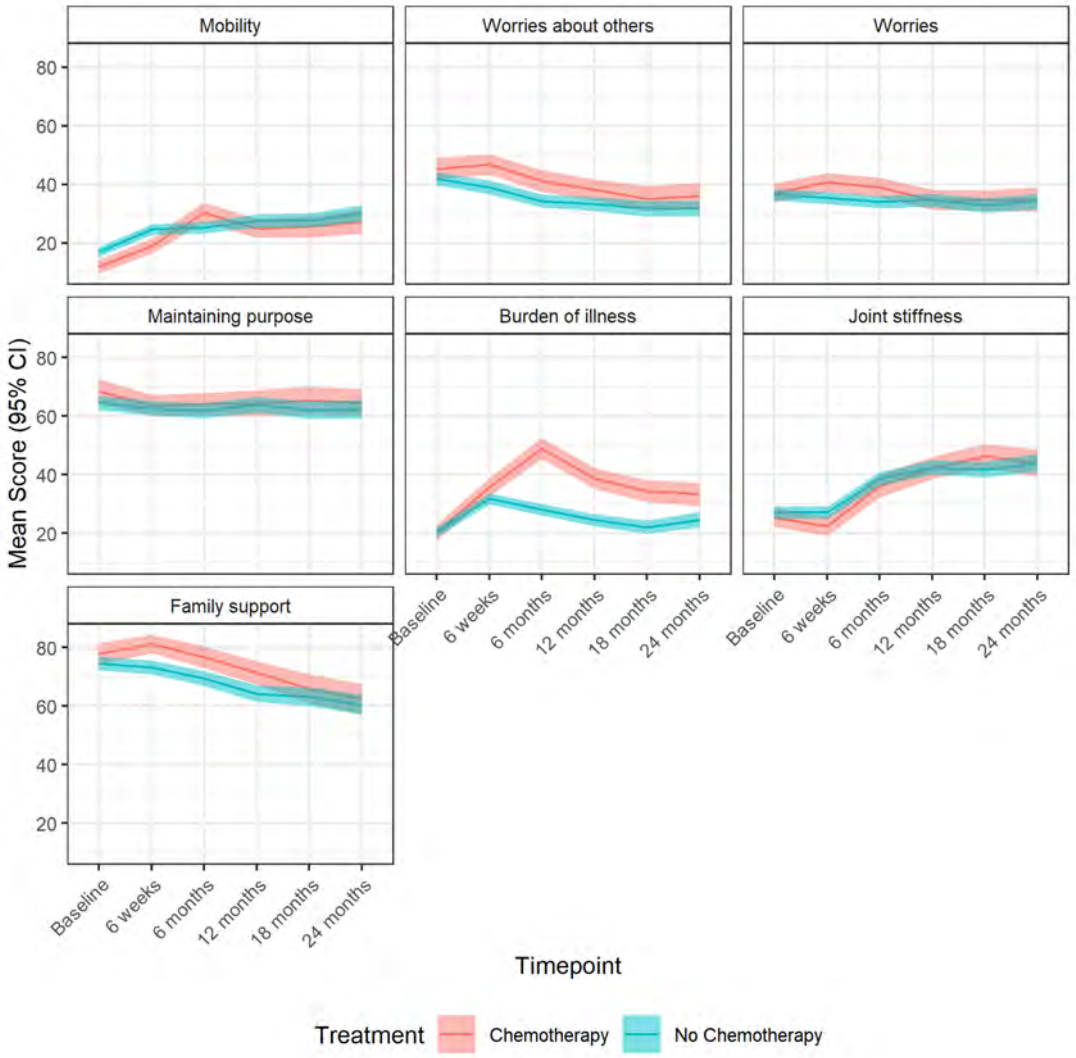
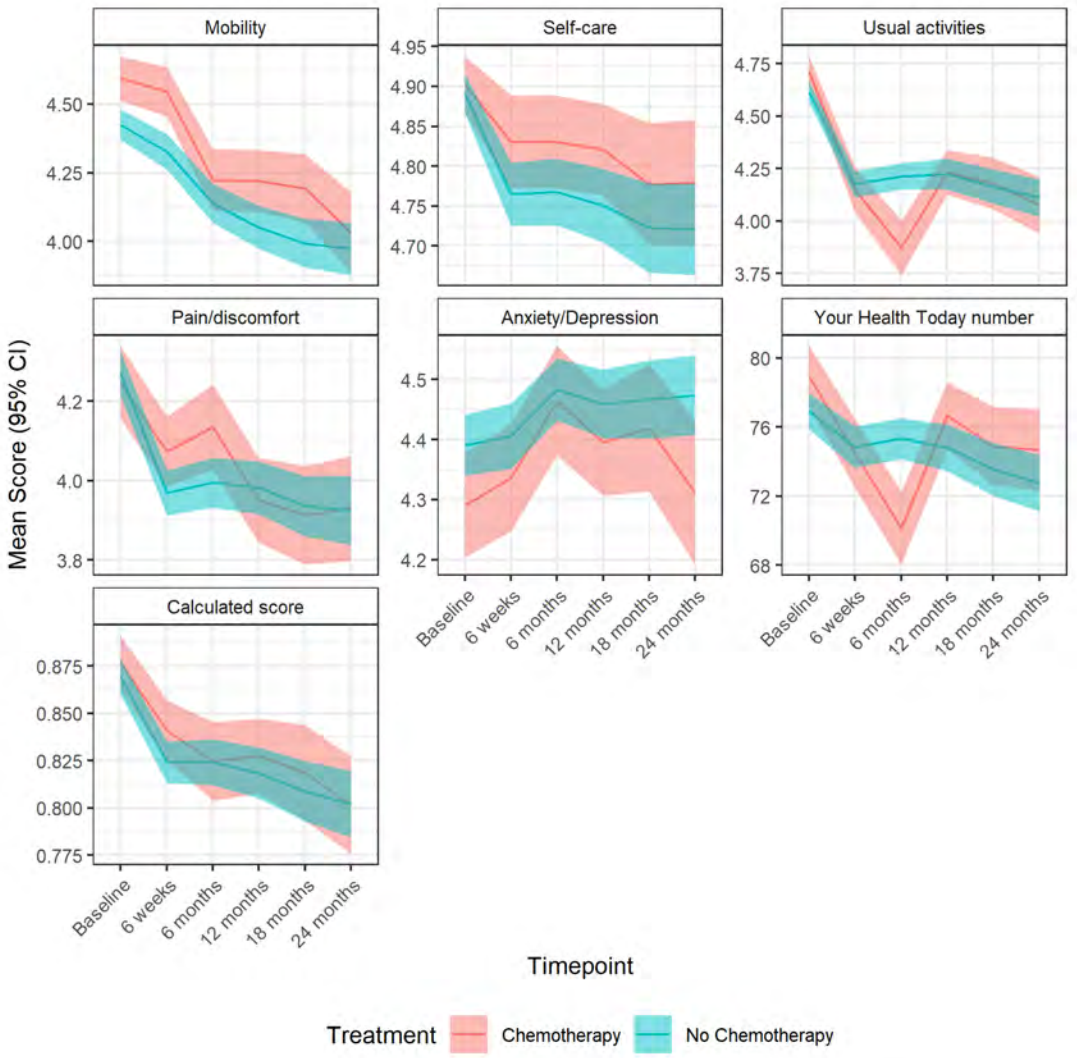
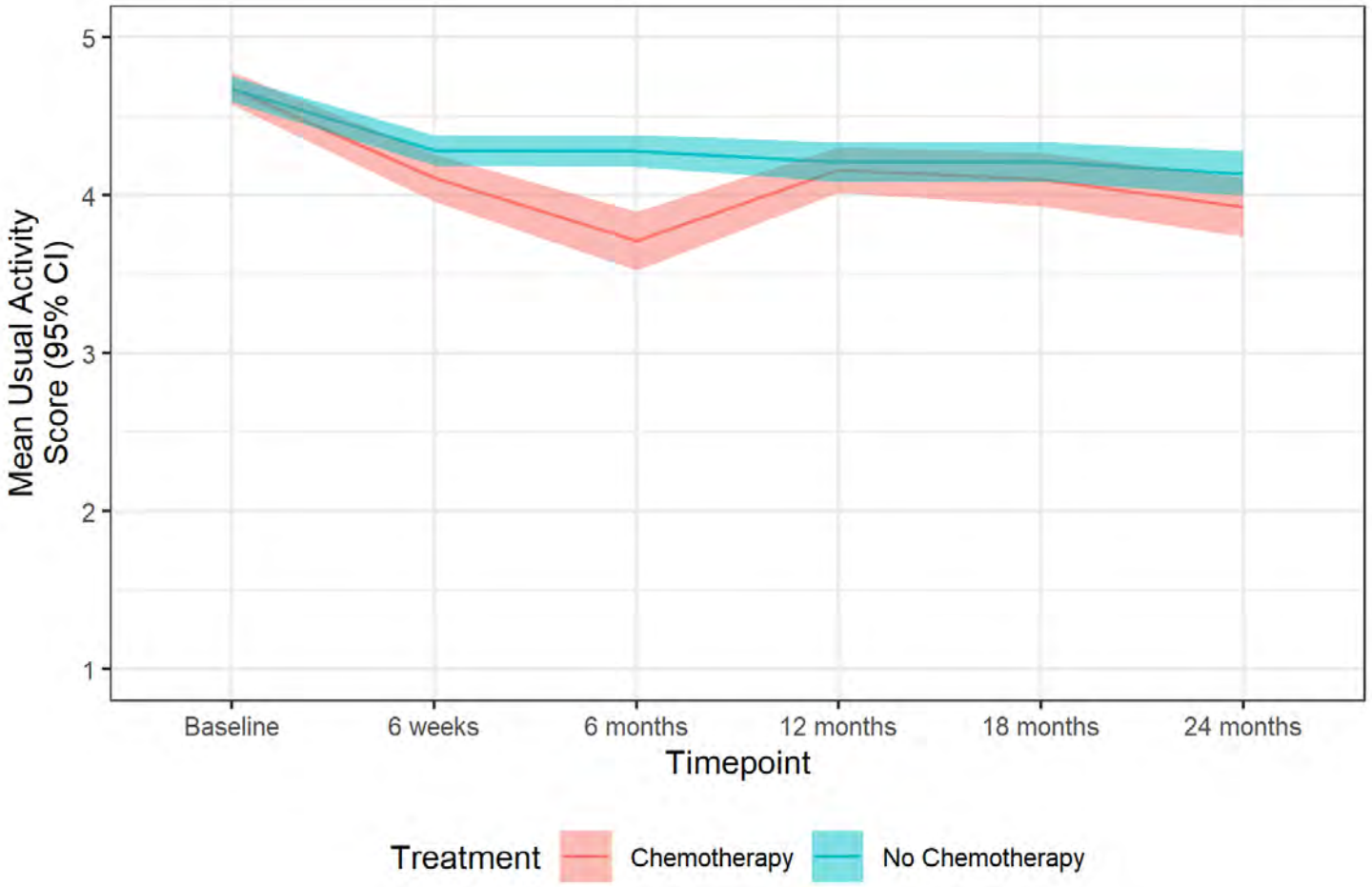


Figure 3.13 – Mean (95% confidence interval) scores over time points for the chemotherapy versus no chemotherapy population measured on the EQ-5D-5L scale.[9]



[9] The calculated score is a single summary number (index value) which reflects the health state in the context of the preferences of the general population of a country/region and is derived by applying a formula attaching weights to each of the levels in each dimension as per the EQ-5D-5L User Guide.

Figure 3.14 – Mean (95% confidence interval) EQ-5D-5L usual activities score over time points for the matched chemotherapy vs no chemotherapy population.



CHAPTER 4. OBSERVATIONAL COHORT STUDY IN OLDER WOMEN WITH EARLY BREAST CANCER: USE OF RADIATION THERAPY AND IMPACT ON HEALTH-RELATED QUALITY OF LIFE AND MORTALITY

4.1. ABSTRACT

Radiotherapy reduces in-breast recurrence risk in early breast cancer (EBC) in older women. This benefit may be small and should be balanced against treatment effect and holistic patient assessment. This study described treatment patterns according to fitness and impact on health-related quality of life (QoL).

A multicentre, observational study of EBC patients aged ≥70 years, undergoing breast-conserving surgery (BCS) or mastectomy, was undertaken. Associations between radiotherapy use, surgery, clinico-pathological parameters, fitness based on geriatric parameters and treatment centre were determined. QoL was measured using the European Organisation for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaires (QLQs).

In 2013-2018 2,811 women in 56 UK study centres underwent surgery with a median follow-up of 52 months. On multivariable analysis, age and tumour risk predicted radiotherapy use. Among healthier patients (based on geriatric assessments) with high-risk tumours, 534/613 (87.1%) having BCS and 185/341 (54.2%) having mastectomy received radiotherapy. In less fit individuals with low-risk tumours undergoing BCS, 149/207 (72.0%) received radiotherapy. Radiotherapy effects on QoL domains, including breast symptoms and fatigue were seen, resolving by 18 months.

Radiotherapy use in EBC patients ≥70 years is affected by age and recurrence risk, whereas geriatric parameters have limited impact regardless of type of surgery. There was geographical variation in treatment, with some fit older women with high-risk tumours not receiving radiotherapy, and some older, low-risk, EBC patients receiving radiotherapy after BCS despite evidence of limited benefit. The impact on QoL is transient.

4.2. INTRODUCTION

Half of breast cancer cases are diagnosed ≥65 years.[1] Nonetheless, outcomes are worse in older individuals[2, 3] who are underrepresented in trials.[4-6] In older patients outcomes may be influenced by competing risks, late presentation, and treatment variation:[7, 8] frailty data are crucial to aid decision-making.

Whole-breast radiotherapy is routinely used following breast-conserving surgery (BCS) to reduce the risk of locoregional recurrence and breast cancer death. These benefits were demonstrated by a meta-analysis performed by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), which included 10,801 women (with either pathologically node-negative or positive disease) recruited in 17 trials.[9] The meta-analysis showed a nearly 50% reduction in the 10-year risk of any first recurrence compared with BCS alone (19% versus 35%, respectively; relative risk [RR] 0.52, 95% CI 0.48-0.56) and a reduction in the 15-year risk of breast cancer death (21% versus 25%; RR 0.82, 95% CI 0.75-0.90). The reduction in recurrence rate associated with radiotherapy was due to a decrease in locoregional rather than distant recurrences.

Radiotherapy may also be offered after a mastectomy in individuals with a higher risk of recurrence as determined by nodal involvement, T4 disease, positive margins with other poor prognostic features (e.g., age ≤50 years, T2 or higher primary lesions, triple-negative histology, high grade, or lymphovascular invasion) and T2 and T3 disease with other poor prognostic features (e.g., age ≤50 years, triple-negative histology, high grade, or lymphovascular invasion). The benefits of post-mastectomy radiotherapy (PMRT) have been consistently reported in a number of studies.[10-12] An EBCTCG meta-analysis including 8,500 patients with mastectomy, axillary dissection, and node-positive disease enrolled in trials of radiotherapy (generally to the chest wall and regional lymph nodes) versus no radiotherapy documented better breast cancer-specific survival (60.1% versus 54.7% with no radiotherapy) and reduced local recurrence at 15 years (7.8% versus

29.2% with no radiotherapy) in this specific cohort.[10] In patients with less than 4 involved lymph nodes, data in support of PMRT come from a 2014 EBCTCG meta-analysis included 1,314 women with 1 to 3 involved lymph nodes undergoing mastectomy and axillary dissection:[13] this meta-analysis demonstrated that radiotherapy to the chest wall and regional nodes reduced locoregional recurrence (3.8% versus 20.3%; RR 0.24, 95% CI 0.17-0.34), overall recurrence (34.2% versus 45.7%; RR 0.68, 95% CI 0.57-0.82), and breast cancer mortality (42.3% versus 50.2% percent; RR 0.80, 95% CI 0.67-0.95). The Danish Breast Cancer Cooperative Group 82 b and c trials showed a disease-free and overall survival benefit with PMRT in patients with node-negative tumours larger than 5 cm or invading the skin or fascia.[14, 15] Higher recurrence rates have been observed in patients with age ≤50 years, T2 tumour size, and grade III disease not receiving PMRT.[16] Similarly, better 5-year relapse-free survival (88% versus 75%) and overall survival (90% versus 79%) were observed in patients with triple-negative disease receiving PMRT versus those not receiving it in a randomized study including 681 women (82% with node-negative tumours).[17]

Radiotherapy is generally well tolerated in older women after BCS or mastectomy, although it may cause inconvenience.[18] Local recurrence rates after BCS are lower in older patients although radiotherapy benefits decline with age.[19, 20]

The Cancer and Leukaemia Group B (CALGB) 9343 and PRIME II trials showed that omitting radiotherapy following BCS in older women with small, node-negative, oestrogen receptor (ER)-positive tumours is associated with higher loco-regional recurrence risk but no survival disadvantage.[21-24] In the CALGB 9343 study, at 10 years 90% of patients receiving tamoxifen alone (95% CI 85%-93%) were free from locoregional recurrence compared with 98% of those receiving tamoxifen plus radiotherapy (95% CI 96%-99%), while there were no differences in 5-year rates of overall survival (hazard ratio [HR] 0.5, 95% CI 0.77-1.18).[21, 22] In the PRIME II study, after a median follow-up of 5 years, ipsilateral breast cancer recurrence was 1.3% (95% CI 0.2-0.3) in patients receiving whole breast radiotherapy and 4.1% (95% CI 2.4-5.7) in

those not receiving it with a HR of 5.19 (95% CI 1.99-13.52, p=0.0007), while overall survival at 5 years was 93.9% (95% CI 91.8%-96.0%) in both groups.[23] The EBCTCG meta-analysis found that whole breast radiotherapy reduced the 10-year absolute local recurrence risk and 15-year mortality, although the annual recurrence probability without radiotherapy inversely correlated with age.[9] However, survival effects may be less pronounced in older frail patients. Radiotherapy omission may be appropriate in frail older women. Conversely, there is a risk of undertreating fit older patients at higher risk of recurrence and longer life expectancy.

As previously described, the Bridging The Age Gap study recruited older women with breast cancer and included baseline geriatric assessments.[25-28] This analysis describes patients' characteristics undergoing radiotherapy and investigates the factors associated with radiotherapy use and impacts on health-related quality of life (QoL). The study methods are presented in Chapter 2.

The Bridging the Age Gap study had completed recruitment by the time of registration of my research degree. Within this study, I have been responsible for the cleaning of the study database, the statistical analysis in conjunction with the trial statistician and the formulation of specific research questions to be investigated in the study cohort.

4.3. RESULTS

Between January 2013 and June 2018, 3,456 women were recruited in 56 centres in England and Wales (Supplementary table 2.1). This analysis included 2,811 women undergoing surgery within 6 months of diagnosis (Figure 4.1).[29] Of these, 397 (14.1%) received chemotherapy. Overall, 2,239/2,354 (95.1%) ER-positive patients received endocrine therapy. Surgery was BCS in 1,669 patients and mastectomy in 1,087 patients (Table 4.1 and 4.2). Detailed tumour, patient and treatment characteristics are reported in Supplementary tables 4.1, 4.2 and 4.3.

4.3.1. Use of radiotherapy

Of the 1,669 patients undergoing BCS, 1,385 (83.0%) received radiotherapy within 12 months of surgery. Of 1,383 patients undergoing BCS where the radiotherapy volume was known, 1,372 (99.2%) received breast radiotherapy and 154 (11.2%) nodal radiotherapy (62 [4.5%] to axilla, 92 [6.7%] to supraclavicular fossa [SCF]). Internal mammary chain radiotherapy was not recorded. Of the 1,087 patients undergoing a mastectomy, 341 (31.4%) received radiotherapy within 12 months. Of those 338 patients undergoing a mastectomy where the radiotherapy volume was known, 247 (73.1%) received chest wall radiotherapy and 221 (65.4%) nodal radiotherapy (68 [20.1%] to axilla, 153 [45.3%] to SCF) (Supplementary table 4.4).

In the BCS cohort, younger patients with higher risk tumours (high grade, node positive) were more likely to receive radiotherapy (Table 4.3 and 4.4). In the mastectomy cohort, patients with larger tumours and higher nodal involvement were more likely to receive it.

In the BCS cohort, high-risk tumours were present in 820/1,669 patients (49.1%); of these, 709/820 (86.5%) received radiotherapy compared with 676/849 (79.6%) of patients with low-risk tumours (Table 4.5). Of those who were fit, 613 had high-risk tumours, and of these patients, 534/613 (87.1%)

received radiotherapy (Table 4.6). Of those 207 vulnerable individuals with low-risk tumours, 149/207 (72.0%) received radiotherapy.

In the mastectomy group, high-risk tumours were present in 479/1,087 patients (44.1%) and 255/479 (53.2%) received radiotherapy compared with 86/608 (14.1%) of patients with non-high-risk tumours (Table 4.7). Of those who were fit, 341 had high-risk tumours, and of these patients 185/341 (54.2%) received radiotherapy (Table 4.8).

Radiotherapy use varied from 17.6% to 90.9% between sites, although the number of patients recruited varied widely (Figure 4.2; Supplementary table 4.5).

4.3.2. Impact on quality of life

Among 2,811 patients undergoing surgery, the QoL analysis was restricted to 1,789/2,811 (63.6%) who did not receive chemotherapy and who consented to full participation. Of the patients included, 1,125/1,789 (62.9%) underwent BCS and 628/1,789 (35.1%) underwent a mastectomy. Out of those undergoing BCS, 927/1,125 (82.4%) received radiotherapy; out of those undergoing a mastectomy, 177/628 (28.2%) received radiotherapy. Supplementary table 4.6 and Figures 4.3-4.8 show QoL questionnaires completion rates. The impacts of radiotherapy on QoL are summarised in Figure 4.9.

4.3.2.1. Breast cancer-specific quality of life domains (EORTC QLQ-BR23)

Among those undergoing BCS, 1,042/1,125 patients (92.6%) completed some or all of the EORTC QLQ-BR23 questionnaire at baseline (Supplementary table 4.6). No significant effects were observed at 6 weeks (after surgery but before radiotherapy). Patients undergoing radiotherapy reported worse breast symptoms at 6 months compared with those not receiving it (mean difference 6.27, 95% CI 3.34 to 9.19, $p<0.001$) which persisted at 12 months (mean

difference 3.89, 95% CI 1.13 to 6.64, p=0.006) but not at 18 months or thereafter (Supplementary table 4.7; Figure 4.10).

Among those undergoing a mastectomy, 588/628 patients (93.6%) completed some or all of the EORTC QLQ-BR23 questionnaire at baseline (Supplementary table 4.6). No significant effects were seen at 6 weeks. At 6 months, a significant difference was observed in breast symptoms (5.52, 95% CI 2.67 to 8.37, p<0.001). At 12 months, the effect persisted in breast symptoms (7.12, 95% CI 4.07 to 10.17, p<0.001) and arm symptoms (6.34, 95% CI 2.99 to 9.70, p<0.001). No differences were found at 18 months; at 24 months these were observed in arm symptoms (6.19, 95% CI 1.21 to 11.17, p=0.015) (Supplementary table 4.7; Figure 4.11).

4.3.2.2. Overall quality of life (EORTC QLQ-C30)

1,004/1,125 patients (89.2%) undergoing BCS and 567/628 patients (90.3%) undergoing a mastectomy completed all questions included in the EORTC QLQ-C30 questionnaire at baseline (Supplementary table 4.6). In the BCS cohort the radiotherapy effect on global health status was statistically (but not clinically) significant at 12 months (adjusted mean difference 3.19, 95% CI -0.08 to -6.29, p=0.044) but not afterwards (Supplementary tables 4.8 and 4.9; Figure 4.12).

Patients undergoing mastectomy and given radiotherapy experienced global health decline at 6 weeks (-3.18, 95% CI -6.32 to -0.04, p=0.047) which resolved subsequently (Supplementary tables 4.8 and 4.9; Figure 4.13). Radiotherapy impacted fatigue at 6 months (adjusted mean difference 4.45, 95% CI 0.77 to 8.14, p=0.018), 12 months (7.26, 95% CI 3.07 to 11.46, p=0.001), 18 months (5.44, 95% CI 0.64 to 10.23, p=0.026) and 24 months (6.56, 95% CI 1.76 to 11.37, p=0.008), although this effect was clinically significant only at 12 months. No other effects were observed.

4.3.2.3. Older age-specific quality of life (EORTC QLQ-ELD15)

1,002/1,125 patients (89.1%) undergoing BCS and 559/628 patients (89.0%) undergoing a mastectomy completed all EORTC QLQ-ELD15 questions at

baseline (Supplementary table 4.6). In the BCS cohort, no significant impact was observed at 6 weeks in patients receiving radiotherapy compared with those not receiving it (usually preceding radiotherapy). At 6 months, radiotherapy impacted on illness burden (5.49, 95% CI 1.33 to 9.64, p=0.010). At 12-18 months, no significant differences were observed; at 24 months, only on worries about others (-6.21, 95% CI -11.70 to -0.71, p=0.027) (Supplementary table 4.10; Figure 4.14).

In the mastectomy cohort, illness burden was impacted in patients receiving radiotherapy versus not at 6 weeks (5.54, 95% CI 0.84 to 10.24, p=0.021), 6 months (9.66, 95% CI 4.67 to 14.66, p<0.001), 12 months (5.70, 95% CI 0.34 to 11.06, p=0.037), 18 months (8.19, 95% CI 2.64 to 13.74, p=0.004) and 24 months (8.34, 95% CI 1.25 to 15.43, p=0.021) (Supplementary table 4.10; Figure 4.15).

4.3.2.4. Quality of life health utility score (EQ-5D-5L)

Baseline 5-level Euroqol-5D (EQ-5D-5L) version score was calculated in 1,060/1,125 patients undergoing BCS (94.2%) and in 593/628 patients (94.4%) undergoing mastectomy. No significant differences were observed in the BCS cohort (Supplementary table 4.11; Figure 4.16).

In the mastectomy cohort, radiotherapy impacted the visual analogue scale at 18 months (adjusted mean difference -0.04, 95% CI -0.07 to -0.01, p=0.029) and 24 months (-0.05, 95% CI -0.08 to -0.02, p=0.004) (Supplementary table 4.11; Figure 4.17).

Table 4.9 and 4.10 report adverse events.

4.3.3. Mortality

At a median of 52 months of follow-up, mortality data were available for 2,757/2,811 patients (98.1% of cohort) and cause of death for 2,738/2,811 (97.4% of cohort). Of 464/2,757 (16.8%) deaths due to all causes, 193/464 (41.6%) were due to breast cancer (Table 4.11).

In patients undergoing BCS, mortality data were available for 1,631/1,669 (97.7%) and death cause data for 1,624/1,669 (97.3%). Of those receiving radiotherapy with mortality data available, 149/1,354 (11.0%) died from any cause; among those receiving radiotherapy for whom a death cause was known, 51/1,348 (3.8%) died from breast cancer. For those not receiving radiotherapy with mortality data available, 48/277 (17.3%) died from any cause; among those receiving radiotherapy for whom a death cause was known, 9/276 (3.3%) died from breast cancer.

In patients undergoing a mastectomy, mortality data were available for 1,073/1,087 (98.7%) and cause of death data for 1,062/1,087 (97.7%). Of those receiving radiotherapy with mortality data available, 93/336 (27.7%) died from any cause; among those receiving radiotherapy for whom a death cause was known, 63/332 (19.0%) died from breast cancer. For those not receiving radiotherapy with mortality data available, 163/737 (22.1%) died from any cause; among those receiving radiotherapy for whom a death cause was known, 65/730 (8.9%) died from breast cancer.

4.4. DISCUSSION

This analysis is the largest prospective cohort study describing radiotherapy use patterns and its impact on QoL, adverse events and mortality in older EBC patients, which integrates both tumour characteristics and geriatric assessments data. Life expectancy is increasing in Western countries[30] and older patients may experience disease relapse within their lifetime. Recurrence has symptomatic, adverse psychological and cost implications even without influencing survival.[20] Therefore, ensuring that older patients are adequately treated is a priority. Nonetheless, radiotherapy use after BCS or mastectomy declines with age[31]. It is not known where this relates to age *per se*, or comorbidities, frailty, patient reluctance, or QoL impact.

Radiotherapy following BCS is standard-of-care for all EBC patients not at low risk. However, some older women may prefer to avoid adjuvant radiotherapy, particularly those with small (<2 cm), ER-positive breast cancer and no evidence of nodal disease who agree to take endocrine therapy. Large, randomized trials, such as the PRIME II study, have suggested that omission of radiotherapy in this subset is an acceptable strategy, assuming that endocrine therapy is administered.

The PRIME II study recruited 1,326 women aged ≥65 years undergoing BCS for EBC deemed low-risk based on the following characteristics: hormone receptor-positive, axillary node-negative, T1-T2 up to 3 cm at the longest dimension, and clear margins; grade 3 tumour histology or lymphovascular invasion (but not both). Trial participants were randomised to either whole-breast radiotherapy (40-50 Gy in 15-25 fractions) or no radiotherapy, with ipsilateral breast cancer recurrence as the primary endpoint. The rate of local recurrence after 10 years was significantly greater in patients who did not receive radiation therapy compared with patients who did (9.8% versus 0.9%),[24] similarly to findings previously documented at 5 years of follow-up.[23] Additionally, at 10 years patients who did not receive radiotherapy had similar rates of distant metastasis (1.4% versus 3.6%), recurrence in the opposite breast (1.0% versus 2.2%), and overall survival (80.4% versus

81.0%) as patients who did receive it. Therefore, guidelines support omitting radiotherapy in low-risk patients ≥70 years assuming that they remain on endocrine therapy. However, compliance cannot be guaranteed when radiotherapy is omitted[32] and the definition of recurrence risk differs among national[33] and international guidelines[34, 35] and might explain radiotherapy uptake variations.

Based on the PRIME II study findings, the PRIMETIME trial (ISRCTN41579286) is investigating the omission of radiotherapy after BCS in patients ≥60 years at very low risk of recurrence based on the following features: T1, N0, grade 1-2, ER and progesterone receptor (PR)-positive status and human epidermal growth factor receptor 2 (HER2)-negative status.[36] The trial design includes the IHC4+C algorithm to risk stratify patients into a very low risk group (allocated to avoidance of radiotherapy) or a low, intermediate or high risk group (allocated to standard radiotherapy), while patients are followed for 10 years. Within this study, endocrine therapy is given as per standard of care.

PMRT is indicated for patients at high risk for local recurrence. Frequent indications for the use of T in this setting include the involvement of axillary lymph nodes, the presence of T4 tumours, the presence of positive margins or selected cases of T2-3 disease along with other poor prognostic features (e.g., age ≤50 years, T2 or higher primary lesions, triple-negative histology, high grade or lymphovascular invasion). In women aged ≥70 years, the impact of adjuvant radiotherapy on the need for a subsequent mastectomy for disease recurrence is not clear, as data are conflicting. One study suggested that the rate of subsequent mastectomy was not significantly different with or without radiotherapy (4% versus 2%, respectively),[21] while in another study, adjuvant radiotherapy resulted in a lower risk (3% versus 6%).[37] Nonetheless, in both studies overall survival was similar, despite higher rates of locoregional failure. A meta-analysis did not document any differential benefit of PMRT on locoregional recurrence in patients ≥60 years.[13]. On the other hand, the SUPREMO study excluded patients defined as high-risk in this Bridging The Age Gap study analysis.[38]

Radiotherapy fractionation is also a key consideration in older adults with EBC. A hypofractionated schedule has been associated with equivalent tumour control and fewer toxicities, and is now preferred for many patients. The FAST FORWARD trial recruited 4,096 patients with T1-3 N0-1 M0 tumours after BCS or mastectomy and randomised them to either 40 Gy in 15 fractions (over 3 weeks), 27 Gy in five fractions (over 1 week), or 26 Gy in five fractions (over 1 week) to the whole breast or chest wall.[39] In this study, the 5-year incidence of ipsilateral breast tumour relapse was 2.1% with the standard 40 Gy in 15 fractions over three weeks versus 1.4% with 26 Gy in five fractions over one week (5.2 Gy per fraction) and 1.7% with 27 Gy in five fractions over one week (5.4 Gy per fraction). This trial showed not only that a hypofractionated regimen is non-inferior to standard fractionation, but also that this is as safe up to 5 years. Shorter fractionation may represent an attractive approach for older patients not requiring regional radiotherapy in the context of the reduced burden of associated procedures and appointments and the similar efficacy and safety profile compared with standard radiotherapy fractionation.

Accelerated partial-breast irradiation is considered for patients aged ≥50 years with small (≤2 cm), node-negative tumours and negative surgical margins. This approach offers a shorter course of treatment than whole breast radiotherapy (e.g., five days versus several weeks) and may have similar disease outcomes, particularly among those with low-risk disease. Trials have yielded differing results regarding acute and late toxicities for accelerated partial breast versus whole breast radiotherapy, although cosmesis seems to be more consistently better with the latter. For example, the IMPORT-LOW trial recruited 2,018 women aged ≥50 years undergoing BCS for unifocal, grade 1-3 T1-2 N0-1 invasive ductal carcinomas and minimum microscopic margins of non-cancerous tissue of 2 mm or more.[40] Patients were randomised to receive 40 Gy whole-breast radiotherapy in the control arm, 36 Gy whole-breast radiotherapy and 40 Gy to the partial breast in the reduced-dose group, or 40 Gy to the partial breast only in the partial-breast group in 15 daily treatment fractions. At 5 years, local relapse cumulative incidence was 1.1% in the control group, 0.2% in the reduced-dose group, and 0.5% in the partial-

breast group. Therefore, compared with a standard approach this study demonstrated non-inferior breast tumour recurrence on accelerated partial-breast irradiation, that may be more practical and attractive in the older age group.

In our analysis almost 13% of fit, high-risk patients undergoing BCS and more than 45% of fit, high-risk patients undergoing mastectomy did not receive radiotherapy. This may relate to patient, clinician and geographical factors. Recently 5 radiotherapy fractions over one week were found non-inferior to the previous standard for local control in patients with pT1-3 N0-1 tumours after BCS or mastectomy.[39] This may facilitate compliance with radiotherapy schedules.

In low-risk older patients, there is a low additional ipsilateral recurrence risk and no survival or breast preservation benefits without radiotherapy.[21-23, 41] In the PRIME II study, at 10 years 93.4% of mortality was not due to BC,[24] despite the rate of ipsilateral breast recurrence (1.3% with radiotherapy versus 4.1% with no radiotherapy) observed also in this specific age group. In our analysis, in the BCS cohort only one third of mortality was due to BC and radiotherapy might be safely omitted in low-risk older patients with a shorter life expectancy.[42] In our study, despite 849/1669 patients (50.9%) having a low risk of recurrence after BCS (some of whom were vulnerable/frail), 82.1% received radiotherapy. This suggests a degree of over-treatment which reflects the lack of concordance between national and international guidelines for the omission of radiotherapy after BCS and underlines the importance of considering risk profile and health status in decision-making.

Previous trials did not include fitness data which may impact life expectancy and mitigate local recurrence benefits. This study overcomes these limitations, by defining risk of recurrence and fitness, and still demonstrates a low impact of fitness considerations on radiotherapy uptake. Some clinicians overestimate the benefits of radiotherapy[43] although this does not always correspond with patients' perceived risks, lack of benefit and

inconvenience.[44] Geriatric assessments are standard-of-care to evaluate fitness and guide anticancer treatment decisions in older adults with cancer based on international consensus.[45-47] This may also prove valuable for to radiotherapy decision-making and reduce treatment variation. Our findings demonstrate significant radiotherapy use variation as previously confirmed,[31, 48, 49] although caution is required in view of case-mix and geography bias.

This analysis demonstrates that radiotherapy has limited and temporary impact on toxicities and QoL, a meaningful endpoint due to the lack of survival benefits and increased toxicity risk on standard treatments in this population. The most significant impact occurred on breast symptoms, although this resolved by 18 months. Our findings are consistent with the PRIME study documenting no effect of radiotherapy on overall QoL in patients ≥65 years at low risk of recurrence after BCS[50] and with the SUPREMO trial showing an effect of PMRT on chest wall symptoms up to 2 years in patients undergoing a mastectomy.[51] The recent UK IMPORT LOW study demonstrated that partial breast radiotherapy could be employed with a reduction in breast effects and a non-inferior impact on local recurrence.[40]

This analysis also has some limitations. The study criteria to define high-risk EBC did not include data on lymphovascular invasion, which is considered for radiotherapy decision-making after a mastectomy and an eligibility criterion for the adjuvant radiotherapy trials.[16, 52] The definitions of recurrence risk, whilst based on published data and justifiable, would no doubt be debated between clinicians. Similarly, the definitions of fitness could be challenged. Nonetheless, there are no universally agreed definitions in the published literature, these definitions were predefined and have been used consistently across our analyses.[26, 27] Despite broad eligibility criteria and a pragmatic design selection bias was possible due to clinician issues, staffing resources, patients' lack of interest and trial burden.[53] Missing data on longitudinal QoL assessments may have influenced our findings. The impact of endocrine therapy was not factored in the QoL analysis although this can be prolonged.[54] We could not investigate the impact of radiotherapy dose and

nodal radiotherapy on QoL as those data were not routinely collected within the study and only 13.7% of patients received it to the regional nodes. Our findings may not be applicable to other countries, although previous data appear comparable.[55] Some statistically significant effects of radiotherapy on QoL might not be clinically relevant, whereas small effects may still substantially influence patients' perceived well-being. Finally, we have not evaluated the impact of radiotherapy on ipsilateral recurrence risk as data on relapse laterality were not captured.

Our study has some important implications. Geriatric impairments have a significant impact on the prognosis and survival outcomes for older adults with cancer.[47] Yet, in this analysis overall health was not found to influence radiotherapy use. Since the life expectancy of older patients with cancer and geriatric impairments may be more limited, they may not experience a breast cancer recurrence in their lifespan and therefore not benefit from receipt of radiotherapy after the surgery. Similarly, fit, older individuals may be at increased risk of experiencing a breast cancer recurrence in the context of a more prolonged life expectancy. Therefore, they may be better placed to benefit from the addition of postoperative radiotherapy. Hence, geriatric assessments are a crucial consideration to mitigate the risk of over- and under-treatment also in radiotherapy decision-making to better inform treatment recommendations and discussions with patients. This analysis also highlights the effect of radiotherapy availability on the variation in its uptake across England for this specific age group. This aspect is critical to better inform the provision of radiotherapy services at national level and to reduce anticancer treatment disparities for older adults with curable breast cancer. For individual patients, this study confirms the findings of the PRIME II study and the safety of omitting radiotherapy for older patients with lower risk tumours treated in the real world. Moreover, this study provides reassurance on the absence of detrimental impact of radiotherapy on QoL, which is a key endpoint for older individuals with cancer.

More research is warranted on the impact of radiotherapy on functional outcomes and cardiac toxicity in older patients with EBC, for whom treatment

tolerability and independence are key endpoints. More broadly, the integration of geriatric assessments to improve the definition of overall health along with tumour-specific considerations (including biomarkers) is a key direction for future research in this field. Several trials are investigating the role of biomarkers to select patients at low recurrence risk who may be spared radiotherapy, such as PRIMETIME (ISRCTN41579286),[36] PRECISION (NCT02653755), LUMINA (NCT01791829), NATURAL (NCT03646955) and EUROPA (NCT04134598) and will be highly relevant to older patients with EBC. Nonetheless, none of these studies include objective measures of fitness that may still have a significant impact on potential treatment benefits. Therefore, the integration of geriatric assessments in radiotherapy trial design remains a key unmet need in clinical research but it should still guide routine clinical practice and discussions with patients.

In summary, this study demonstrates that fitness is not a major determinant of radiotherapy decisions for older EBC patients undergoing BCS or mastectomy and a significant number of vulnerable older women with both high-risk and low-risk EBC receive adjuvant radiotherapy. Some may derive little benefit from radiotherapy. There was also a low PMRT rate of in women at high-risk suggesting some under-treatment. Potential risks and benefits require discussion in view of the toxicity risk and the transient negative impact on breast symptoms. Nonetheless, individualised treatment decisions and discussions should be made to ensure the best outcomes. These findings argue for the routine measurement of fitness in older patients to be included in radiotherapy practice guidelines for older patients with operable breast cancer.

4.5. PROGRESS TO PRESENTATION AND PUBLICATION

This analysis was conducted on behalf of the Bridging The Age Gap study steering group, with specific contribution by statisticians Esther Herbert and Mike Bradburn and by Professor Lynda Wyld (University of Sheffield). I have published this study manuscript in Radiotherapy and Oncology (impact factor 6.28) as first author.[56]

4.6. REFERENCES

1. Ferlay, J., et al., Global Cancer Observatory: Cancer Today. 2018: Lyon, France.
2. Statistics, O.f.N., Cancer survival in England: Patients diagnosed between 2010 and 2014 and followed up to 2015. 2016: Newport, UK.
3. Moller, H., G. Flatt, and A. Moran, High cancer mortality rates in the elderly in the UK. Cancer Epidemiol, 2011. 35(5): p. 407-12.
4. Hutchins, L.F., et al., Underrepresentation of patients 65 years of age or older in cancer-treatment trials. N Engl J Med, 1999. 341(27): p. 2061-7.
5. Al-Refaie, W.B., et al., Cancer trials versus the real world in the United States. Ann Surg, 2011. 254(3): p. 438-42; discussion 442-3.
6. Sedrak, M.S., et al., Older adult participation in cancer clinical trials: A systematic review of barriers and interventions. CA: A Cancer Journal for Clinicians. n/a(n/a).
7. Battisti, N.M.L., et al., Is age a barrier to chemotherapy? Rates of treatment in older patients treated with breast, colon and lung cancer in England in 2014: a national registry study. Annals of Oncology, 2018. 29: p. viii562-viii575.
8. Derks, M.G.M., et al., Variation in treatment and survival of older patients with non-metastatic breast cancer in five European countries: a population-based cohort study from the EURECCA Breast Cancer Group. Br J Cancer, 2018. 119(1): p. 121-129.
9. Darby, S., et al., Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet, 2011. 378(9804): p. 1707-16.
10. Clarke, M., et al., Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. 2005. 366: p. 2087-2106.
11. Ragaz, J., et al., Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of

the British Columbia randomized trial. J Natl Cancer Inst, 2005. 97(2): p. 116-26.

12. Nielsen, H.M., et al., Study of failure pattern among high-risk breast cancer patients with or without postmastectomy radiotherapy in addition to adjuvant systemic therapy: long-term results from the Danish Breast Cancer Cooperative Group DBCG 82 b and c randomized studies. J Clin Oncol, 2006. 24(15): p. 2268-75.
13. McGale, P., et al., Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet, 2014. 383(9935): p. 2127-35.
14. Overgaard, M., et al., Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. N Engl J Med, 1997. 337(14): p. 949-55.
15. Overgaard, M., et al., Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. Lancet, 1999. 353(9165): p. 1641-8.
16. Truong, P.T., et al., A positive margin is not always an indication for radiotherapy after mastectomy in early breast cancer. Int J Radiat Oncol Biol Phys, 2004. 58(3): p. 797-804.
17. Wang, J., et al., Adjuvant chemotherapy and radiotherapy in triple-negative breast carcinoma: a prospective randomized controlled multi-center trial. Radiother Oncol, 2011. 100(2): p. 200-4.
18. Cree, A., A. O'Donovan, and S. O'Hanlon, New horizons in radiotherapy for older people. Age and Ageing, 2019. 48(5): p. 605-612.
19. Veronesi, U., et al., Radiotherapy after breast-preserving surgery in women with localized cancer of the breast. N Engl J Med, 1993. 328(22): p. 1587-91.
20. Smith, B.D., et al., Effectiveness of radiation therapy for older women with early breast cancer. J Natl Cancer Inst, 2006. 98(10): p. 681-90.
21. Hughes, K.S., et al., Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer:

long-term follow-up of CALGB 9343. J Clin Oncol, 2013. 31(19): p. 2382-7.

22. Hughes, K.S., et al., Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer. 2004. 351: p. 971-977.
23. Kunkler, I.H., et al., Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. Lancet Oncol, 2015. 16(3): p. 266-73.
24. Kunkler, I.H., et al. PRIME 2 randomized trial (Postoperative Radiotherapy in Minimum-Risk Elderly): wide local excision and adjuvant hormonal therapy +/- whole breast irradiation in women ≥65 years with early invasive breast cancer: 10 year results [GS2-03]. in 2020 San Antonio Breast Cancer Symposium. 2020. Virtual.
25. Wyld, L., et al., Bridging the age gap in breast cancer. Impacts of omission of breast cancer surgery in older women with oestrogen receptor positive early breast cancer. A risk stratified analysis of survival outcomes and quality of life. Eur J Cancer, 2021. 142: p. 48-62.
26. Battisti, N.M.L., et al., Abstract P2-14-08: Use of systemic therapy for early stage breast cancer in older adults: Results from the Bridging the Age Gap study. Cancer Research, 2020. 80(4 Supplement): p. P2-14-08-P2-14-08.
27. Battisti, N.M.L., et al., Impact of chemotherapy for early stage breast cancer on quality of life in older adults: results from 2811 women enrolled in the Bridging the Age Gap study (#2586), in European Society for Medical Oncology (ESMO) Virtual Congress. 2020.
28. Morgan, J.L., et al., Observational cohort study to determine the degree and causes of variation in the rate of surgery or primary endocrine therapy in older women with operable breast cancer. Eur J Surg Oncol, 2020.
29. von Elm, E., et al., The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol, 2008. 61(4): p. 344-9.

30. World Population Aging. 2019, United Nations: Department of Economic and Social Affairs.
31. National Audit of Breast Cancer in Older Patients. 2020 Annual Report: Results of the prospective audit in England and Wales for women diagnosed between January 2014 and December 2018. 2020, NABCOP project team.
32. Postoperative radiotherapy for breast cancer: UK consensus statements. 2016, The Royal College of Radiologists: Faculty of Clinical Oncology.
33. (NICE), N.I.f.H.a.C.E., Early and locally advanced breast cancer: diagnosis and management. 2018.
34. Breast Cancer. Version 2.2021 (12/03/2021), in NCCN Clinical Practice Guidelines in Oncology. 2021, National Comprehensive Cancer Network.
35. Burstein, H.J., et al., Estimating the benefits of therapy for early-stage breast cancer: the St. Gallen International Consensus Guidelines for the primary therapy of early breast cancer 2019. Ann Oncol, 2019. 30(10): p. 1541-1557.
36. Kirwan, C.C., et al., It's PRIMETIME. Postoperative Avoidance of Radiotherapy: Biomarker Selection of Women at Very Low Risk of Local Recurrence. Clinical Oncology, 2016. 28(9): p. 594-596.
37. Albert, J.M., et al., Effectiveness of radiation for prevention of mastectomy in older breast cancer patients treated with conservative surgery. Cancer, 2012. 118(19): p. 4642-51.
38. Kunkler, I.H., et al., Elucidating the Role of Chest Wall Irradiation in ‘Intermediate-risk’ Breast Cancer: the MRC/EORTC SUPREMO Trial. Clinical Oncology, 2008. 20(1): p. 31-34.
39. Murray Brunt, A., et al., Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial. The Lancet, 2020. 395(10237): p. 1613-1626.
40. Coles, C.E., et al., Partial-breast radiotherapy after breast conservation surgery for patients with early breast cancer (UK IMPORT LOW trial):

5-year results from a multicentre, randomised, controlled, phase 3, non-inferiority trial. The Lancet, 2017. 390(10099): p. 1048-1060.

41. de Boer, A.Z., et al., Effectiveness of radiotherapy after breast-conserving surgery in older patients with T1-2N0 breast cancer. Breast Cancer Res Treat, 2019. 178(3): p. 637-645.
42. van de Water, W., et al., Breast-conserving surgery with or without radiotherapy in older breast patients with early stage breast cancer: a systematic review and meta-analysis. Ann Surg Oncol, 2014. 21(3): p. 786-94.
43. Shumway, D.A., et al., Surgeon and Radiation Oncologist Views on Omission of Adjuvant Radiotherapy for Older Women with Early-Stage Breast Cancer. Ann Surg Oncol, 2017. 24(12): p. 3518-3526.
44. Wang, T., et al., Patient Perspectives on Treatment Options for Older Women With Hormone Receptor-Positive Breast Cancer: A Qualitative Study. JAMA Netw Open, 2020. 3(9): p. e2017129.
45. Older Adult Oncology. Version 1.2020 (07/02/2020), in NCCN Clinical Practice Guidelines in Oncology. 2020, National Comprehensive Cancer Network.
46. Decoster, L., et al., Screening tools for multidimensional health problems warranting a geriatric assessment in older cancer patients: an update on SIOG recommendations†. Ann Oncol, 2015. 26(2): p. 288-300.
47. Wildiers, H., et al., International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. J Clin Oncol, 2014. 32(24): p. 2595-603.
48. McCormick, B., et al., Impact of Guideline Changes on Use or Omission of Radiation in the Elderly with Early Breast Cancer: Practice Patterns at National Comprehensive Cancer Network Institutions. Journal of the American College of Surgeons, 2014. 219(4): p. 796-802.
49. Chu, Q.D., et al., Impact of CALGB 9343 Trial and Sociodemographic Variation on Patterns of Adjuvant Radiation Therapy Practice for Elderly Women (≥70 Years) with Stage I, Estrogen Receptor-positive Breast Cancer: Analysis of the National Cancer Data Base. Anticancer Res, 2017. 37(10): p. 5585-5594.

50. Williams, L.J., et al., A randomised controlled trial of post-operative radiotherapy following breast-conserving surgery in a minimum-risk population. Quality of life at 5 years in the PRIME trial. 2011. 15: p. 12.
51. Velikova, G., et al., Quality of life after postmastectomy radiotherapy in patients with intermediate-risk breast cancer (SUPREMO): 2-year follow-up results of a randomised controlled trial. Lancet Oncol, 2018. 19(11): p. 1516-1529.
52. Smitt, M.C., et al., The importance of the lumpectomy surgical margin status in long-term results of breast conservation. Cancer, 1995. 76(2): p. 259-67.
53. Todd, A., et al., Age specific recruitment and retention to a large multicentre observational breast cancer trial in older women: The Age Gap Trial. Journal of Geriatric Oncology, 2020.
54. Ferreira, A.R., et al., Differential impact of endocrine therapy and chemotherapy on quality of life of breast cancer survivors: a prospective patient-reported outcomes analysis. Ann Oncol, 2019. 30(11): p. 1784-1795.
55. Bastiaannet, E., et al., Breast cancer in elderly compared to younger patients in the Netherlands: stage at diagnosis, treatment and survival in 127,805 unselected patients. Breast Cancer Res Treat, 2010. 124(3): p. 801-7.
56. Battisti, N.M.L., et al., Observational cohort study in older women with early breast cancer: Use of radiation therapy and impact on health-related quality of life and mortality. Radiother Oncol, 2021. 161: p. 166-176.

4.7. TABLES

Table 4.1 - Postoperative tumour, patient and treatment characteristics by surgery type.

Variables	Categories	BCS	Mastectomy	Unknown	Total
		N = 1,669	N = 1,087	N = 55	N = 2,811
Age (years)	70-74	813 (48.7%)	342 (31.5%)	18 (32.7%)	1,173 (41.7%)
	75-79	521 (31.2%)	356 (32.7%)	22 (40.0%)	899 (32.0%)
	80-84	243 (14.5%)	253 (23.3%)	10 (18.2%)	506 (18.0%)
	≥85	92 (5.6%)	136 (12.5%)	5 (9.1%)	233 (8.3%)
Tumour size (mm)	≤ 20	1,001 (60.0%)	278 (25.6%)	0 (0.0%)	1,279 (45.5%)
	21-50	641 (38.4%)	644 (59.2%)	0 (0.0%)	1,285 (45.7%)
	> 50	24 (1.4%)	163 (15.0%)	1 (1.8%)	188 (6.7%)
	Unknown	3 (0.2%)	2 (0.2%)	54 (98.2%)	59 (2.1%)
Nodal status	pN0	1,302 (78.0%)	610 (56.1%)	1 (1.8%)	1,913 (68.1%)
	pN1	302 (18.1%)	310 (28.5%)	0 (0.0%)	612 (21.8%)
	pN2	48 (2.9%)	99 (9.1%)	0 (0.0%)	147 (5.2%)
	pN3	13 (0.8%)	64 (5.9%)	0 (0.0%)	77 (2.7%)
	Unknown	4 (0.2%)	4 (0.4%)	54 (98.2%)	62 (2.2%)
Grade	1	306 (18.3%)	75 (6.9%)	0 (0.0%)	381 (13.6%)
	2	920 (55.1%)	565 (52.0%)	0 (0.0%)	1,485 (52.8%)
	3	427 (25.6%)	437 (40.2%)	1 (1.8%)	865 (30.8%)
	Unknown	16 (1.0%)	10 (0.9%)	54 (98.2%)	80 (2.8%)
ER status	Negative	167 (10.0%)	205 (18.9%)	0 (0.0%)	372 (13.2%)
	Positive	1,487 (89.1%)	866 (79.7%)	1 (1.8%)	2,354 (83.7%)
	Unknown	15 (0.9%)	16 (1.5%)	54 (98.2%)	85 (3.0%)
HER2 status	Negative	1,424 (85.3%)	847 (77.9%)	1 (1.8%)	2,272 (80.8%)

Variables	Categories	BCS	Mastectomy	Unknown	Total
		N = 1,669	N = 1,087	N = 55	N = 2,811
	Positive	146 (8.7%)	186 (17.1%)	0 (0.0%)	332 (11.8%)
	Inconclusive	16 (1.0%)	6 (0.6%)	0 (0.0%)	22 (0.8%)
	Unknown	83 (5.0%)	48 (4.4%)	54 (98.2%)	185 (6.6%)
ADL category	No dependency	1,203 (72.1%)	759 (69.8%)	42 (76.4%)	2,004 (71.3%)
	Mild dependency	184 (11.0%)	122 (11.2%)	2 (3.6%)	308 (11.0%)
	Moderate/severe dependency	152 (9.1%)	123 (11.3%)	3 (5.5%)	278 (9.9%)
	Unknown	130 (7.8%)	83 (7.6%)	8 (14.5%)	221 (7.9%)
IADL category	No dependency	1,269 (76.0%)	767 (70.6%)	33 (60.0%)	2,069 (73.6%)
	Mild dependency	134 (8.0%)	108 (9.9%)	7 (12.7%)	249 (8.9%)
	Moderate/severe dependency	128 (7.7%)	122 (11.2%)	8 (14.5%)	258 (9.2%)
	Unknown	138 (8.3%)	90 (8.3%)	7 (12.7%)	235 (8.4%)
MMSE category	Normal function	1,498 (89.8%)	945 (86.9%)	51 (92.7%)	2,494 (88.7%)
	Mild impairment	135 (8.1%)	111 (10.2%)	2 (3.6%)	248 (8.8%)
	Moderate impairment	19 (1.1%)	16 (1.5%)	1 (1.8%)	36 (1.3%)
	Severe impairment	17 (1.0%)	15 (1.4%)	1 (1.8%)	33 (1.2%)
aPG-SGA category	Low	1,310 (78.5%)	834 (76.7%)	36 (65.5%)	2,180 (77.6%)
	Moderate	159 (9.5%)	122 (11.2%)	7 (12.7%)	288 (10.2%)
	High	27 (1.6%)	13 (1.2%)	0 (0.0%)	40 (1.4%)
	Unknown	173 (10.4%)	118 (10.9%)	12 (21.8%)	303 (10.8%)
ECOG PS	0	1,197 (71.7%)	717 (66.0%)	30 (54.5%)	1,944 (69.2%)
	1	332 (19.9%)	259 (23.8%)	16 (29.1%)	607 (21.6%)
	2	39 (2.3%)	38 (3.5%)	3 (5.5%)	80 (2.8%)
	3	15 (0.9%)	21 (1.9%)	0 (0.0%)	36 (1.3%)
	4	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)
	Unknown	86 (5.2%)	51 (4.7%)	6 (10.9%)	143 (5.1%)

Variables	Categories	BCS	Mastectomy	Unknown	Total
		N = 1,669	N = 1,087	N = 55	N = 2,811
Charlson comorbidity index (no age)	n	1,607	1,052	48	2,707
	Mean (SD)	1.00 (1.26)	1.05 (1.36)	1.58 (1.32)	1.03 (1.30)
	Median (IQR)	1.00 (0.00, 2.00)	0.00 (0.00, 2.00)	2.00 (1.00, 2.00)	1.00 (0.00, 2.00)
	Min, Max	0, 9	0, 9	0, 6	0, 9
Number of concurrent medications	n	1,447	961	38	2,446
	Mean (SD)	4.02 (2.63)	4.11 (2.66)	4.37 (2.55)	4.06 (2.64)
	Median (IQR)	4.00 (2.00, 6.00)	4.00 (2.00, 5.00)	4.00 (3.00, 5.75)	4.00 (2.00, 5.75)
	Min, Max	0, 15	0, 18	1, 13	0, 18
Axillary surgery	Axillary sampling	49 (2.9%)	37 (3.4%)	2 (3.6%)	88 (3.1%)
	Axillary clearance	113 (6.8%)	292 (26.9%)	9 (16.4%)	414 (14.7%)
	Sentinel lymph node biopsy	1329 (79.6%)	628 (57.8%)	23 (41.8%)	1,980 (70.4%)
	Internal mammary node biopsy	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)
	No axillary surgery	44 (2.6%)	34 (3.1%)	2 (3.6%)	80 (2.8%)
	Unknown	134 (8.0%)	95 (8.7%)	19 (34.5%)	248 (8.8%)
Chemotherapy use	Yes	186 (11.1%)	202 (18.6%)	9 (16.4%)	397 (14.1%)
	No	1,483 (88.9%)	885 (81.4%)	46 (83.6%)	2,414 (85.9%)
Radiotherapy use	Yes	1,385 (83.0%)	341 (31.4%)	27 (49.1%)	1,753 (62.4%)
	No	284 (17.0%)	746 (68.6%)	28 (50.9%)	1,058 (37.6%)

Abbreviations: ER: oestrogen receptor; HER2: human epidermal growth factor receptor; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ADL: activities of daily living; IADL: instrumental activities of daily living; aPG-SGA: abridged patient-generated subjective global assessment; MMSE: Mini Mental State Examination.

Table 4.2 – Postoperative tumour, patient and treatment characteristics by receipt of radiotherapy.

Variables	Categories	No radiotherapy	Radiotherapy	Total
		N = 1,058	N = 1,753	N = 2,811
Age (years)	70-74	374 (35.3%)	799 (45.6%)	1,173 (41.7%)
	75-79	318 (30.1%)	581 (33.1%)	899 (32.0%)
	80-84	225 (21.3%)	281 (16.1%)	506 (18.0%)
	≥85	141 (13.3%)	92 (5.2%)	233 (8.3%)
Tumour size (mm)	≤ 20	432 (40.8%)	847 (48.3%)	1,279 (45.5%)
	21-50	530 (50.1%)	755 (43.1%)	1,285 (45.7%)
	> 50	66 (6.2%)	122 (7.0%)	188 (6.7%)
	Unknown	30 (2.8%)	29 (1.7%)	59 (2.1%)
Nodal status	pN0	764 (72.2%)	1,149 (65.5%)	1,913 (68.1%)
	pN1	204 (19.3%)	408 (23.3%)	612 (21.8%)
	pN2	36 (3.4%)	111 (6.3%)	147 (5.2%)
	pN3	21 (2.0%)	56 (3.2%)	77 (2.7%)
	Unknown	33 (3.1%)	29 (1.7%)	62 (2.2%)
Grade	Grade 1	147 (13.9%)	234 (13.3%)	381 (13.6%)
	Grade 2	540 (51.0%)	945 (53.9%)	1,485 (52.8%)
	Grade 3	331 (31.3%)	534 (30.5%)	865 (30.8%)
	Unknown	40 (3.8%)	40 (2.3%)	80 (2.8%)
ER status	Negative	166 (15.7%)	206 (11.8%)	372 (13.2%)
	Positive	844 (79.8%)	1510 (86.1%)	2,354 (83.7%)
	Unknown	48 (4.5%)	37 (2.1%)	85 (3.0%)
HER2 status	Negative	816 (77.1%)	1,456 (83.1%)	2,272 (80.8%)
	Inconclusive	9 (0.9%)	13 (0.7%)	22 (0.8%)
	Positive	153 (14.5%)	179 (10.2%)	332 (11.8%)
	Unknown	80 (7.6%)	105 (6.0%)	185 (6.6%)

Variables	Categories	No radiotherapy	Radiotherapy	Total
		N = 1,058	N = 1,753	N = 2,811
ADL category	No dependency	729 (68.9%)	1,275 (72.7%)	2,004 (71.3%)
	Mild dependency	125 (11.8%)	183 (10.4%)	308 (11.0%)
	Moderate/severe dependency	120 (11.3%)	158 (9.0%)	278 (9.9%)
	Unknown	84 (7.9%)	137 (7.8%)	221 (7.9%)
IADL category	No dependency	739 (69.8%)	1,330 (75.9%)	2,069 (73.6%)
	Mild dependency	104 (9.8%)	145 (8.3%)	249 (8.9%)
	Moderate/severe dependency	126 (11.9%)	132 (7.5%)	258 (9.2%)
	Unknown	89 (8.4%)	146 (8.3%)	235 (8.4%)
MMSE category	Normal function	907 (85.7%)	1,587 (90.5%)	2,494 (88.7%)
	Mild impairment	112 (10.6%)	136 (7.8%)	248 (8.8%)
	Moderate impairment	15 (1.4%)	21 (1.2%)	36 (1.3%)
	Severe impairment	24 (2.3%)	9 (0.5%)	33 (1.2%)
aPG-SGA category	Low	805 (76.1%)	1,375 (78.4%)	2,180 (77.6%)
	Moderate	122 (11.5%)	166 (9.5%)	288 (10.2%)
	High	12 (1.1%)	28 (1.6%)	40 (1.4%)
	Unknown	119 (11.2%)	184 (10.5%)	303 (10.8%)
ECOG PS	0	675 (63.8%)	1,269 (72.4%)	1,944 (69.2%)
	1	270 (25.5%)	337 (19.2%)	607 (21.6%)
	2	42 (4.0%)	38 (2.2%)	80 (2.8%)
	3	18 (1.7%)	18 (1.0%)	36 (1.3%)
	4	1 (0.1%)	0 (0.0%)	1 (0.0%)
	Unknown	52 (4.9%)	91 (5.2%)	143 (5.1%)
Charlson comorbidity index (no age)	n	1,021	1,686	2,707
	Mean (SD)	1.06 (1.29)	1.02 (1.31)	1.03 (1.30)
	Median (IQR)	1.00 (0.00, 2.00)	0.00 (0.00, 2.00)	1.00 (0.00, 2.00)

Variables	Categories	No radiotherapy	Radiotherapy	Total
		N = 1,058	N = 1,753	N = 2,811
	Min, Max	0, 9	0, 9	0, 9
Number of concurrent medications	n	926	1,520	2,446
	Mean (SD)	4.12 (2.70)	4.03 (2.60)	4.06 (2.64)
	Median (IQR)	4.00 (2.00, 6.00)	4.00 (2.00, 5.00)	4.00 (2.00, 5.75)
	Min, Max	0, 18	0, 15	0, 18
Breast surgery	Breast-conserving surgery	284 (26.8%)	1,385 (79.1%)	1,669 (59.4%)
	Mastectomy	746 (70.5%)	341 (19.4%)	1,087 (38.7%)
	Unknown	28 (2.7%)	27 (1.5%)	55 (1.9%)
Axillary surgery	Axillary sample	32 (3.0%)	56 (3.2%)	88 (3.1%)
	Axillary clearance	166 (15.7%)	248 (14.1%)	414 (14.7%)
	Sentinel lymph node biopsy	724 (68.4%)	1,256 (71.6%)	1,980 (70.4%)
	Internal mammary node biopsy	0 (0.0%)	1 (0.1%)	1 (0.0%)
	No axillary surgery	55 (5.2%)	25 (1.4%)	80 (2.8%)
	Unknown	81 (7.7%)	167 (9.5%)	248 (8.8%)
Chemotherapy	Chemotherapy	146 (13.8%)	251 (14.3%)	397 (14.1%)
	No chemotherapy	912 (86.2%)	1,502 (85.7%)	2,414 (85.9%)

Abbreviations: ER: oestrogen receptor; HER2: human epidermal growth factor receptor; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ADL: activities of daily living; IADL: instrumental activities of daily living; aPG-SGA: abridged patient-generated subjective global assessment; MMSE: Mini Mental State Examination.

Table 4.3 – Relationship between radiotherapy use and patient characteristics: results for univariate logistic regression models.

Variable	Level	OR (95% CI)	P-value
BREAST-CONSERVING SURGERY COHORT			
Increasing age		0.94 (0.92, 0.97)	<0.001
Increasing ADL score		1.02 (1.00, 1.05)	0.07
Increasing IADL score		1.34 (1.17, 1.53)	<0.001
Increasing CCI (not age-adjusted)		0.93 (0.84, 1.03)	0.163
Increasing APG SGA score		0.94 (0.89, 1.00)	0.051
MMSE category	Normal function	-	-
	Mild impairment	0.64 (0.42, 0.99)	0.039
	Moderate impairment	0.72 (0.26, 2.53)	0.555
	Severe impairment	0.17 (0.06, 0.45)	<0.001
Tumour grade	Grade 1	-	-
	Grade 2	1.97 (1.44, 2.69)	<0.001
	Grade 3	2.49 (1.70, 3.66)	<0.001
ER-positive status		1.10 (0.71, 1.65)	0.657
HER2 status[1]	Negative	-	-
	Positive	0.87 (0.57, 1.38)	0.539
Nodal status[2]	pN0	-	-
	pN1	2.50 (1.66, 3.95)	<0.001
	pN2	0.86 (0.44, 1.84)	0.674
	pN3	0.26 (0.09, 0.83)	0.017
MASTECTOMY COHORT			
Increasing age		0.99 (0.97, 1.02)	0.519
Increasing ADL score		1.00 (0.98, 1.02)	0.906
Increasing IADL score		1.01 (0.90, 1.15)	0.831
Increasing CCI (not age-adjusted)		1.07 (0.97, 1.17)	0.184

Variable	Level	OR (95% CI)	P-value
Increasing APG SGA score		1.01 (0.93, 1.09)	0.8
MMSE category	Normal function	-	-
	Mild impairment	0.82 (0.52, 1.25)	0.364
	Moderate impairment	0.96 (0.30, 2.66)	0.938
	Severe	0.15 (0.01, 0.75)	0.068
Tumour grade	Grade 1	-	-
	Grade 2	3.08 (1.58, 6.75)	0.002
	Grade 3	4.24 (2.16, 9.33)	<0.001
ER-positive status		0.89 (0.64, 1.23)	0.472
HER2 status[1]	Negative	-	-
	Positive	1.04 (0.74, 1.46)	0.821
T stage	T1	-	-
	T2	3.38 (2.30, 5.08)	<0.001
	T3	11.39 (7.14, 18.58)	<0.001
Nodal status[2]	pN0	-	-
	pN1	4.46 (3.24, 6.16)	<0.001
	pN2	17.11 (10.48, 28.71)	<0.001
	pN3	19.90 (10.94, 38.21)	<0.001

[1] Tests marked as ‘Inconclusive’ were removed from this analysis.

[2] Those with nodal status pNx were removed from this analysis.

Table 4.4 – Relationship between radiotherapy use and patient characteristics: results for multivariable logistic regression models.

Variable	Level	OR (95% CI)	P-value
BREAST-CONSERVING SURGERY COHORT			
Increasing age		0.95 (0.92, 0.99)	0.008
Increasing IADL score		1.14 (0.93, 1.38)	0.208
Increasing APG SGA score		0.96 (0.90, 1.03)	0.212
Tumour grade	Grade 1	-	-
	Grade 2	1.87 (1.23, 2.83)	0.003
	Grade 3	3.68 (2.14, 6.46)	<0.001
MMSE category	Normal function	-	-
	Mild impairment	0.64 (0.37, 1.11)	0.103
	Moderate/severe impairment[1]	1.14 (0.34, 5.30)	0.851
Nodal status**	pN0	-	-
	pN1	2.55 (1.45, 4.87)	0.002
	pN2	0.90 (0.38, 2.50)	0.825
	pN3	1.03 (0.16, 20.43)	0.976
MASTECTOMY COHORT			
Tumour grade	Grade 1	-	-
	Grade 2	1.55 (0.74, 3.58)	0.269
	Grade 3	1.73 (0.82, 4.02)	0.172
T stage	T1	-	-
	T2	2.27 (1.47, 3.58)	<0.001
	T3	7.52 (4.42, 13.06)	<0.001
	pN0	-	-
	pN1	4.37 (3.12, 6.16)	<0.001

[1] Moderate and severe categories have been combined due to small numbers in the severe category.

Variable	Level	OR (95% CI)	P-value
Nodal status[2]	pN2	14.19 (8.48, 24.38)	<0.001
	pN3	14.22 (7.59, 27.98)	<0.001

[2] Those with nodal status pNx were removed from this analysis.

Table 4.5 – Use of radiotherapy after breast-conserving surgery by risk of recurrence and fitness.[1]

Risk	Radiotherapy	No radiotherapy	Total
Risk of recurrence			
Higher risk	709 (86.5%)	111 (13.5%)	820 (100.0%)
Lower risk	676 (79.6%)	173 (20.4%)	849 (100.0%)
Total	1,385 (14.1%)	284 (85.9%)	1,669 (100.0%)
Fitness			
Fit	1,061 (84.5%)	194 (15.4%)	1,255 (100.0%)
Vulnerable	323 (78.2%)	90 (21.8%)	413 (100.0%)
Frail	1 (100.0%)	0 (0.0%)	1 (100.0%)
Total	1,385 (83.0%)	284 (17.0%)	1,669 (100.0%)

Table 4.6 – Use of radiotherapy after breast-conserving surgery by combined risk of recurrence and fitness.[1]

Fitness	Higher risk		Lower risk		Total
	Radiotherapy	No radiotherapy	Radiotherapy	No radiotherapy	
Fit	534 (42.55%)	79 (6.29%)	527 (41.99%)	115 (9.16%)	1,255 (100.00%)
Vulnerable	174 (42.1%)	32 (7.7%)	149 (36.1%)	58 (14.0%)	413 (100.0%)
Frail	1 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100%)
Total	709 (42.5%)	111 (6.7%)	676 (40.5%)	173 (10.4%)	1,669 (100.0%)

[1] Risk of recurrence and fitness defined as shown in Table 4.2 and Table 2.3.

Table 4.7 - Use of radiotherapy after mastectomy by risk of recurrence and fitness.[1]

Risk	Radiotherapy	No radiotherapy	Total
Risk of recurrence			
Higher risk	255 (53.2%)	224 (46.8%)	479 (100.0%)
Lower risk	86 (14.1%)	522 (85.9%)	608 (100.0%)
Total	341 (31.4%)	746 (68.6%)	1,087 (100.0%)
Fitness			
Fit	242 (31.6%)	524 (68.4%)	766 (100.0%)
Vulnerable	98 (30.6%)	222 (69.4%)	320 (100.0%)
Frail	1 (100.0%)	0 (0.0%)	1 (100.0%)
Total	341 (31.4%)	746 (68.6%)	1,087 (100.0%)

Table 4.8 - Use of radiotherapy after mastectomy by combined risk of recurrence and fitness.[1]

Fitness	Higher risk		Lower risk		Total
	Radiotherapy	No Radiotherapy	Radiotherapy	No Radiotherapy	
Fit	185 (24.2%)	156 (20.4%)	57 (7.4%)	368 (48.0%)	766 (100.0%)
Vulnerable	70 (21.88%)	68 (21.25%)	28 (8.75%)	154 (48.12%)	320 (100.00%)
Frail	0 (0.0%)	0 (0.0%)	1 (100%)	0 (0.0%)	1 (100%)
Total	255 (23.5%)	224 (20.6%)	86 (7.9%)	522 (48.0%)	1,087 (100.0%)

[1] Risk of recurrence and fitness defined as shown in Table 4.2 and Table 2.3.

Table 4.9 – Radiotherapy adverse events for patients receiving radiotherapy after breast-conserving surgery.

Adverse events	Events	Individuals
	N = 1,385	N = 1,385
Any adverse event	629	620 (44.8%)
Skin erythema	532	526 (38.0%)
Pain	218	216 (15.6%)
Breast oedema	77	76 (5.5%)
Breast shrinkage	13	13 (0.9%)

Table 4.10 – Radiotherapy adverse events for patients receiving radiotherapy after a mastectomy.

Adverse events	Events	Individuals
	N = 341	N = 341
Any adverse event	158	157 (46.0%)
Skin erythema	136	135 (39.6%)
Pain	50	50 (14.7%)
Chest wall oedema	12	12 (3.5%)

Table 4.11 – Mortality rates in the overall cohort, in the breast-conserving surgery cohort and in the mastectomy cohort.

OVERALL COHORT				
		No radiotherapy	Radiotherapy	Total
		N = 1,058	N = 1,753	N = 2,811
Overall death (any cause)	n	1,041	1,716	2,757
	No	824 (79.2%)	1,469 (85.6%)	2,293 (83.2%)
	Yes	217 (20.8%)	247 (14.4%)	464 (16.8%)
Death due to breast cancer-related cause	n	1,032	1,706	2,738
	No	955 (92.5%)	1,590 (93.2%)	2,545 (93.0%)
	Yes	77 (7.5%)	116 (6.8%)	193 (7.0%)
BREAST-CONSERVING SURGERY COHORT				
		No radiotherapy	Radiotherapy	Total
		N = 284	N = 1,385	N = 1,669
Overall death (any cause)	n	277	1,354	1,631
	No	229 (82.7%)	1,205 (89.0%)	1,434 (87.9%)
	Yes	48 (17.3%)	149 (11.0%)	197 (12.1%)
Death due to breast cancer-related cause	n	276	1,348	1,624
	No	267 (96.7%)	1,297 (96.2%)	1,564 (96.3%)
	Yes	9 (3.3%)	51 (3.8%)	60 (3.7%)
MASTECTOMY COHORT				
		No radiotherapy	Radiotherapy	Total
		N = 746	N = 341	N = 1,087
Overall death (any cause)	n	737	336	1,073
	No	574 (77.9%)	243 (72.3%)	817 (76.1%)
	Yes	163 (22.1%)	93 (27.7%)	256 (23.9%)
Death due to breast cancer-related cause	n	730	332	1,062
	No	665 (91.1%)	269 (81.0%)	934 (87.9%)

	Yes	65 (8.9%)	63 (19.0%)	128 (12.1%)

4.8. FIGURES

Figure 4.1 – STROBE flow diagram for the radiotherapy versus no radiotherapy analyses.

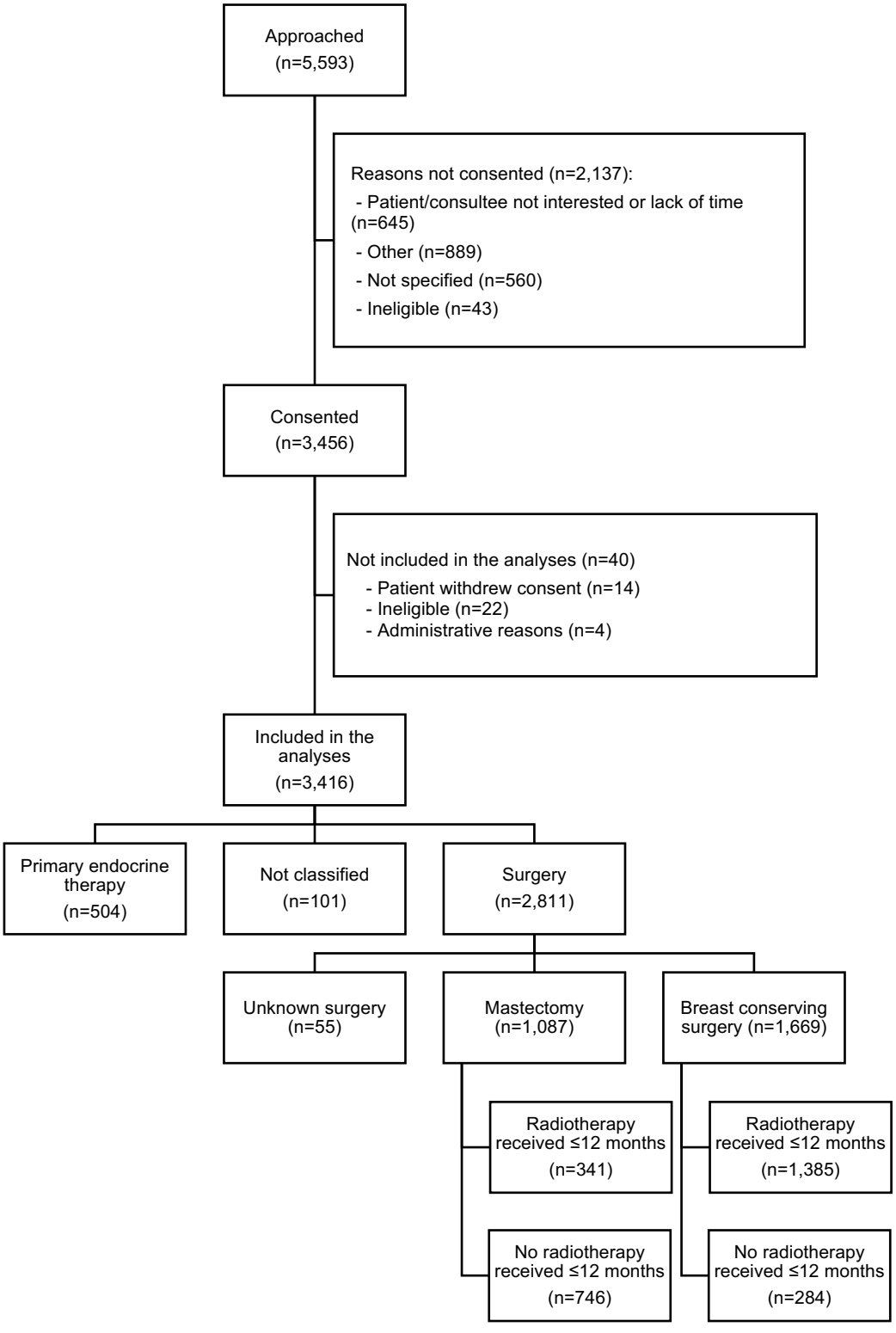


Figure 4.2 – Funnel plot of radiotherapy use by site (N=56): proportion of patients enrolled in cohort study receiving radiotherapy against number of patients enrolled.

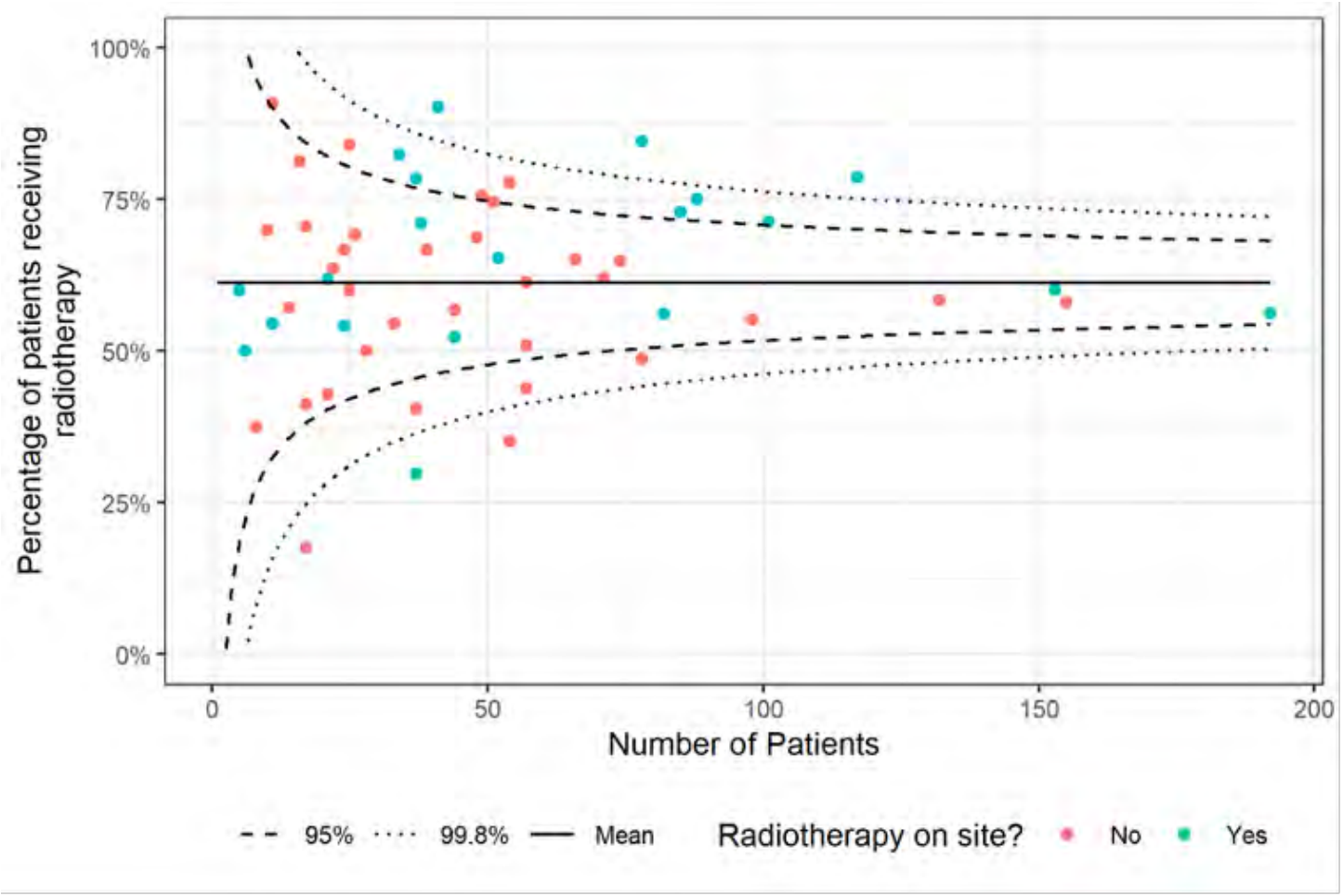


Figure 4.3 – Completion of the EORTC-QLQ-BR23 at each time point in patients undergoing breast-conserving surgery.

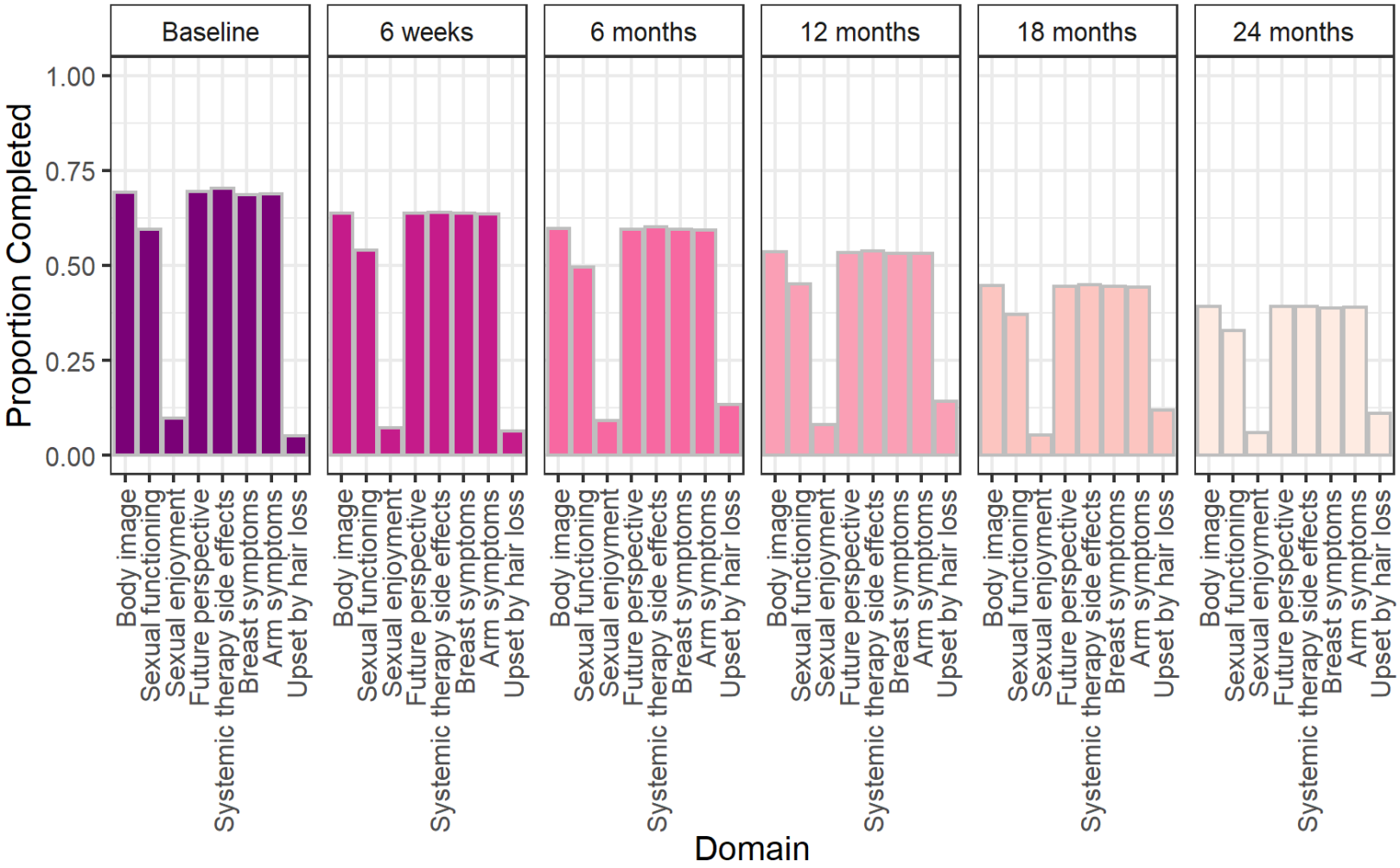


Figure 4.4 – Completion of the EORTC-QLQ-BR23 at each time point in patients undergoing a mastectomy.

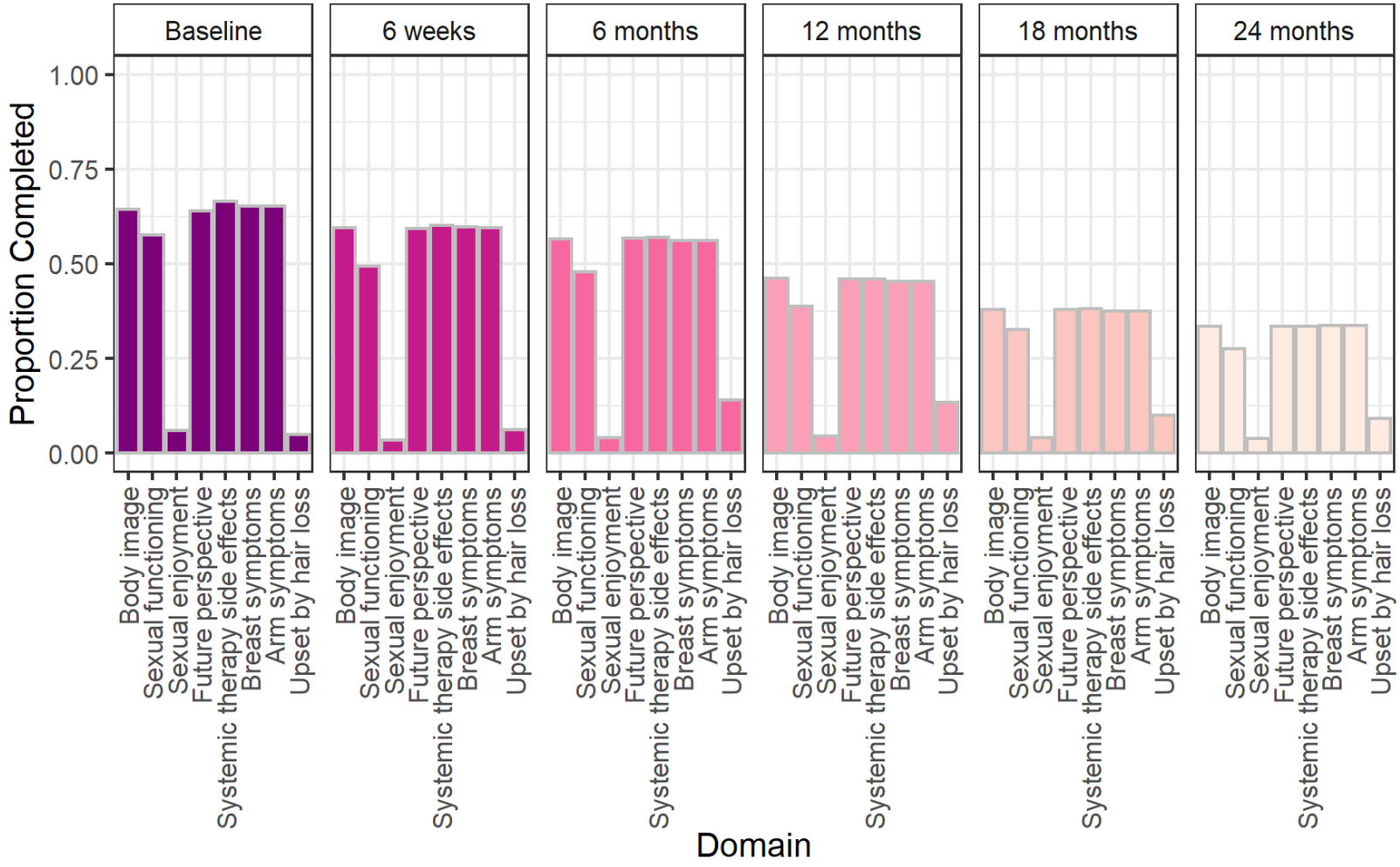


Figure 4.5 – Completion of the EORTC-QLQ-C30 at each time point in patients undergoing breast-conserving surgery.

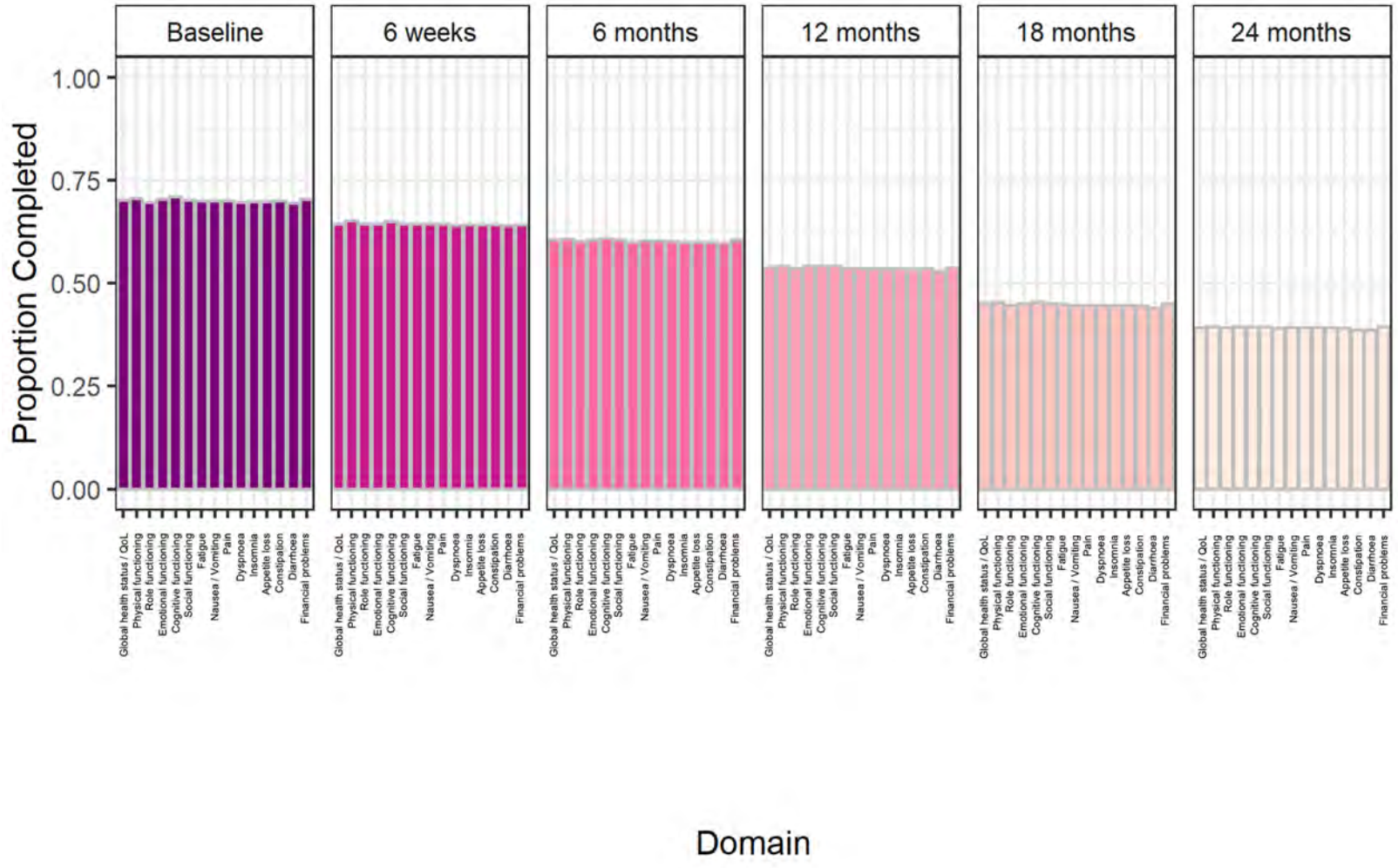


Figure 4.6 – Completion of the EORTC-QLQ-C30 at each time point in patients undergoing a mastectomy.

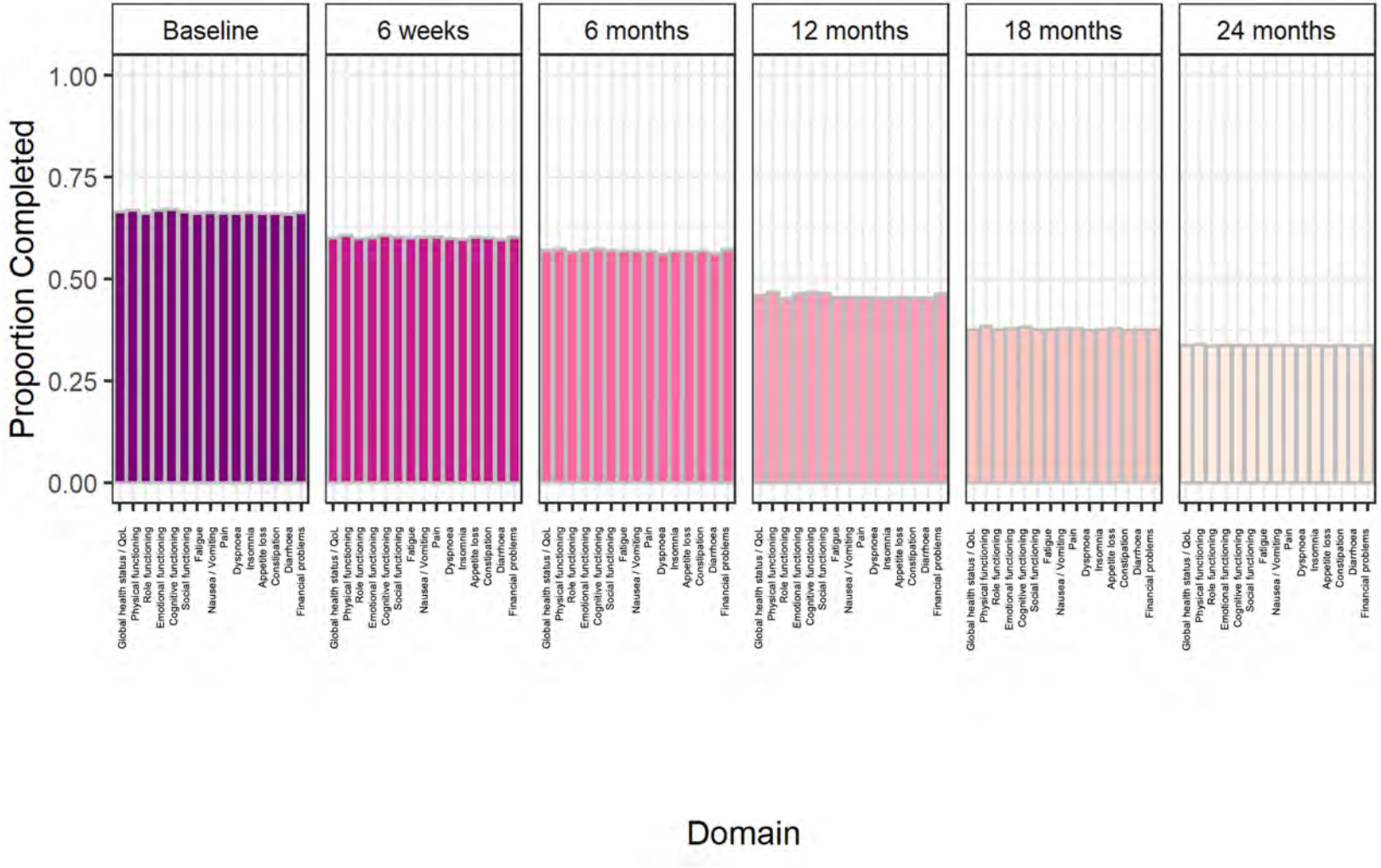


Figure 4.7 – Completion of the EORTC-QLQ-ELD15 at each time point in patients undergoing breast-conserving surgery.

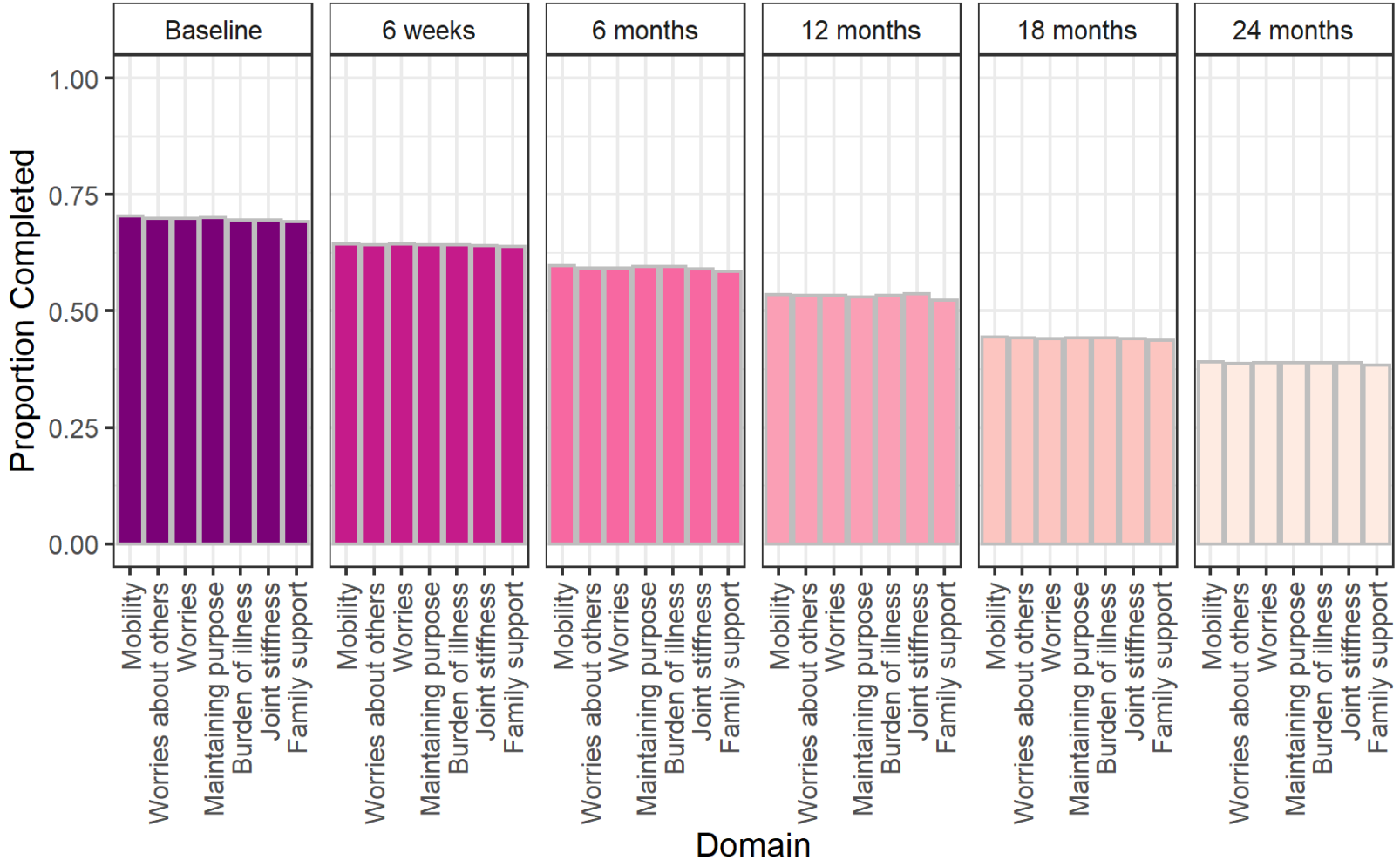


Figure 4.8 – Completion of the EORTC-QLQ-ELD15 at each time point in patients undergoing a mastectomy.

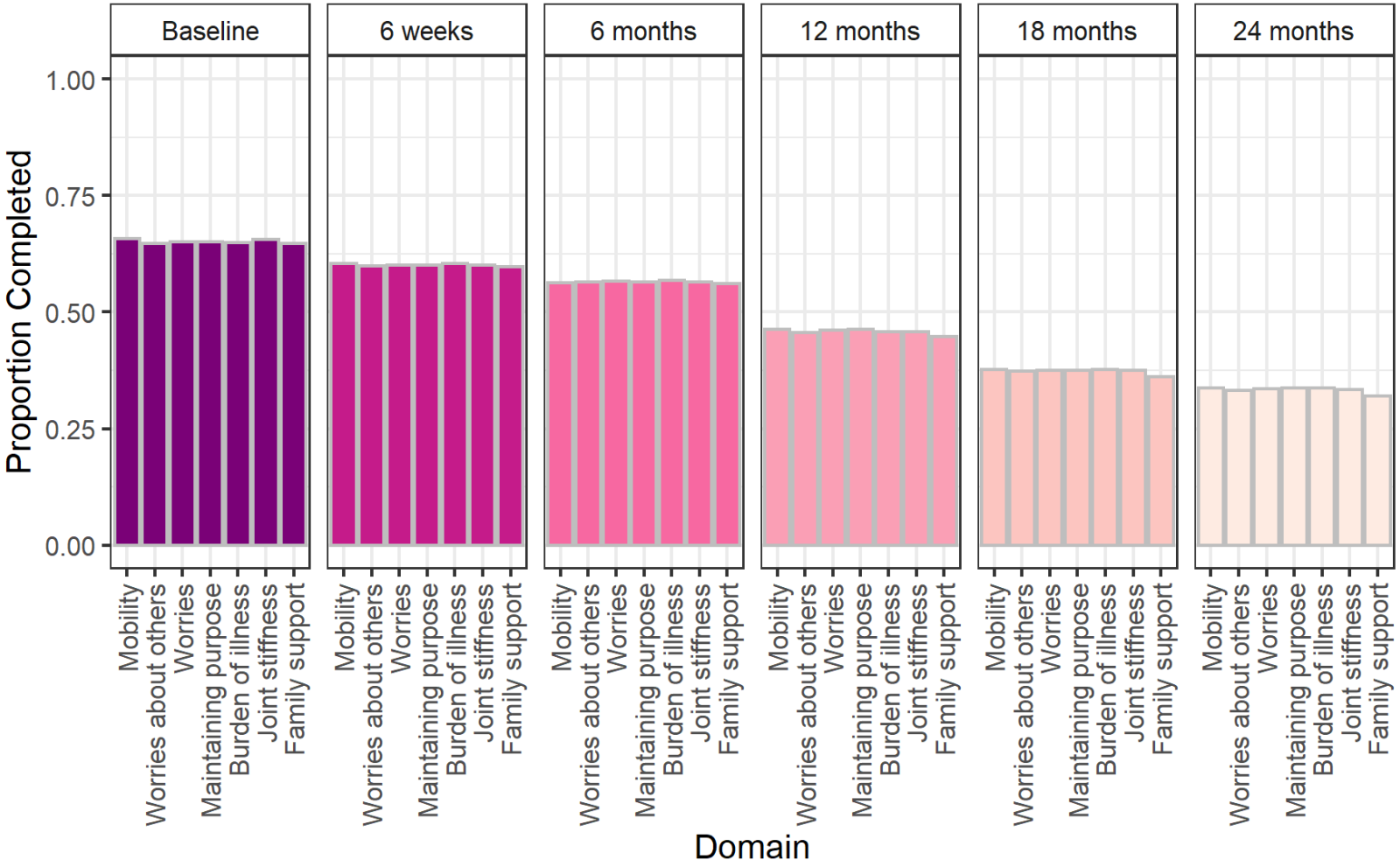


Figure 4.9 – Impacts of radiotherapy on quality of life over time.

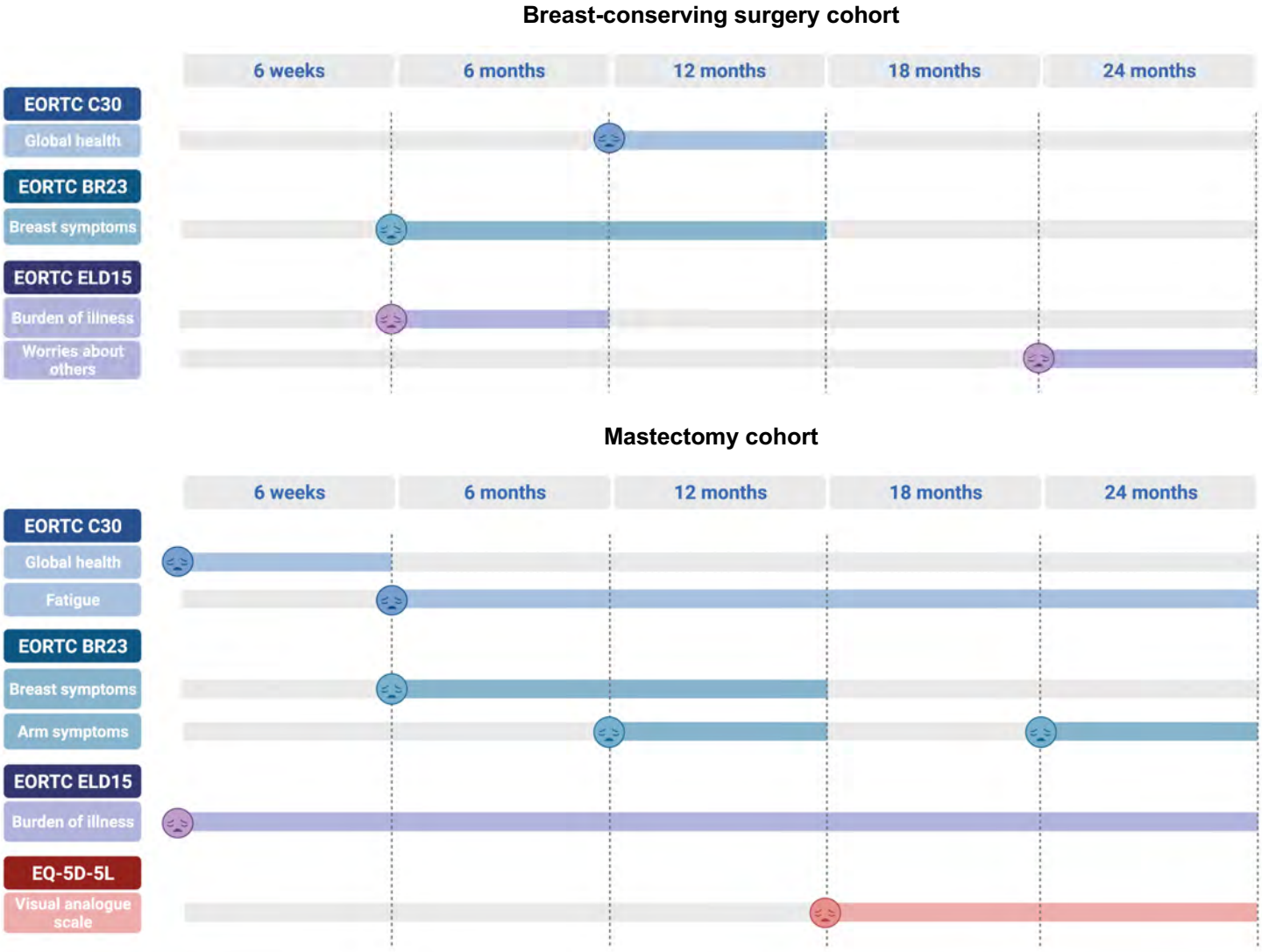


Figure 4.10 – Mean (95% confidence interval) scores over time points for the radiotherapy versus no radiotherapy population measured on the EORTC-QLQ-BR23 in patients undergoing breast-conserving surgery.

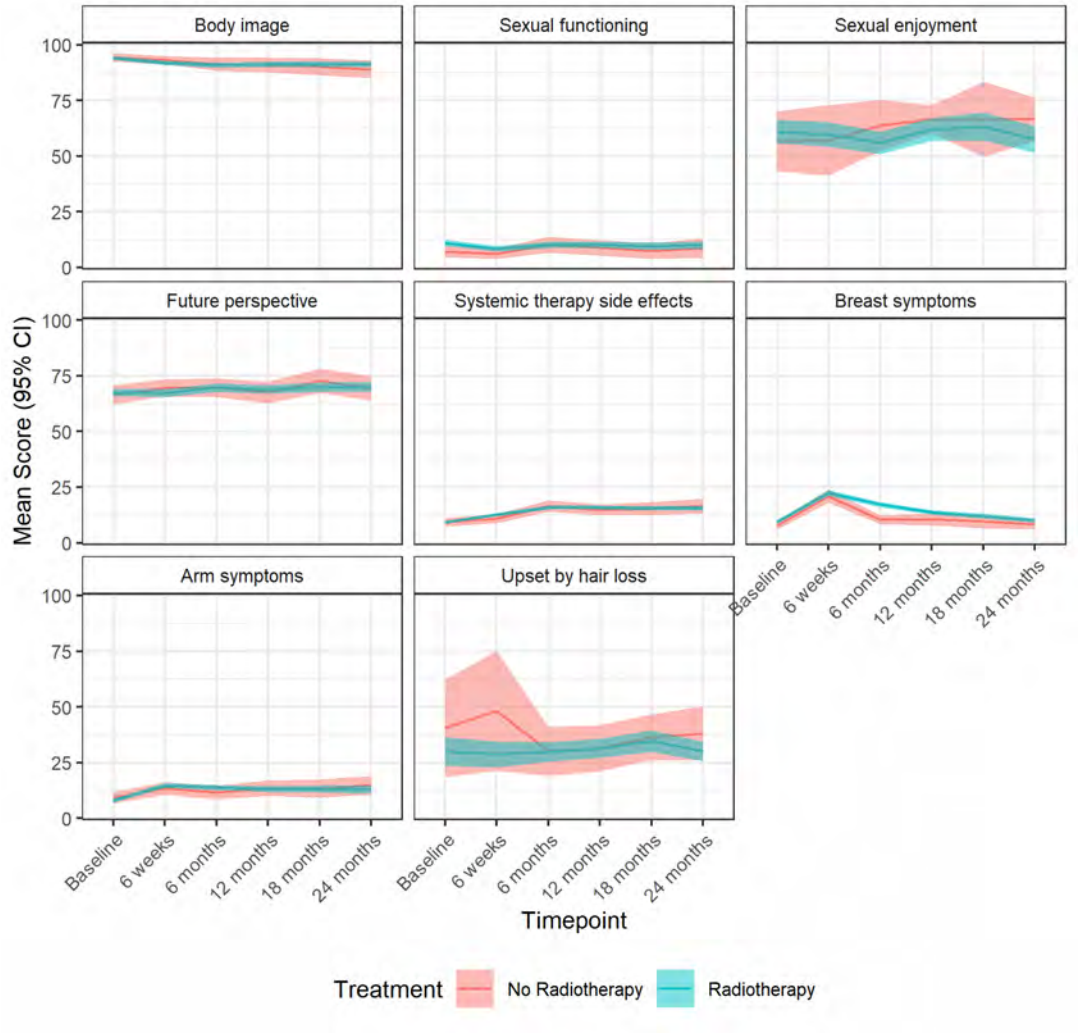


Figure 4.11 – Mean (95% confidence interval) scores over time points for the radiotherapy versus no radiotherapy population measured on the EORTC-QLQ-BR23 in patients undergoing a mastectomy.

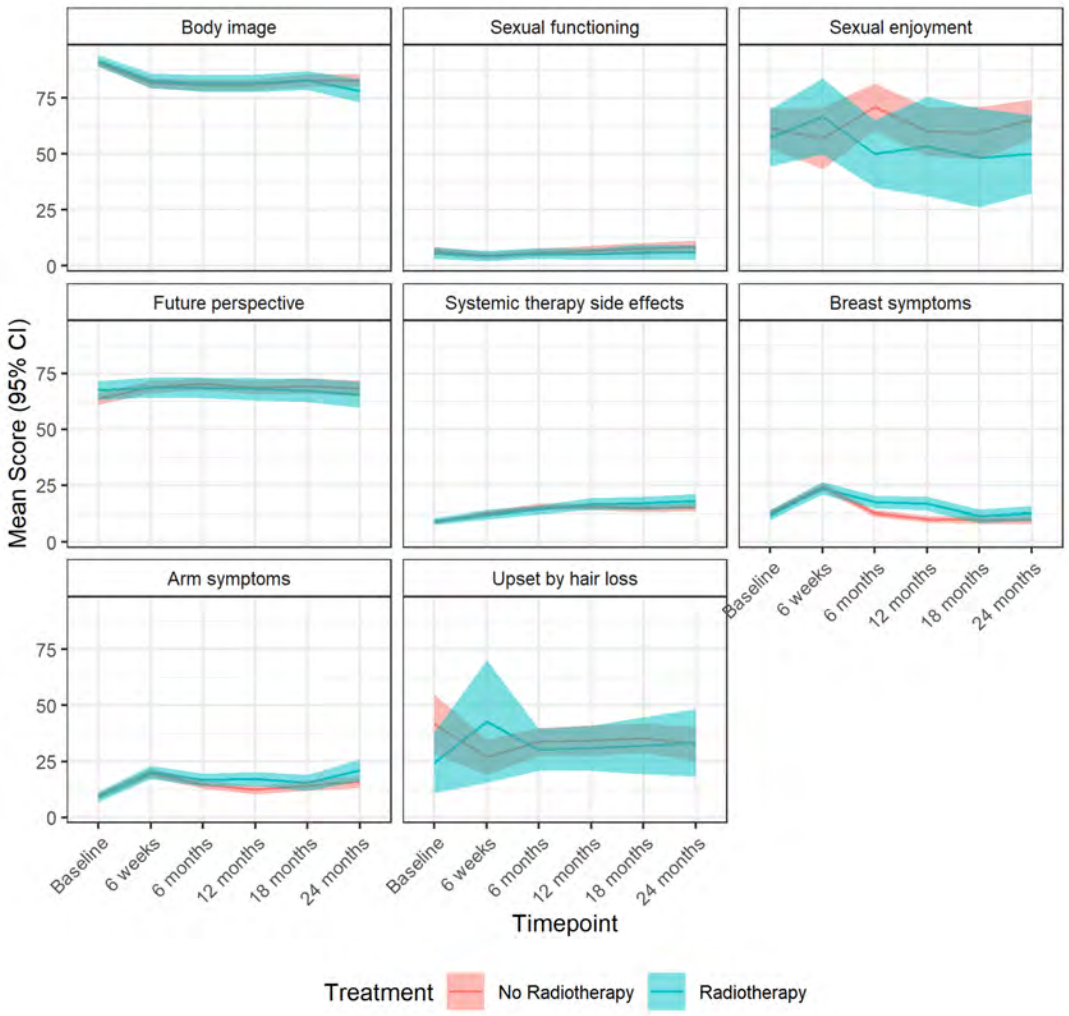


Figure 4.12 – Mean (95% confidence interval) scores over time points for the radiotherapy versus no radiotherapy population measured on the EORTC-QLQ-C30 in patients undergoing breast-conserving surgery.

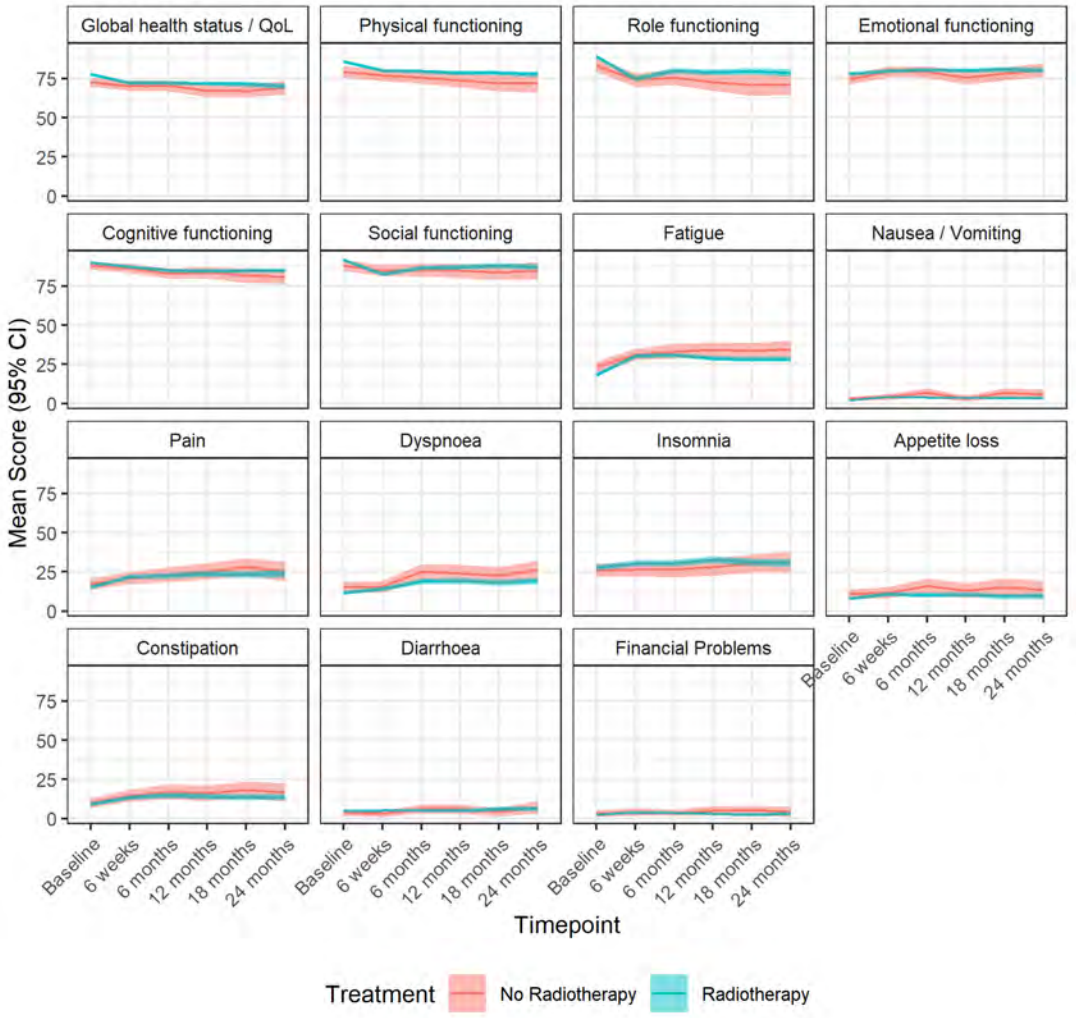


Figure 4.13 – Mean (95% confidence interval) scores over time points for the radiotherapy versus no radiotherapy population measured on the EORTC-QLQ-C30 in patients undergoing a mastectomy.

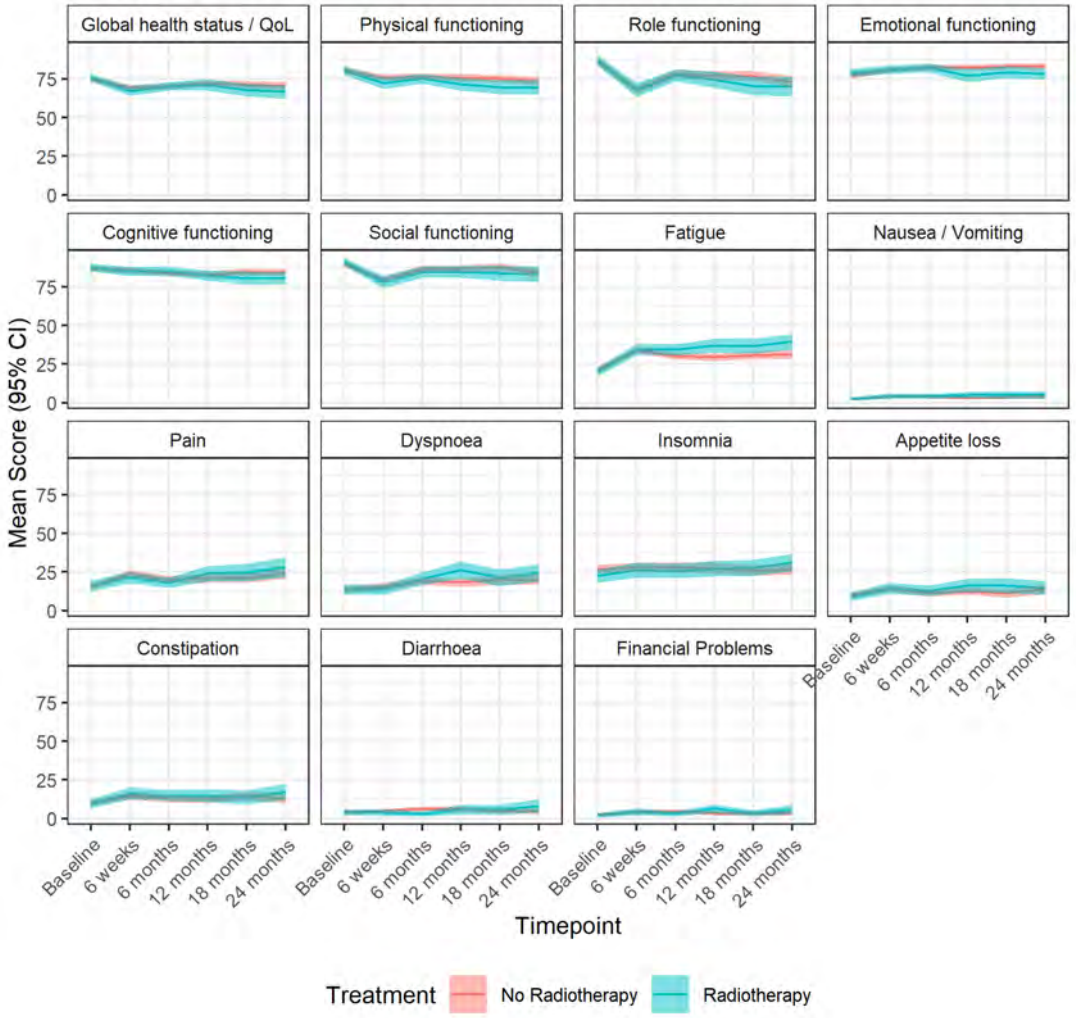


Figure 4.14 – Mean (95% confidence interval) scores over time points for the radiotherapy versus no radiotherapy population measured on the EORTC-QLQ-ELD15 in patients undergoing breast-conserving surgery.

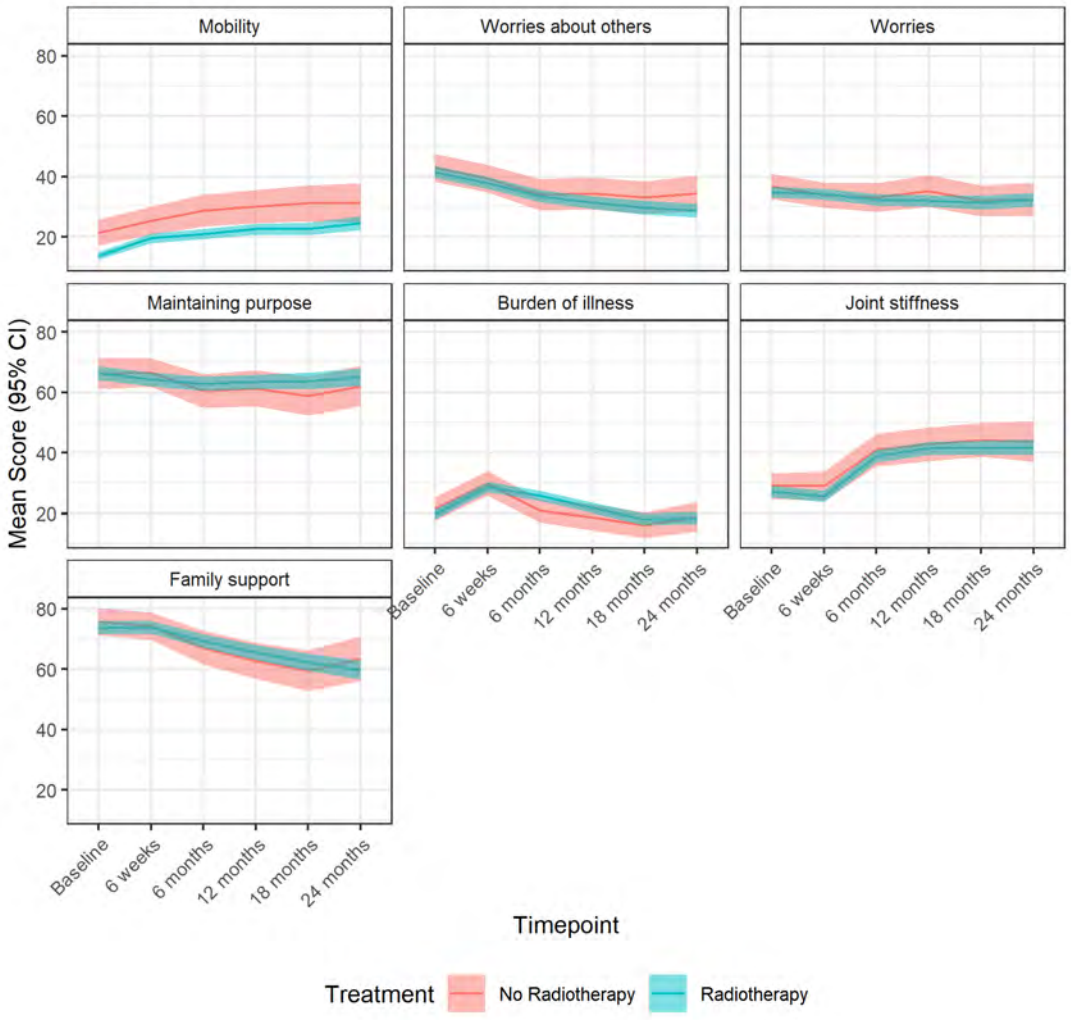


Figure 4.15 – Mean (95% confidence interval) scores over time points for the radiotherapy versus no radiotherapy population measured on the EORTC-QLQ-ELD15 in patients undergoing a mastectomy.

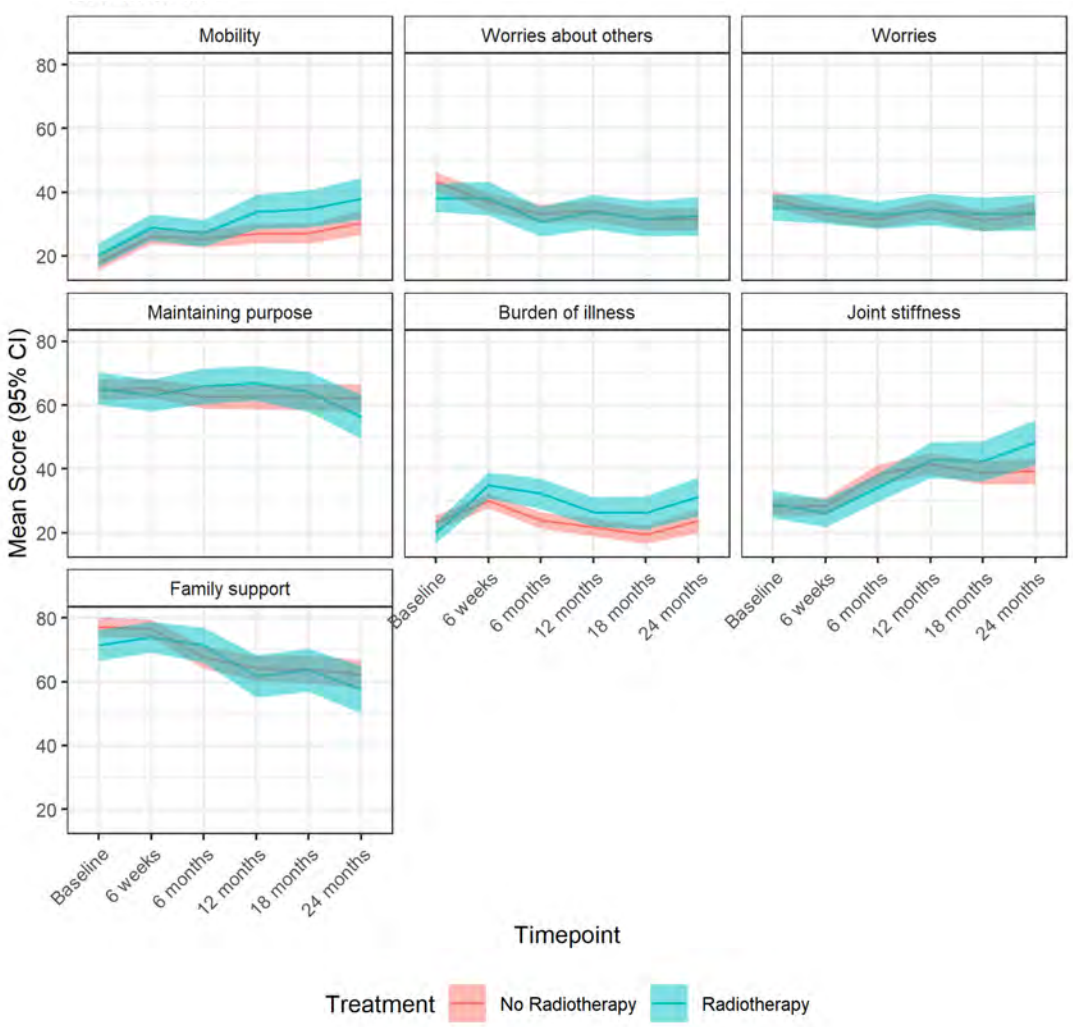


Figure 4.16 – Mean (95% confidence interval) scores over time points for the radiotherapy versus no radiotherapy population measured on the EQ-5D-5L scale in patients undergoing breast-conserving surgery.

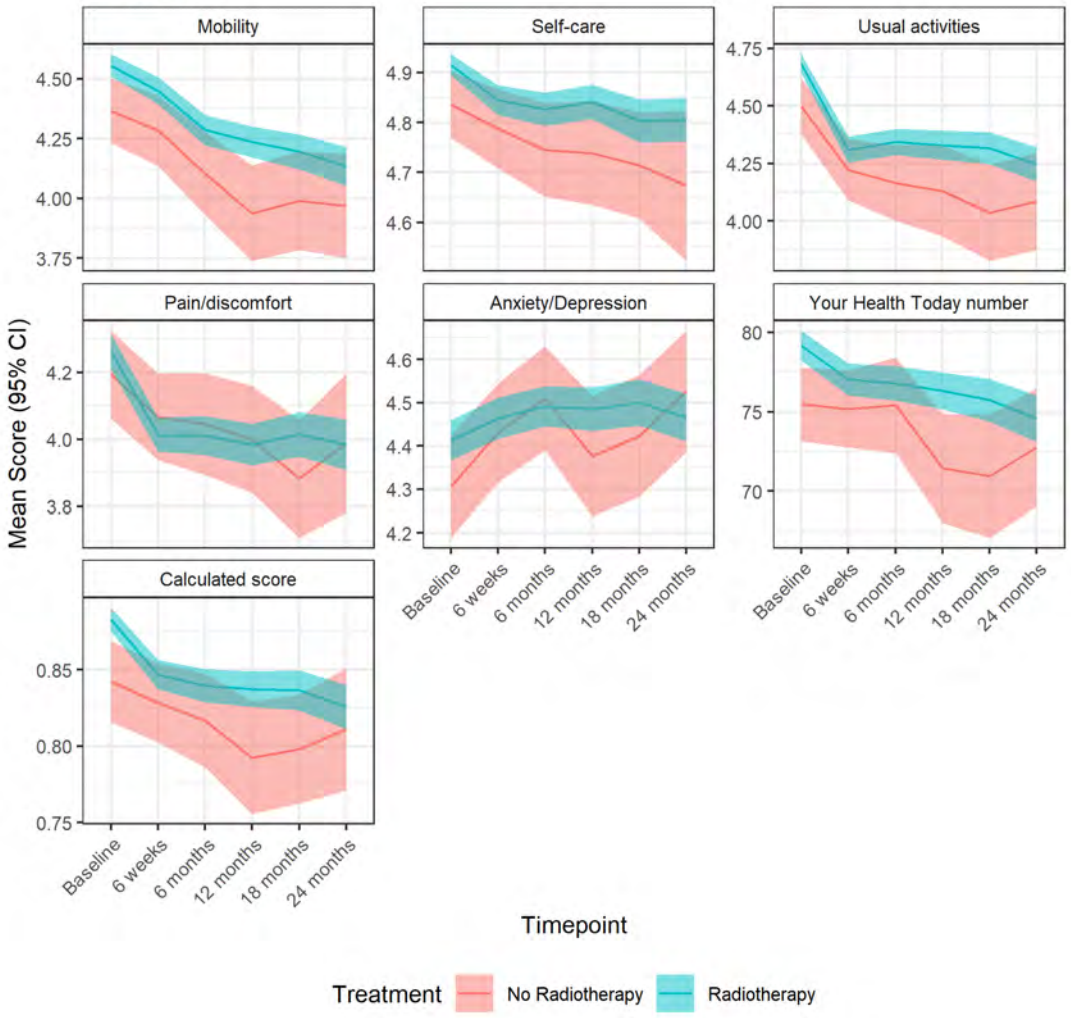
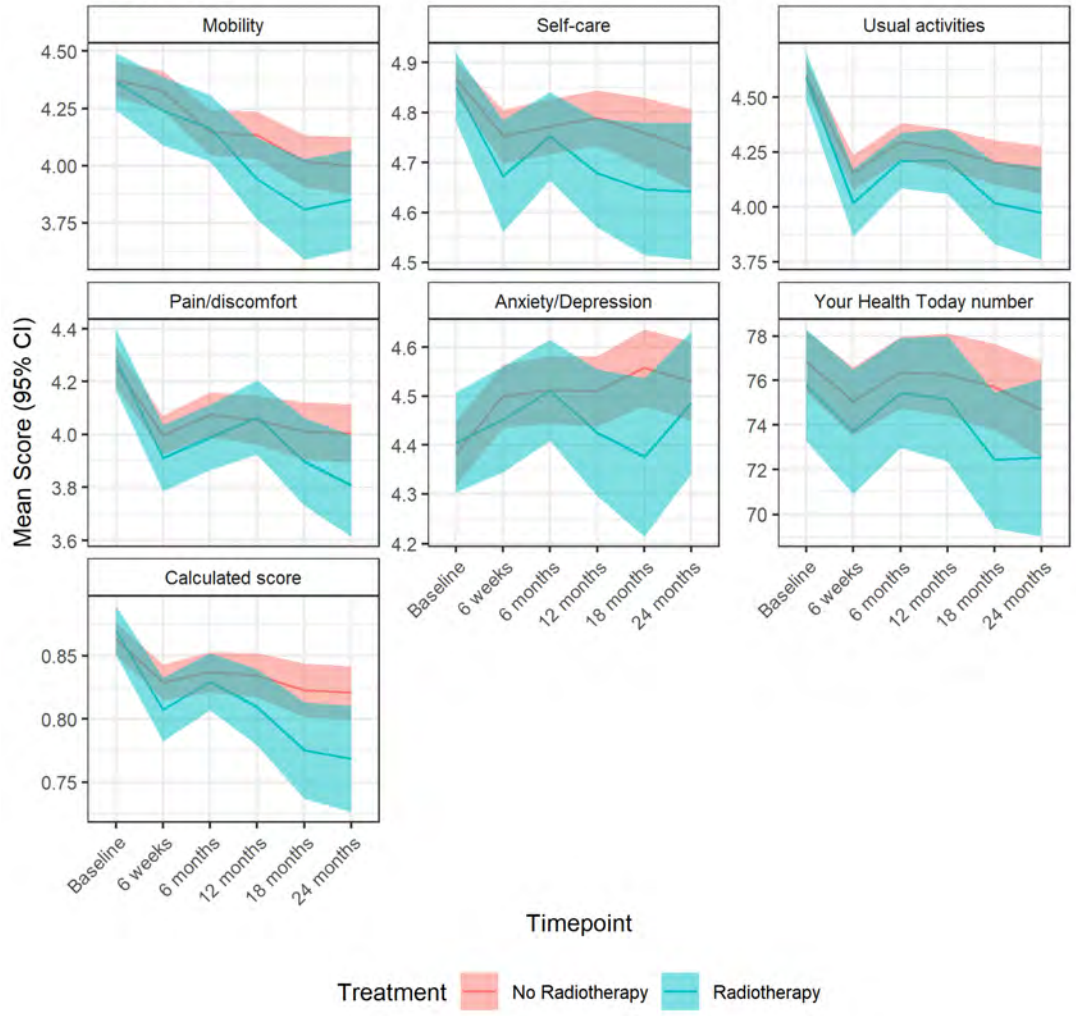


Figure 4.17 – Mean (95% confidence interval) scores over time points for the radiotherapy versus no radiotherapy population measured on the EQ-5D-5L scale in patients undergoing a mastectomy.



CHAPTER 5. PREVALENCE OF PRIOR HOSPITALISATION FOR CARDIOVASCULAR AND CEREBROVASCULAR DISEASE IN PATIENTS DIAGNOSED WITH SIX COMMON CURABLE MALIGNANCIES: A VIRTUAL CARDIO-ONCOLOGY RESEARCH INSTITUTE NATIONAL REGISTRY DATASET ANALYSIS

5.1. ABSTRACT

Although a common challenge for patients and clinicians, there is little population-level evidence on the prevalence of cardiovascular disease (CVD) in individuals diagnosed with potentially curable cancer.

We investigated CVD rates in patients with common potentially curable malignancies and evaluated the associations between patient and disease characteristics and CVD prevalence.

We included cancer registry patients diagnosed in England with stage I-III breast cancer, stage I-III colon/rectal cancer, stage I-III prostate cancer, stage I-IIIA non-small cell lung cancer (NSCLC), stage I-IV diffuse large B cell lymphoma (DLBCL) and stage I-IV Hodgkin lymphoma from 2013 to 2018. Linked hospital records and national cardiovascular disease databases identified CVD. We investigated the rates of CVD according to tumor type and determined the associations between patient and disease characteristics and CVD prevalence.

Among the 634,240 patients included, 102,834 (16.2%) had prior CVD. Men, older patients and those living in deprived areas had higher CVD rates. Prevalence was highest for NSCLC (36.1%) and lowest for breast cancer (7.7%). After adjustment for age, sex, the income domain of the Index of

Multiple Deprivation and Charlson Comorbidity Index, CVD remained higher in other tumor types compared to breast cancer patients.

There is a significant overlap between cancer and CVD burden. It is essential to consider CVD when evaluating national and international treatment patterns and cancer outcomes.

5.2. INTRODUCTION

Cancer is a significant cause of morbidity and mortality in the general population in the England, accounting for approximately 320,000 cases and 136,000 deaths in 2018.[1] Survival outcomes for both cancer and cardiovascular disease (CVD) are improving.[2, 3] However, increasing evidence suggests a relationship between CVD and cancer.[4] Both conditions share common risk factors (obesity, diabetes mellitus, hypertension, hyperlipidaemia, tobacco use, dietary habits, alcohol consumption and sedentary lifestyle) and common pathophysiological processes (chronic inflammation). Therefore, they may co-exist in a significant proportion of individuals.[5] Furthermore, cancer and its treatment, including cytotoxics, targeted agents and radiotherapy, may result in cardiac damage and further increase the risk of adverse outcomes in the context of pre-existing CVD.[6] As a result, pre-existing CVD may influence cancer diagnosis and treatment decision-making and contribute to the existing disparities in cancer care and outcomes.[7] Within the UK, there is a significant degree of variation in cancer care and survival,[8-12] which is particularly pronounced for the older age group.[13, 14]

As part of preliminary work for this research, we were involved in the Age is no Barrier to Chemotherapy study to determine which factors affect the likelihood of older patients receiving systemic anticancer therapy and their outcomes. This work was presented at the 2018 European Society for Medical Oncology (ESMO) Congress[13] and at the 2019 National Cancer Research Institute Conference.[15] Within this national registry-based cohort study, we have analysed data on 97,846 patients with cancer aged ≥18 years diagnosed in England from January 1st 2013 to December 31st 2015 and for which clinical guidelines recommend the use of systemic anticancer therapy: stage II-III breast, stage III colon, and stage IIIB-IV non-small cell lung cancer (NSCLC). Following adjustment for variables including age and comorbidity and case-mix adjustment, we calculated treatment rates at hospital level and two-year net survival was assessed for younger (18-69 years) and older (≥70 years) patients. Patients aged ≥70 years were less likely to receive systemic

anticancer therapy compared to those aged 18-69 years (breast cancer cohort: 70% versus 18%; colon cancer cohort: 83% versus 45%; NSCLC cohort: 59% versus 33%). Two-year net survival for patients receiving systemic anticancer therapy was similar irrespective of age. These data provide an initial national benchmark for monitoring different subgroups of cancer. This study documented that older patients receiving systemic anticancer therapy may derive comparable benefits to younger patients but are less likely to receive it. A key finding from this research was that across all cohorts there was variation between hospitals in prescribing systemic anticancer therapy, which persisted following case-mix adjustment.

Furthermore, cancer outcomes are markedly different between countries.[2, 16] Some part of this national and international variation may be explained by co-existent CVD. These considerations are particularly relevant for older patients with curable cancers.

Nonetheless, the prevalence of CVD for patients with specific malignancies and the impact of CVD on patient and tumour characteristics is unknown. Investigating the intersection of cancer and CVD is central to understanding outcome data and vital when planning cancer policy interventions and the provision of cancer services at national and regional levels. Whilst the focus of my MD has been breast cancer, this project provided the opportunity to examine data across different tumour types, where this issue is equally relevant.

The Virtual Cardio-Oncology Research Institute (VICORI) programme is an initiative to link data from the English National Cancer Registration and Analysis Service (NCRAS), part of Public Health England,[17] with national cardiac audits held by the National Institute for Cardiovascular Outcome Research (NICOR).[18, 19] The goals are to: 1) provide a quality-assured data resource for research into cancer and cardiac disease; and 2) identify new scientific avenues that will further knowledge of cardio-oncology through a portfolio of research projects aligned with the VICORI programme grant. These research projects are studying how existing conditions and related treatments

affect subsequent disease risk and will optimize patient management through informing evidence-based guidelines.

As part of the VICORI programme, we used data from the Public Health England National Cancer Registration Dataset[20] linked with Hospital Episode Statistics (HES) and NICOR data to identify hospitalised CVD recorded in hospital coding records and registry datasets. In this chapter, we describe the prevalence of CVD in individuals with a new diagnosis of common malignancies at stages suitable for treatment with curative intent. We also investigated the patient and tumour characteristics associated with CVD in this cohort of individuals with cancer.

Within this study, I have been responsible for the cleaning of the study database, the statistical analysis in conjunction with the trial statistician and the formulation of specific research questions to be investigated in the study cohort.

5.3. METHODS

The Virtual Cardio-Oncology Research Initiative research programme was established to investigate the interplay between CVD and cancer. To achieve this aim, we linked together English cancer registry data (National Cancer Registration Dataset [NCRD]) and six CVD specific audits managed by NICOR (Supplementary table 5.1). Four NICOR databases were included in this study: Myocardial Ischaemia National Audit Project (MINAP),[21] National Adult Cardiac Surgery Audit (NACSA),[22] National Adult Percutaneous Coronary Intervention (NAPCI)[23] and National Heart Failure Audit (NHFA).[24] NCRD provides a comprehensive and quality-assured data over the patient care pathway. While MINAP and NHFA are audit programmes including respectively data on patients with suspected acute coronary syndrome and on those with heart failure, NACSA and NAPCI collect data respectively on those undergoing cardiac surgery and those receiving percutaneous coronary procedures. Patients are included in the audits if they have certain diagnoses or procedures, but they may have other CVD diagnoses which were not the reason they were included in the specific audit. Importantly, the NICOR audit datasets do not report International Statistical Classification of Diseases and Related Health Problems (ICD)-10 codes. To include a wider range of CVD in our analysis compared to those included in the four NICOR audits, we included HES administrative data collected during a patient's time in hospital allowing hospitals to be paid for the care they deliver. NICOR and HES include diagnoses captured in the inpatient setting. Robust quality assurance checks are in place for the NICOR and HES datasets.[25, 26]

NCRD has existing linkages with the National Radiotherapy Dataset and Systemic Anti-Cancer Therapy database. Since 2009, the National Radiotherapy Dataset (RTDS)[27] requires all National Health Service (NHS) Acute Trust providers of radiotherapy services in England to collect standardised data so RTDS data analysis is consistent across England. From April 2014, it became mandatory for English NHS Trusts providing systemic anticancer therapy (SACT) to submit data to the SACT database, a population-based resource of systemic anticancer therapy activity. However, data quality

is considered sufficient for data analysis from 2013. All databases used in the analysis are described in detail Supplementary table 5.1.

5.3.1. Identification of the patient cohort

We analysed data from the NCRD to identify a cohort of patients from England with a potentially curable cancer diagnosis. We used the ICD-10 codes[28] to identify the first record of breast cancer (ICD-10 code C50), colon cancer (ICD-10 codes C18 and C19), rectal cancer (ICD-10 code C20), prostate cancer (ICD-10 code C61) and NSCLC (ICD-10 code C34 excluding small cell ICD-O-2 morphology codes 8041, 8042, 8043, 8044 or 8045), diffuse large B-cell lymphoma (DLBCL) (ICD-10 code C83.3) and Hodgkin lymphoma (ICD-10 code C81) from 1st January 2013 to 31st December 2018.

If patients had more than one tumour diagnosed at different sites, we included the first tumour diagnosed in the analysis. If patients had synchronous cancer diagnoses, we included only the tumour with the worst prognosis based on a comparison of tumour stage and grade, receptor status (for the breast cancer cohort) and Gleason group (for the prostate cancer cohort) as outlined in Supplementary table 5.2. We opted for this approach in order to determine the prevalence of CVD only in individuals diagnosed with malignancies more impactful on survival outcomes (as CVD may also influence their management). We excluded patients with synchronous tumours diagnosed in the same site with similar prognostic features and those with synchronous tumours diagnosed in different sites for whom a different impact on prognosis could not be determined based on the available evidence.

We included patients aged between 25 and 100 years at cancer diagnosis, resident in England, and with complete and comparable data on vital status, sex and NHS number (to allow linkage). We restricted the analysis to tumours eligible for treatment with curative intent (stage I-III breast cancer, stage I-III colon/rectal cancer, stage I-III prostate cancer, stage I-IIIA NSCLC, stage I-IV DLBCL and stage I-IV Hodgkin lymphoma). Therefore, we did not include tumours at stages with advanced (incurable) cancer. Full inclusion/exclusion

criteria are shown in Table 5.1. Patients with missing data on age, sex, NHS number, mortality status or cancer stage were excluded from the analysis.

We extracted the Cancer Alliance (CA) of the hospital where the patients were diagnosed with cancer (Table 5.2). Patient-specific information was extracted at cancer diagnosis on age, sex, ethnicity, income deprivation group (quintiles of the income domain of the Index of Multiple Deprivation [IMD]) and cancer histology, grade and stage (classified using TNM scoring system). In addition, site-specific characteristics for each cancer were extracted as follows: breast cancer (laterality, oestrogen receptor [ER] status, progesterone receptor [PR] status, human epidermal growth factor receptor 2 [HER2] status, Nottingham Prognostic Index [NPI], screen-detected status); colon/rectal cancer (Duke's stage); prostate cancer (Gleason score); NSCLC (laterality).

Using pre-existing linkages with the RTDS, SACT dataset and HES,[20] a database containing details of all hospital admissions, surgical procedures, radiation therapy and systemic anticancer treatments performed at NHS hospitals in England was extracted. We identified curative treatments (surgery, radiotherapy and chemotherapy) using previously agreed cancer registry algorithms.[29]

5.3.2. Comorbidities

We extracted individual comorbidities defined within the Charlson Comorbidity Index (CCI),[30] identified using HES admitted patient care diagnoses recorded within five years before cancer diagnosis, and derived a CCI excluding CVD to avoid counting them in both the CVD exposure and the index (Supplementary table 5.3).

We identified hospitalised CVD comorbidities from diagnoses recorded in any diagnostic position in HES admitted patient care (inpatient) data or in the NICOR databases[31] MINAP, NACSA, NAPCI and NHFA within five years before cancer diagnosis as this is typically a requirement for trial participation in oncology. The criteria to define CVD diagnoses are reported in

Supplementary table 5.4.[32] ICD-10 CVD diagnoses codes were obtained from a previous VICORI study[33] and divided into the following main phenotypes: cerebrovascular; stroke (cerebrovascular subgroup); congestive heart failure (CHF); ischemic heart disease; acute myocardial infarction (ischemic heart disease subgroup); peripheral artery disease; valvular heart disease (Supplementary table 5.5).

5.3.3. Statistical analysis

We produced summary tables of patient and tumour characteristics for each cancer site. We also explored how hospitalised CVD prevalence (identified using HES and NICOR CVD diagnosis code list) varied by patient and tumour characteristics with p-values calculated using chi-squared tests. Due to the large sample size of the study, even trivial differences (which may not be scientifically important or clinically relevant) are likely to have small p-values. Whilst we report p-values, we chose to focus on presenting point estimates (and 95% confidence intervals [CI]), as we feel these communicate sufficient information to understand differences in characteristics across groups. We fit logistic regression models to find the unadjusted association between CVD and each patient and tumour characteristic, overall and by cancer site.

We analysed observed hospitalised CVD prevalence, overall and by CVD phenotype (using each CVD code list), by cancer site. As the distribution of age varies by cancer site, we calculated standardised CVD prevalence by age and sex distribution of the 2016 English population obtained from the Office of National Statistics. Uncertainty in the prevalence estimates was displayed in the figures with 95% CIs obtained assuming a binomial distribution. To assess the burden of CVD comorbidity, we plotted absolute numbers of patients with CVD comorbidity by cancer site and age. Finally, we investigated the association between cancer site and CVD comorbidity using logistic regression analysis adjusting for age, sex, income domain of IMD and CCI. Finally, we produced an unadjusted logistic regression analysis to investigate the association between the income domain of IMD and CVD, cancer stage,

surgery, chemotherapy and radiotherapy with interactions between each covariate and the income domain of IMD.

To investigate the association between CVD prevalence and CA, we divided the 20 CAs into three groups (tertiles, with roughly equal patient numbers in each group) by CVD prevalence. The minimum group consisted of the CAs with the lowest CVD prevalence, the maximum group consisted of the CAs with the highest CVD prevalence and the remaining CAs were placed in the middle group.

We described cancer type, age, sex, ethnicity, income domain of IMD, CCI, stage, grade and treatment received by patients of each CA tertile. For patients with CVD identified using HES data, we described the CVD phenotype by CA tertile. To investigate the source of the CVD comorbidity, we reported the overlap between recording of patient with a CVD record from each source by CA tertile.

To evaluate burden of disease, we reported bar charts showing numbers of patients, number of patients with a CVD comorbidity and CVD prevalence in each CA. We showed regional variation by presenting maps of England we report CVD prevalence in each CA separately for each cancer type.

Finally, we used funnel plots to investigate variations in regional CVD rates by plotting standardised CVD ratios separately for each cancer type, calculated by dividing the observed number of patient with a CVD comorbidity in each CA by the predicted number of patients with a CVD comorbidity, obtained from a logistic regression model.[34] Standardised CVD ratios that fell outside the 99.8% confidence bands were flagged. Logistic models progressively adjusted for main effects of age at diagnosis, sex (if appropriate for the cancer type), cancer stage, income domain of IMD and CCI. Non-linear effects of age-at-diagnosis were modelled using a restricted cubic spline function with three knots, calculated separately for each cancer type.

All analyses were performed in Stata MP version 16 and R version 4.0.2.27.[35, 36]

5.4. RESULTS

We extracted data from 1,034,569 diagnoses of breast, colon, rectal, prostate, non-small cell lung cancer, DLBCL or Hodgkin lymphoma in England in 2013-2018. After exclusions owing to predefined eligibility criteria (Table 5.1), 1,009,141 records remained. We then excluded 347,960 tumour records not eligible for the analysis based on cancer stage or missing stage, 13,728 metachronous tumour records, and 6,475 records of tumours with sarcomatous or small-cell histology (Figure 5.1). Finally, to analyse data at patient (rather than tumour) level, we excluded 393 patients with 798 synchronous tumours diagnosed in ≥2 different sites and 1,216 patients with 2,454 synchronous tumours diagnosed in the same site with the same prognostic features (Supplementary table 5.2).

Overall, the analysis included 634,240 patients distributed as follows: 226,516 with stage I-III breast cancer, 91,210 with stage I-III colon cancer, 39,688 with stage I-III rectal cancer, 175,639 with stage I-III prostate cancer, 70,458 with stage I-IIIA NSCLC, 23,426 with stage I-IV DLBCL and 7,303 with stage I-IV Hodgkin lymphoma (Figure 5.1).

The mean age of the overall cohort was 67.2 years, ranging from a mean age of 62.5 years in the breast cancer cohort to 72.9 years in the NSCLC cohort. 303,021 (47.8%) diagnoses were male, 564,687 (89.0%) had white ethnicity, 417,407 (65.8%) had the income domain of IMD score 1-3 and 295,961 (46.7%) had no CCI comorbidities (excluding cardiovascular diseases) recorded within 5 years before cancer diagnosis. Patient, disease and tumour characteristics are reported in Table 5.3. The characteristics of the individual cancer cohorts and tumour-specific features by calendar year are outlined in Supplementary tables 5.6-5.12.

5.4.1. Cardiovascular disease

Although ischaemic heart disease was by far the most common, many HES CVD codes were cerebrovascular, which would not feature in NICOR audits

unless accompanied by other CVD diagnostic codes. Similarly, most tumours with hospitalised CVD records included in an individual NICOR audit dataset also featured in HES with a cardiovascular diagnostic code in the 5-year period before cancer diagnosis (Supplementary table 5.13; Figure 5.2). Likewise, most tumours with specific hospitalised CVD category records were retrieved from HES. Prior hospitalised CVD was identified from linked HES and NICOR data in 102,834 (16.2%) of the overall cohort (Tables 5.4 and 5.5). While 0.2% of hospitalised CVD records were identified in NICOR only, 18,182 (17.7%) were found in both HES and NICOR datasets, with the majority of records [84,424 (82.1%)] identified from HES only (Figure 5.2).

In the overall cohort, the prevalence and the odds of prior hospitalised CVD increased with increasing age and CCI and prevalence was higher in men versus women (Tables 5.4 and 5.5). In the individual cancer cohorts, CVD was identified in 17,453/2,265,162 patients in the breast cancer cohort (7.7%; 95% CI 7.6-7.8%), 20,161/91,210 in the colon cancer cohort (22.1%; 95% CI 21.8-22.3%), 6,699/39,688 patients in the rectal cancer cohort (16.8%; 95% CI 16.5-17.2%), 27,123/175,639 in the prostate cancer cohort (15.4%), 25,459/70,458 in the NSCLC cohort (36.1%; 95% CI 35.7-36.4%), 5,091/23,426 in the DLBCL cohort (21.7%; 95% CI 21.2-22.2%) and 850/7,303 in the Hodgkin lymphoma cohort (11.6%; 95% CI 10.8-12.3%) (Table 5.17). Among individuals with rectal cancer and NSCLC, the percentage of patients with hospitalised CVD was over 4 percentage points higher in those with stage I versus stage III disease (5.3% [95% CI 4.4-6.2%] and 4.3% [95% CI 3.5-5.1)], respectively), whilst in Hodgkin lymphoma hospitalised CVD prevalence was 4.2 percentage points lower (95% CI 1.6-6.7%) (Table 5.4). Increasing income domain of IMD score was associated with higher rates of CVD in all tumour groups except the Hodgkin lymphoma cohort. Rates of prior hospitalised CVD showed no laterality differences in the breast cancer and NSCLC cohorts.

An increasing income domain of the IMD was also associated with more advanced stage in the individual tumour cohorts (Supplementary table 5.14). Increasing income domain of the IMD was associated with higher CVD rates

in all tumour groups except the Hodgkin lymphoma cohort (Supplementary tables 5.6-5.12). In the overall cohort, the CVD rates ranged from 13.3% for patients living in an area with income domain of IMD of 1 (least deprived) to 20.7% in those with an income domain of IMD of 5 (most deprived). The CVD prevalence ranged from 6.1% to 10.1% in the breast cancer cohort, from 19.7% to 25.9% in the colon cancer cohort, from 14.9% to 20.4% in the rectal cancer cohort, from 13.5% to 18.9% in the prostate cancer cohort, from 32.6% to 38.4% in the NSCLC cohort, from 19.6% to 23.4% in the DLBCL cohort and from 11.3% to 12.7% in the Hodgkin lymphoma cohort.

Figure 5.3 and Table 5.4 outlines the burden of hospitalised CVD across the various tumour cohorts and its distribution across different age groups. The prostate cancer cohort had the largest burden of hospitalised CVD (n=27,123), followed by the NSCLC cohort (n=25,459), the colon cancer cohort (n=20,161), the breast cancer cohort (n=17,453) and the rectal cancer cohort (n=6,699). The DLBCL cohort and the Hodgkin lymphoma cohort had the lowest burden of hospitalised CVD (n=5,091 and n=850, respectively). The highest burden of hospitalised CVD comorbidity occurred between the ages of 65 and 84 in all cancer cohorts. The overall proportion of patients with CVD diagnosis in each cancer cohort and by age group is shown in Figure 5.4.

The observed prevalence of hospitalised CVD across different tumour groups is shown in Figure 5.5. Patients with NSCLC had the highest overall hospitalised CVD prevalence (36.1%; 95% CI 35.7%-36.4%), followed by patients with colon cancer (22.1%; 95% CI 21.8%-22.3%), DLBCL (21.7%; 95% CI 21.2%-22.2%), rectal cancer (16.8%; 95% CI 16.5%-17.2%), Hodgkin lymphoma (11.6%; 95% CI 10.8%-12.3%) and breast cancer (7.7%; 95% CI 7.6%-7.8%). Age-sex standardised hospitalised CVD prevalence was much lower than the observed prevalence reflecting the fact that cancer patients were typically older than the general population. The NSCLC cohort had a much higher standardised prevalence compared to other cancer sites. The NSCLC cohort also had the highest observed prevalence of hospitalised cerebrovascular disease (7.8%; 95% CI 7.6%-8.0%), stroke (3.0%; 95% CI 2.9%-3.2%), CHF (8.5%; 95% CI 8.3%-8.6%), acute myocardial infarction

(3.8%; 95% CI 3.6%-3.9%), ischaemic heart disease (22.0%; 95% CI 21.7%-22.3%), peripheral vascular disease (11.1%; 95% CI 10.8%-11.3%) and valvular heart disease (6.1%; 95% CI 5.9%-6.2%). The prevalence of all hospitalised CVD subtypes was lowest in breast cancer patients (cerebrovascular disease [1.9%; 95% CI 1.9%-2.0%], stroke [0.8%; 95% CI 0.8%-0.9%], CHF [1.8%; 95% CI 1.7%-1.8%], acute myocardial infarction [0.7%; 95% CI 0.6%-0.7%], ischaemic heart disease [4.2%; 95% CI 4.1%-4.2%], peripheral vascular disease [1.2%; 95% CI 1.1%-1.2%] and valvular heart disease [1.5%; 95% CI 1.5%-1.6%]).

Compared to breast cancer, all other cancer sites reported significantly higher prevalence of hospitalised CVD, with the unadjusted odds ratios (ORs) for each cancer site compared to breast cancer greater than 1.5, and for NSCLC an OR of 6.75 (95% CI 6.60-6.89) (Figure 5.6). After adjustment for potential confounders age, sex, income domain of IMD and CCI, all cancer sites apart from HL were still significantly different to breast cancer but with attenuated ORs. Also, HL was no longer significantly different compared with breast cancer after adjusting only for age and sex. The odds of hospitalised CVD in NSCLC patients were significantly higher than in breast cancer patients even after adjustment (OR 3.06; 95% CI 2.98-3.14).

In the overall population, compared with patients not undergoing any specific anticancer treatment, those receiving surgery, radiotherapy or chemotherapy had lower odds of CVD (surgery: OR 0.41 [95% CI 0.41-0.42]; radiotherapy: OR 0.50 [95% CI 0.50-0.51]; chemotherapy: OR 0.43 [95% CI 0.42-0.44]) (Table 5.5). Similarly, patients receiving surgery, radiotherapy or chemotherapy had lower odds of CVD compared with those not treated in most individual tumour cohorts (breast, colon, rectal, DLBCL and Hodgkin lymphoma), but not in the prostate and NSCLC cohorts.

5.4.2. Geographical distribution

Table 5.6 outlines patients, tumour and treatment characteristics with CA grouped in tertiles of CVD prevalence. Supplementary table 5.16 prevalence

of hospitalised CVD according to the distribution of CA in tertiles. The hospitalised CVD prevalence was 14.5% in the 7 CA included in the lower tertile, 15.5% in the 5 CA included in the middle tertile and 18.6% in the 8 CA included in the higher tertile. We did not observe any significant differences in patient and tumour characteristics and treatment modalities among the tertiles. Similarly, the prevalence of individual hospitalised CVD categories did not significantly differ among tertiles (cerebrovascular disease: 3.0% in the lower tertile versus 3.2% in the middle tertile versus 3.4% in the higher tertile; stroke: 1.2% versus 1.3% versus 1.5%; CHF: 2.9% versus 3.2% versus 4.0%; ischaemic heart disease: 9.0% versus 9.7% versus 11.9%; acute myocardial infarction: 1.5% versus 1.5% versus 1.9%; peripheral artery disease: 2.8% versus 3.0% versus 4.1%; valvular heart disease: 2.4% versus 2.8% versus 3.2%) (Supplementary table 5.16). Supplementary table 5.17 outlines the number of hospitalised CVD records retrieved from various datasets within each tertile.

Among individual CA, in the overall population the prevalence of hospitalised CVD ranged from 13.4% to 19.6% (Supplementary table 5.18). Figure 5.7 outlines the burden and the prevalence of hospitalised CVD across the various CAs. Within each tumour cohort, there was a significant difference in the range of hospitalised CVD prevalence among CA (breast cancer cohort: 6.0%-9.2%; colon cancer cohort: 19.2%-26.8%; rectal cancer cohort: 14.1%-20.4%; prostate cancer cohort: 11.6%-19.6%; NSCLC cohort: 31.4%-41.1%; DLBCL cohort: 19.4%-25.7%; Hodgkin lymphoma cohort: 6.7%-16.9%) (Supplementary table 5.18). Figures 5.8-5.14 include heat maps showing the hospitalised CVD prevalence within each cancer cohort. The funnel plots included in Figure 5.15 show the variation in hospitalised CVD rates for each tumour cohort in an unadjusted model and following adjustment for confounding factors including age, sex, CCI, income domain of IMD and stage. The CA corresponding to the outlier IDs reported in Figure 5.15 are shown in Supplementary table 5.19.

5.5. DISCUSSION

Our study is a large-scale, population-based analysis describing the prevalence of hospitalised CVD in individuals with curable cancers. Understanding the intersection between cancer and CVD is key to informing anticancer treatment decisions, interpreting outcome data, and planning healthcare provision.[37] In our analysis, we used linked national registry datasets of patients diagnosed with curable malignancies over six years in England and found an overlap between cancer and hospitalised CVD in 16.2% of individuals included in the overall cohort.

An analysis of 2014 English National Cancer Diagnosis Audit data linked to primary care records found that more than three quarters of patients with a cancer diagnosis had at least one of 11 chronic comorbid conditions.[38] In this cohort, the standardised prevalence of hospitalised CVD was broadly comparable across various tumour types. Our investigations revealed a much higher standardised prevalence in NSCLC patients, reflecting the very high observed prevalence in this cohort (>35%) and suggesting that age and sex can only partially explain the high hospitalised CVD burden in this group. This difference is likely to be driven not only by the older age of individuals with NSCLC, but also by the role of risk factors common to CVD and lung malignancies, particularly smoking.[4] This may also explain the higher rate of hospitalised CVD in this specific cohort compared with patients with prostate cancer seen in our study. Lifestyle factors may also explain the difference in CVD prevalence observed among the various tumour groups, including the higher CVD rate in the NSCLC cohort. On the other hand, the difference in the odds of CVD between the Hodgkin lymphoma and the breast cancer cohort disappeared after adjusting for age and sex (Figure 5.6), which suggests that these are key drivers of the CVD prevalence in this specific lymphoma cohort.

This finding is consistent with previous evidence showing that comorbidities are more common among lung cancer survivors and less frequent among breast and prostate cancer survivors.[39] Relatively few studies exist examining the frequency of hospitalised CVD, specifically in patients with

cancer at the time of diagnosis. However, one previous study documented that 43.6% of patients diagnosed with curable NSCLC in England in 2012-2016 had hospitalised CVD,[32] which also significantly impacted resection and mortality rates in this population.

The relationship between CVD and anticancer treatments is a key area of investigation. In the general population, older age is associated with a higher prevalence of CVD[40] and CVD contributes to an increasing burden of morbidity and disability in community-dwelling older individuals. Prospective trials and cancer registry analyses have documented higher risk of congestive heart failure in patients with potentially curable malignancies (including Hodgkin lymphoma and breast cancer) and CVD and cardiovascular risk factors receiving cytotoxic or targeted therapies.[41-45] Similar concerns exist for patients potentially suitable for locoregional treatments such as surgery and radiotherapy.[33, 46] Pre-existing CVD may represent an absolute contraindication for pursuing specific anticancer treatment options or requires adjustments possibly hindering the chances of cure in individuals with potentially curable cancer diagnosed with this specific comorbidity. Therefore, this is a relevant concern in routine oncology clinical practice warranting further investigation. In future analyses, we plan to examine the geographical variation of hospitalised CVD rates and the impact of pre-existing hospitalised CVD on anticancer treatments received.

Elucidating the burden of hospitalised CVD in patients with cancer is also important because this is an increasingly prevalent exclusion criterion for studies investigating novel anticancer therapeutic developments.[47] This has substantial implications on limiting not only the access of patients with cancer to experimental options, but also the applicability of trial findings to populations seen in the real world.[48] These considerations are also crucial for the development of clinical trials and drug labelling purposes.[49]

Our study confirms that men, older individuals and those living in socio-economically deprived areas had a higher burden of hospitalised CVD. Population studies have identified male gender as a risk factor for higher rates

of coronary artery disease and associated mortality.[50] Patients undergoing surgery, radiotherapy or chemotherapy have lower odds of CVD compared with those not treated in the overall and in most individual tumour cohorts (Table 5.5). As individuals with cancer age, the number of comorbid conditions increases,[39, 51] which may substantially influence overall and non-cancer-related mortality,[52-54] but may also affect tolerance to anticancer treatments.[55] For patients diagnosed with breast cancer, hospitalised CVD was also found to impact on tumour-specific mortality.[56]

This study has also demonstrated an increasing prevalence of hospitalised CVD for patients with cancer associated with deprivation in all tumour cohorts except Hodgkin lymphoma. In this analysis, increasing IMD income domain was also associated with more advanced tumour stage in the individual cancer cohorts. Socio-economic inequalities have a significant impact on cancer presentation, diagnosis and treatment.[57] Despite the efforts of government strategies aiming to reduce socio-economic inequalities in England, their impact on cancer survival has not substantially changed in recent years.[58] An accurate review of care pathways for patients with cancer and comorbidities may be able to mitigate their detrimental effect on oncological outcomes.[59]

Interestingly, our analysis also suggests that hospitalised CVD cases can be ascertained in HES although it is unclear whether this is valid for specified conditions and how accurate their coding is. A significant number of CVD codes were retrieved from HES, while fewer were included also in the various NICOR datasets. Despite both NICOR and HES data focus on hospital-based diagnoses captured in the inpatient setting, NICOR includes data on procedures and HES data are derived from admission codes. Therefore, these datasets include different populations. Since HES was the primary source of CVD records (Figure 5.2), this finding suggests that HES is a sensitive source of data to ascertain the burden of CVD in this population. While NICOR databases may be more specific and have better diagnostic accuracy to determine specific hospitalised CVD categories and its severity, HES is a

valuable source of data to elucidate the co-existence of cancer and this specific comorbidity.

This analysis also documented significant variation in the prevalence of hospitalised CVD based on geographical area. The variation across various CA persisted even after adjusting for risk factors potentially influencing the burden of cardiovascular comorbidities (such as age, sex, income deprivation and comorbidities). This is a key finding to better inform allocation of resources to local health authorities and the provision of cardio-oncology services able to provide specialist input on the management of CVD in a population of individuals diagnosed with curable malignancies.[60]

There are also some limitations of this study. First, we have not analysed several risk factors, such as smoking, diet, physical activity, obesity, alcohol and concurrent medications, that are not routinely recorded in cancer registry datasets. These may influence both hospitalised CVD and cancer and may have contributed to our findings. On the other hand, social deprivation might represent a proxy for some health and lifestyle risk factors. Data on cardiovascular risk factors are captured only by the NICOR datasets: therefore, these are available only for a subset of the individuals included in this study. Second, our analysis is focused on secondary care events and does not investigate events only recorded in primary care. This approach has the advantage of diagnostic accuracy (including more “significant” CVD diagnoses) and the disadvantages of not assessing the burden of primary care CVD diagnoses and not accounting for the potential gaps between primary and secondary care in different groups of patients. This may have led to under-estimating the prevalence of CVD,[61] although HES outpatient has limited diagnoses data and integrating NICOR data has not substantially altered our results. Also, we have not analysed data on the severity of CVD since these data are not captured in HES. Next, we excluded patients with missing data on several variables which results in a large amount of missing data. We performed a complete case analysis (analysing records with available records) which requires a plausible missing at random assumption (i.e., the data we included is representative of the whole database).[62] We may have achieved

inaccurate results because we cannot necessarily assume the data are missing at random. However, the data we included in our analysis was from 2013 when recording of variables such as cancer stage in NCRD improved to minimise this potential limitation.[63] An additional limitation is related to the fact that the population included is not racially diverse and these findings may not necessarily be applicable in different geographical areas. Also, in this analysis we have not investigated the impact of CVD on cancer management, although this will be the primary endpoint of a subsequent VICORI study. Additionally, it remains to be confirmed whether HES is a valuable data source to investigate the prevalence of cerebrovascular comorbidities in patients with cancer. Finally, we have excluded CVD diagnosed after a cancer diagnosis to avoid including conditions caused by anticancer treatments similarly to previous studies.[33]

In conclusion, as expected this study found a significant overlap between hospitalised CVD and diagnoses of potentially curable cancers, along with substantial differences based on age, gender, socio-economic deprivation and across different types of tumours. A key innovative feature of our analysis is the use of both cancer registry and CVD audit datasets to elucidate the burden of CVD in cancer patient cohorts alongside key variables such as comorbidities and IMD income domain. Overall, these results have crucial implications at two levels. At patient level, for individuals diagnosed with these potentially curable malignancies the presence of CVD may have significant impact not only on mortality and treatment benefits and tolerability, but also on trial eligibility and therefore on the applicability of the existing evidence that should inform their management. At population level, these findings are important to interpreting survival differences, treatment uptakes and outcomes existing within and among countries and to informing healthcare policy strategies and provision of specialised cardio-oncology services.

Further research is needed to investigate the reasons for variation in the prevalence of hospitalised CVD in individuals with cancer. As part of the VICORI, we plan to evaluate the impact of hospitalised CVD on the management of these common curable malignancies. In particular, we will

investigate the effect of pre-existing CVD on treatments received (including specific systemic anticancer agents, surgical procedures and radiotherapy). We will also examine the regional variation in treatments received for each tumour type according to CVD history and examine all-cause mortality and cancer versus non cancer-specific mortality based on cancer type, specific treatments delivered and CVD. These investigations are key to interpret cancer outcome and treatment variation in England that CVD may (at least partially) contribute to. Additional areas of investigation may also involve comparing the burden of CVD in England with other countries where cardiology and cancer registry datasets are available. This aspect would be important in order to interpret cancer outcome and treatment variation at international level and to develop tailored cancer policy strategies. This research also complements other analyses included in the VICORI initiative that are currently being conducted on the following topics: 1) the impact of cancer diagnosis on the management of cardiovascular conditions; 2) the effect of cardiovascular treatments, interventions and surgery on the risk of developing cancer and its outcomes; 3) the influence of cancer treatments on the risk of developing CVD and its outcomes.[18]

5.6. PROGRESS TO PRESENTATION AND PUBLICATION

This analysis was performed in collaboration with Dr David Adlam, Dr Michael Sweeting and Dr Catherine A. Welch (University of Leicester). I have presented these findings at the 2021 ESMO conference[64] and, as an oral presentation, at the 2021 European Network of Cancer Registries Scientific Meeting.[65] I have published this study manuscript in the Journal of the American College of Cardiology Cardio-Oncology (impact factor 8.422) as first author.[66]

5.7. REFERENCES

1. CancerData. 2018 07/02/2020]; Available from: https://www.cancerdata.nhs.uk/.
2. Arnold, M., et al., Progress in cancer survival, mortality, and incidence in seven high-income countries 1995-2014 (ICBP SURVMARK-2): a population-based study. Lancet Oncol, 2019. 20(11): p. 1493-1505.
3. Jones, N.R., et al., Survival of patients with chronic heart failure in the community: a systematic review and meta-analysis. Eur J Heart Fail, 2019. 21(11): p. 1306-1325.
4. Koene, R.J., et al., Shared Risk Factors in Cardiovascular Disease and Cancer. Circulation, 2016. 133(11): p. 1104-14.
5. Vincent, L., et al., Cardiovascular Disease and Cancer: Is There Increasing Overlap? Curr Oncol Rep, 2019. 21(6): p. 47.
6. Curigliano, G., et al., Cardiotoxicity of anticancer treatments: Epidemiology, detection, and management. CA Cancer J Clin, 2016. 66(4): p. 309-25.
7. Renzi, C., et al., Comorbid chronic diseases and cancer diagnosis: disease-specific effects and underlying mechanisms. Nat Rev Clin Oncol, 2019. 16(12): p. 746-761.
8. National Lung Cancer Audit. Royal College of Physicians.
9. Blum, T.G., et al., The European initiative for quality management in lung cancer care. Eur Respir J, 2014. 43(5): p. 1254-77.
10. Iacobucci, G., Cancer survival in England: rates improve and variation falls. Bmj, 2019. 365: p. l1532.
11. Jones, R.P., et al., Effect of specialist decision-making on treatment strategies for colorectal liver metastases. Br J Surg, 2012. 99(9): p. 1263-9.
12. Morris, E. and T. Treasure, Surgical management and outcomes of colorectal cancer liver metastases. Cancer Epidemiol, 2018. 52: p. 160-161.
13. Battisti, N.M.L., et al. Is age a barrier to chemotherapy? Rates of treatment in older patients with breast, colon or lung cancer in England in 2014: a national registry study. in European Society for Medical Oncology 2018 Congress. 2018. Madrid, Spain.
14. Ring, A., et al., Adjuvant chemotherapy in elderly women with breast cancer (AChEW): an observational study identifying MDT perceptions and barriers to decision making. Ann Oncol, 2013. 24(5): p. 1211-9.

15. Battisti, N.M.L. Is age a barrier to systemic anti-cancer therapy? A national registry study. in National Cancer Research Institute (NCRI) Conference. 2019. Glasgow, UK.
16. Allemani, C., et al., Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. Lancet, 2018. 391(10125): p. 1023-1075.
17. Henson, K.E., et al., Data Resource Profile: National Cancer Registration Dataset in England. International Journal of Epidemiology, 2019. 49(1): p. 16-16h.
18. Virtual Cardio-Oncology Research Initiative (VICORI). 17/02/2021]; Available from: https://vicori.lcbru.le.ac.uk/.
19. Sweeting, M.J., et al., Data Resource Profile: The Virtual Cardio-Oncology Research Initiative (VICORI) linking national English cancer registration and cardiovascular audits. Int J Epidemiol, 2021.
20. Herbert, A., et al., Data Resource Profile: Hospital Episode Statistics Admitted Patient Care (HES APC). International Journal of Epidemiology, 2017. 46(4): p. 1093-1093i.
21. Wilkinson, C., et al., The Myocardial Ischaemia National Audit Project (MINAP). Eur Heart J Qual Care Clin Outcomes, 2020. 6(1): p. 19-22.
22. Adult Cardiac Surgery (Surgery Audit). [cited 2021 17/12/2021]; Available from: https://www.nicor.org.uk/adult-cardiac-surgery-surgery-audit/.
23. Adult Percutaneous Coronary Interventions (Angioplasty audit). [cited 2021 17/12/2021]; Available from: https://www.nicor.org.uk/adult-percutaneous-coronary-interventions-angioplasty-audit/.
24. Heart Failure (Heart Failure audit). [cited 2021 17/12/2021]; Available from: https://www.nicor.org.uk/heart-failure-heart-failure-audit/.
25. 2018/19 Data quality reports for each hospital. 2019 05/11/2021]; Available from: https://www.nicor.org.uk/2018-19-data-quality-reports-for-each-hospital/.
26. The processing cycle and HES data quality. 2021 05/11/2021]; Available from: https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/hospital-episode-statistics/the-processing-cycle-and-hes-data-quality.
27. National Radiotherapy Dataset (RTDS): http://www.ncin.org.uk/collecting_and_using_data/rtds. 05/11/2021]; Available from: http://www.ncin.org.uk/collecting_and_using_data/rtds.

28. International Statistical Classification of Diseases and Related Health Problems (10th Revision). 2010, World Health Organization. p. 201.
29. Bright, C.J., et al., Data Resource Profile: The Systemic Anti-Cancer Therapy (SACT) dataset. Int J Epidemiol, 2020. 49(1): p. 15-15l.
30. Charlson, M.E., et al., A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis, 1987. 40(5): p. 373-83.
31. National Institute for Cardiovascular Outcomes Research (NICOR): https://www.nicor.org.uk/. 17/02/2021]; Available from: https://www.nicor.org.uk/.
32. Unger, J.M., et al., Association of Patient Comorbid Conditions With Cancer Clinical Trial Participation. JAMA Oncol, 2019. 5(3): p. 326-333.
33. Welch, C.A., et al., Impact on survival of modelling increased surgical resection rates in patients with non-small-cell lung cancer and cardiovascular comorbidities: a VICORI study. Br J Cancer, 2020. 123(3): p. 471-479.
34. Spiegelhalter, D.J., Funnel plots for comparing institutional performance. Stat Med, 2005. 24(8): p. 1185-202.
35. Stata Statistical Software: Release 16. 2019, StataCorp: College Station, TX, USA.
36. R: A language and environment for statistical computing. R Foundation for Statistical Computing 2020; Available from: https://www.R-project.org/.
37. Adlam, D. and M.D. Peake, Cancer and heart disease: new bedfellows in the cardiovascular landscape. Eur Heart J Qual Care Clin Outcomes, 2017. 3(3): p. 168-170.
38. Koo, M.M., et al., The prevalence of chronic conditions in patients diagnosed with one of 29 common and rarer cancers: A cross-sectional study using primary care data. Cancer Epidemiol, 2020. 69: p. 101845.
39. Bluethmann, S.M., A.B. Mariotto, and J.H. Rowland, Anticipating the "Silver Tsunami": Prevalence Trajectories and Comorbidity Burden among Older Cancer Survivors in the United States. Cancer Epidemiol Biomarkers Prev, 2016. 25(7): p. 1029-36.
40. Savji, N., et al., Association between advanced age and vascular disease in different arterial territories: a population database of over 3.6 million subjects. J Am Coll Cardiol, 2013. 61(16): p. 1736-43.
41. Chavez-MacGregor, M., et al., Trastuzumab-related cardiotoxicity among older patients with breast cancer. J Clin Oncol, 2013. 31(33): p. 4222-8.

42. Hershman, D.L., et al., Doxorubicin, cardiac risk factors, and cardiac toxicity in elderly patients with diffuse B-cell non-Hodgkin's lymphoma. J Clin Oncol, 2008. 26(19): p. 3159-65.
43. Perez, E.A., et al., Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the North Central Cancer Treatment Group N9831 adjuvant breast cancer trial. J Clin Oncol, 2008. 26(8): p. 1231-8.
44. Pinder, M.C., et al., Congestive heart failure in older women treated with adjuvant anthracycline chemotherapy for breast cancer. J Clin Oncol, 2007. 25(25): p. 3808-15.
45. Tan-Chiu, E., et al., Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. J Clin Oncol, 2005. 23(31): p. 7811-9.
46. Zou, B., et al., Radiotherapy-induced heart disease: a review of the literature. Precision Clinical Medicine, 2019. 2(4): p. 270-282.
47. Oren, M., O. Oren, and D.M. Mintzer, The use of cardiovascular disease states as exclusion criteria in breast cancer trials: A 4-decade perspective. Journal of Clinical Oncology, 2017. 35(15_suppl): p. e18053-e18053.
48. Bonsu, J., et al., Representation of Patients With Cardiovascular Disease in Pivotal Cancer Clinical Trials. Circulation, 2019. 139(22): p. 2594-2596.
49. Cancer Clinical Trial Eligibility Criteria: Patients with Organ Dysfunction or Prior or Concurrent Malignancies. Guidance for Industry. 2020, U.S. Department of Health and Human Services - Food and Drug Administration.
50. D'Agostino, R.B., Sr., et al., General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation, 2008. 117(6): p. 743-53.
51. Yancik, R., Cancer burden in the aged: an epidemiologic and demographic overview. Cancer, 1997. 80(7): p. 1273-83.
52. Asmis, T.R., et al., Age and comorbidity as independent prognostic factors in the treatment of non small-cell lung cancer: a review of National Cancer Institute of Canada Clinical Trials Group trials. J Clin Oncol, 2008. 26(1): p. 54-9.
53. Hines, R.B., et al., Predictive capacity of three comorbidity indices in estimating mortality after surgery for colon cancer. J Clin Oncol, 2009. 27(26): p. 4339-45.

54. Satariano, W.A. and D.R. Ragland, The effect of comorbidity on 3-year survival of women with primary breast cancer. Ann Intern Med, 1994. 120(2): p. 104-10.
55. Frasci, G., et al., Gemcitabine plus vinorelbine versus vinorelbine alone in elderly patients with advanced non-small-cell lung cancer. J Clin Oncol, 2000. 18(13): p. 2529-36.
56. Wu, A.H., et al., Diabetes and other comorbidities in breast cancer survival by race/ethnicity: the California Breast Cancer Survivorship Consortium (CBCSC). Cancer Epidemiol Biomarkers Prev, 2015. 24(2): p. 361-8.
57. Forrest, L.F., et al., Socio-economic inequalities in stage at diagnosis, and in time intervals on the lung cancer pathway from first symptom to treatment: systematic review and meta-analysis. Thorax, 2017. 72(5): p. 430-436.
58. Exarchakou, A., et al., Impact of national cancer policies on cancer survival trends and socioeconomic inequalities in England, 1996-2013: population based study. BMJ, 2018. 360: p. k764.
59. Peake, M.D., Deprivation, distance and death in lung cancer. Thorax, 2015. 70(2): p. 108-109.
60. Andres, M.S., J. Pan, and A.R. Lyon, What Does a Cardio-oncology Service Offer to the Oncologist and the Haematologist? Clin Oncol (R Coll Radiol), 2021. 33(8): p. 483-493.
61. Herrett, E., et al., Completeness and diagnostic validity of recording acute myocardial infarction events in primary care, hospital care, disease registry, and national mortality records: cohort study. BMJ : British Medical Journal, 2013. 346: p. f2350.
62. Carpenter, J.R. and M.G. Kenward, Multiple Imputation and its Application. 2012.
63. McPhail, S., et al., Stage at diagnosis and early mortality from cancer in England. British journal of cancer, 2015. 112 Suppl 1(Suppl 1): p. S108-S115.
64. Battisti, N.M.L., et al., 1831P Prevalence of cardiovascular disease in patients diagnosed with six common curable malignancies: A Virtual Cardio-Oncology Research Institute (VICORI) national registry dataset analysis. Annals of Oncology, 2021. 32: p. S1239.
65. Welch, C., et al. Cardiovascular disease prevalence in patients diagnosed with six curable tumours: a VICORI national registry analysis. in European Network of Cancer Registries Scientific Meeting 2021. 2021.

66. Battisti, N.M.L., et al., Prevalence of Cardiovascular Disease in Patients With Potentially Curable Malignancies: A National Registry Dataset Analysis. JACC CardioOncol, 2022. 4(2): p. 238-253.

5.8. TABLES

Table 5.1 – Eligibility criteria for the analysis.

Inclusion criteria	Exclusion criteria
Cancer diagnosis in the period 2013-2018 Cancer type and stage: • Stage I-III breast cancer (ICD-10 code C50) • Stage I-III colon/rectal cancer (ICD-10 codes C18, C19, C20) • Stage I-III prostate cancer (ICD-10 code C61) • Stage I-IIIA non small-cell lung cancer (ICD-10 C33-C34 with ICD-O-2 morphology not in list 8041, 8042, 8043, 8044, 8045) • Stage I-IV diffuse large B-cell lymphoma (ICD-10 C83.3) • Stage I-IV Hodgkin lymphoma (ICD-10 C81) Lived in England Finalised cancer registration	Age <18 years at diagnosis Missing NHS number All behaviour codes except malignant Age >100 years at diagnosis Missing mortality status Death/censoring date before diagnosis date Carcinoid morphology Stages 3B or 4 at diagnosis Missing disease stage at diagnosis Diagnosis from death certificate only Men diagnosed with breast cancer Females diagnosed with prostate cancer Duplicates

Abbreviations: ICD-10: International Statistical Classification of Diseases and Related Health Problems-10.

Table 5.2 – List of Cancer Alliances included in the geographical analysis.

ID	Cancer Alliance
1	North East and Cumbria
2	Lancashire and South Cumbria
3	Greater Manchester
4	East Midlands
5	Surrey and Sussex
6	Cheshire and Merseyside
7	Thames Valley
8	East of England - North
9	South East London
10	Humber, Coast and Vale
11	Kent and Medway
12	Wessex
13	West Midlands
14	West Yorkshire and Harrogate
15	South Yorkshire and Bassetlaw
16	East of England - South
17	North Central London
18	RM Partners
19	Somerset, Wiltshire, Avon and Gloucestershire
20	Peninsula

Table 5.3 – Patient and tumour characteristics in the overall and individual tumour cohorts.

Variable	Full cohort	Breast	Colon	Rectal	Prostate	NSCLC	DLBCL	Hodgkin lymphoma
Total	634,240	226,516	91,210	39,688	175,639	70,458	23,426	7,303
Age at cancer diagnosis (years), mean (SD)	67.2 (12.7)	62.5 (13.9)	71.2 (12.3)	68.6 (12.2)	69.1 (8.6)	72.9 (10.3)	52.5 (18.3)	68.0 (13.9)
Age at cancer diagnosis (years), n (% of total)								
25-34	7,802 (1.2)	17,286 (7.6)	912 (1.0)	371 (0.9)	4 (0.0)	155 (0.2)	652 (2.8)	1,686 (23.1)
35-44	23,295 (3.7)	50,203 (22.2)	2,036 (2.2)	999 (2.5)	366 (0.2)	444 (0.6)	994 (4.2)	1,170 (16.0)
45-54	73,968 (11.7)	51,844 (22.9)	5,710 (6.3)	3,527 (8.9)	8,534 (4.9)	2,655 (3.8)	2,214 (9.5)	1,125 (15.4)
55-64	131,394 (20.7)	55,876 (24.7)	15,385 (16.9)	8,860 (22.3)	39,927 (22.7)	10,327 (14.7)	3,975 (17.0)	1,076 (14.7)
65-74	207,512 (32.7)	32,983 (14.6)	27,277 (29.9)	12,630 (31.8)	79,141 (45.1)	24,292 (34.5)	7,138 (30.5)	1,158 (15.9)
75-84	144,670 (22.8)	14,302 (6.3)	28,583 (31.3)	9,995 (25.2)	41,980 (23.9)	23,882 (33.9)	6,364 (27.2)	883 (12.1)
≥85	45,599 (7.2)	17,286 (7.6)	11,307 (12.4)	3,306 (8.3)	5,687 (3.2)	8,703 (12.4)	2,089 (8.9)	205 (2.8)
Sex, n (% of total)								
Male	303,021 (47.8)	0 (0.0)	48,431 (53.1)	25,420 (64.0)	175,639 (100)	36,229 (51.4)	12,981 (55.4)	4,321 (59.2)

Female	331,219 (52.2)	226,516 (100)	42,779 (46.9)	14,268 (36.0)	0 (0.0)	34,229 (48.6)	10,445 (44.6)	2,982 (40.8)
Ethnicity, n (% of total)								
White	564,687 (89.0)	198,738 (87.7)	83,317 (91.3)	36,153 (91.1)	153,282 (87.3)	66,312 (94.1)	20,921 (89.3)	5,964 (81.7)
Mixed	2,694 (0.4)	1,184 (0.5)	274 (0.3)	131 (0.3)	762 (0.4)	163 (0.2)	99 (0.4)	81 (1.1)
Asian	16,923 (2.7)	8,044 (3.6)	1,883 (2.1)	1,066 (2.7)	3,309 (1.9)	1,183 (1.7)	952 (4.1)	486 (6.7)
Black	13,579 (2.1)	4,522 (2.0)	1,339 (1.5)	418 (1.1)	6,093 (3.5)	625 (0.9)	351 (1.5)	231 (3.2)
Other	7,124 (1.1)	3,118 (1.4)	911 (1.0)	388 (1.0)	1,723 (1.0)	518 (0.7)	311 (1.3)	155 (2.1)
Missing	29,233 (4.6)	10,910 (4.8)	3,486 (3.8)	1,532 (3.9)	10,470 (6.0)	1,657 (2.4)	792 (3.4)	386 (5.3)
Income domain of the Index of Multiple Deprivation[1]								
1 - Least	140,873 (22.2)	51,814 (22.9)	20,257 (22.2)	8,776 (22.1)	43,793 (24.9)	9,891 (14.0)	5,020 (21.4)	1,322 (18.1)
2	144,911 (22.8)	52,228 (23.1)	21,337 (23.4)	9,039 (22.8)	43,060 (24.5)	12,467 (17.7)	5,317 (22.7)	1,463 (20.0)
3	131,623 (20.8)	47,406 (20.9)	18,932 (20.8)	8,361 (21.1)	36,888 (21.0)	13,612 (19.3)	4,880 (20.8)	1,544 (21.1)
4	114,231 (18.0)	40,605 (17.9)	16,392 (18.0)	7,171 (18.1)	28,899 (16.5)	15,262 (21.7)	4,371 (18.7)	1,531 (21.0)
5 - Most	102,602 (16.2)	34,463 (15.2)	14,292 (15.7)	6,341 (16.0)	22,999 (13.1)	19,226 (27.3)	3,838 (16.4)	1,443 (19.8)

[1] Income domain of the Index of Multiple Deprivation derived in 2015 used for patients diagnosed with cancer in 2013 and income domain of the Index of Multiple Deprivation derived in 2019 used for patients diagnosed with cancer after 2013.

Charlson comorbidity index[2], n (% of total)								
0	295,961 (46.7)	106,251 (46.9)	43,371 (47.6)	18,900 (47.6)	79,618 (45.3)	33,258 (47.2)	11,051 (47.2)	3,512 (48.1)
1	53,655 (8.5)	19,325 (8.5)	7,641 (8.4)	3,364 (8.5)	14,857 (8.5)	6,020 (8.5)	1,840 (7.9)	608 (8.3)
2	155,699 (24.5)	55,420 (24.5)	22,466 (24.6)	9,708 (24.5)	43,368 (24.7)	17,203 (24.4)	5,805 (24.8)	1,729 (23.7)
3	65,527 (10.3)	23,372 (10.3)	9,293 (10.2)	4,078 (10.3)	18,266 (10.4)	7,278 (10.3)	2,504 (10.7)	736 (10.1)
≥4	56,561 (8.9)	20,238 (8.9)	8,193 (9.0)	3,533 (8.9)	15,547 (8.9)	6,283 (8.9)	2,126 (9.1)	641 (8.8)
Missing[3]	6,837 (1.1)	1,910 (0.8)	246 (0.3)	105 (0.3)	3,983 (2.3)	416 (0.6)	100 (0.4)	77 (1.1)
Screen-detected, n (% of total)								
Yes	-	99,072 (43.7)	-	-	-	-	-	-
No	-	75,931 (33.5)	-	-	-	-	-	-
Missing	-	51,513 (22.7)	-	-	-	-	-	-
TNM stage, n (% of total)								
I	255,320 (40.3)	104,899 (46.3)	19,213 (21.1)	12,357 (31.1)	79,477 (45.3)	33,890 (48.1)	4,478 (19.1)	1,006 (13.8)
II	211,316 (33.3)	98,987 (43.7)	36,820 (40.4)	9,365 (23.6)	44,469 (25.3)	15,322 (21.7)	3,973 (17.0)	2,380 (32.6)
III	154,349 (24.3)	22,630 (10.0)	35,177 (38.6)	17,966 (45.3)	51,693 (29.4)	21,246 (30.2)	4,066 (17.4)	1,571 (21.5)
IV	13,255 (2.1)	-	-	-	-	-	10,909 (46.6)	2,346 (32.1)

[2] 5 years before diagnosis and excluding cardiovascular disease.

[3] Missing if not linked to Hospital Episode Statistics.

Laterality, n (% of total)								
Left		115,340 (50.9)	-	-	-	29,043 (41.2)	-	-
Right		108,849 (48.1)	-	-	-	40,480 (57.5)	-	-
Bilateral		2,219 (1.0)	-	-	-	122 (0.2)	-	-
Missing		108 (0.0)	-	-	-	813 (1.2)	-	-

Abbreviations: SD: standard deviation; NSCLC: non-small cell lung cancer; DLBCL: diffuse large B-cell lymphoma.

Table 5.4 – Prevalence of cardiovascular disease n (%) according to patient and tumour characteristics in the overall and individual tumour cohorts.[1]

Variable	Full cohort N = 634,240	Breast N = 226,516	Colon N = 91,210	Rectal N = 39,688	Prostate N = 175,639	NSCLC N = 70,458	DLBCL N = 23,426	Hodgkin lymphoma N = 7,303
Total with prior CVD	102,834 (16.2)	17,453 (7.7)	20,161 (22.1)	6,699 (16.9)	27,123 (15.4)	25,459 (36.1)	5,091 (21.7)	850 (11.6)
Age at cancer diagnosis (years)								
25-34	76/7,802 (1.0)	28/4,022 (0.7)	8/912 (0.9)	3/371 (0.8)	0/4 (0.0)	6/155 (3.9)	16/652 (2.5)	15/1,686 (0.9)
35-44	269/23,295 (1.2)	148/17,286 (0.9)	34/2,036 (1.7)	22/999 (2.2)	6/366 (1.6)	14/444 (3.2)	25/994 (2.5)	20/1,170 (1.7)
45-54	2,112/73,968 (2.9)	858/50,203 (1.7)	289/5,710 (5.1)	143/3,527 (4.1)	322/8,534 (3.8)	282/2,655 (10.6)	155/2,214 (7.0)	63/1,125 (5.6)
55-64	10,240/131,394 (7.8)	1,851/51,844 (3.6)	1,521/15,385 (9.9)	764/8,860 (8.6)	3,245/39,927 (8.1)	2,198/10,327 (21.3)	526/3,975 (13.2)	135/1,076 (12.5)
65-74	32,867/207,512 (15.8)	4,263/55,876 (7.6)	5,177/27,277 (19.0)	1,985/12,630 (15.7)	11,692/79,141 (14.8)	8,007/24,292 (33.0)	1,496/7,138 (21.0)	247/1,158 (21.3)
75-84	40,124/144,670 (27.7)	5,939/32,983 (18.0)	8,709/28,583 (30.5)	2,662/9,995 (26.6)	9,948/41,980 (23.7)	10,558/23,882 (44.2)	2,020/6,364 (31.7)	288/883 (32.6)
≥85	17,148/45,599 (37.6)	4,366/14,302 (30.5)	4,423/11,307 (39.1)	1,120/3,306 (33.9)	1,910/5,687 (33.6)	4,394/8,703 (50.5)	853/2,089 (40.8)	82/205 (40)
Sex								

[1] Numbers refer to tumour diagnoses (and not to patients).

Male	63,318/303,021 (20.9)	-	12,479/48,431 (25.8)	4,902/25,420 (19.3)	-	15,009/36,229 (41.4)	3,240/12,981 (25.0)	565/4,321 (13.1)
Female	39,518/331,219 (11.9)	-	7,682/42,779 (18.0)	1,797/14,268 (12.6)	-	10,450/34,229 (30.5)	1,851/10,445 (17.7)	285/2,982 (9.6)
Ethnicity								
White	96,224/564,687 (17.0)	16,643/202,429 (8.2)	19,060/83,317 (22.9)	6295/36,153 (17.4)	24,993/153,282 (16.3)	24,251/66,312 (36.6)	4,689/20,921 (22.4)	752/5,964 (12.6)
Mixed	264/2,694 (9.8)	60/1199 (5.0)	44/274 (16.1)	19/131 (14.5)	92/762 (12.1)	38/163 (23.3)	12/99 (12.1)	1/81 (1.2)
Asian	2,585/16,923 (15.3)	590/8,133 (7.3)	387/1,883 (20.6)	189/1066 (17.7)	725/3,309 (21.9)	413/1,183 (34.9)	233/952 (24.5)	58/486 (11.9)
Black	1,343/13,579 (9.9)	249/4,576 (5.4)	205/1,339 (15.3)	54/418 (12.9)	613/6,093 (10.1)	171/625 (27.4)	39/351 (11.1)	16/231 (6.9)
Other	744/7,124 (10.4)	138/3,144 (4.4)	132/911 (14.5)	38/388 (9.8)	215/1,723 (12.5)	155/518 (29.9)	54/311 (17.4)	12/155 (7.7)
Income domain of the Index of Multiple Deprivation[2]								
1 - Least	18,715/14,0873 (13.3)	3,153/51,814 (6.1)	3,990/20,257 (19.7)	1,306/8,776 (14.9)	5,903/43,793 (13.5)	3,228/9,891 (32.6)	986/5,020 (19.6)	149/1,322 (11.3)
2	21,433/144,911 (14.8)	3,577/52,228 (6.8)	4,386/21,337 (20.6)	1,367/9,039 (15.1)	6,392/43,060 (14.8)	4,403/12,467 (35.3)	1,147/5,317 (21.6)	161/1,463 (11.0)
3	21,090/131,623 (16.0)	3,715/47,406 (7.8)	4,202/18,932 (22.2)	1,403/8,361 (16.8)	5,729/36,888 (15.5)	4,808/13,612 (35.3)	1,066/4,880 (21.8)	167/1,544 (10.8)

[2] Income domain of the Index of Multiple Deprivation derived in 2015 used for patients diagnosed with cancer in 2013 and income domain of the Index of Multiple Deprivation derived in 2019 used for patients diagnosed with cancer after 2013.

4	20,321/114,231 (17.8)	3,534/40,605 (8.7)	3,877/16,392 (23.7)	1,331/7,171 (18.6)	4,758/28,899 (16.5)	5,631/15,262 (36.9)	995/4,371 (22.8)	195/1,531 (12.7)
5 - Most	21,277/102,602 (20.7)	3,474/34,463 (10.1)	3,706/14,292 (25.9)	1,292/6,341 (20.4)	4,341/22,999 (18.9)	7,389/19,226 (38.4)	897/3,838 (23.4)	178/1,443 (12.3)
Charlson comorbidity index[3]								
0	48,709/29,5961 (16.5)	8,281/10,6251 (7.8)	9,703/43,371 (22.4)	3,213/18,900 (17.0)	12,760/79,618 (16.0)	11,971/33,258 (36.0)	2,391/11,051 (21.6)	390/3,512 (11.1)
1	8,768/53,655 (16.3)	1,485/19,325 (7.7)	1,707/7,641 (22.3)	582/3,364 (17.3)	2,269/14,857 (15.3)	2,244/6,020 (37.3)	403/1,840 (21.9)	78/608 (12.8)
2	25,260/155,699 (16.2)	4,312/55,420 (7.8)	4,774/22,466 (21.2)	1,644/9,708 (16.9)	6,758/43,368 (15.6)	6,283/17,203 (36.5)	1,279/5,805 (22.0)	210/1,729 (12.1)
3	10,671/65,527 (16.3)	1,825/2,3372 (7.8)	2,138/9,293 (23.0)	682/4,078 (16.7)	2,802/18,266 (15.3)	2,605/7,278 (35.8)	533/2,504 (21.3)	86/736 (11.7)
≥4	9,275/56,561 (16.4)	1,542/20,238 (7.6)	1,821/8,193 (22.2)	573/3,533 (16.2)	2,501/15,547 (16.1)	2,270/6,283 (36.1)	484/2,126 (22.8)	84/641 (13.1)
Screen-detected								
Yes	-	3,312/75,931 (4.4)	-	-	-	-	-	-
No	-	9,854/99,072 (9.9)	-	-	-	-	-	-
TNM stage								

[3] 5 years before diagnosis and excluding cardiovascular disease.

I	41,631/259,292 (16.1)	7,368/104,899 (7)	4,460/19,213 (23.2)	2,416/12,357 (19.6)	12,714/79,477 (16.0)	12,927/33,890 (38.1)	924/4,478 (20.6)	104/1,006 (10.3)
II	31,190/213,237 (14.6)	8,381/98,987 (8.5)	8,291/36,820 (22.5)	1,724/9,365 (18.4)	6,198/44,469 (13.9)	5,344/15,322 (34.9)	750/3,973 (18.9)	186/2,380 (7.8)
III	28,398/155,162 (18.3)	1,704/22,630 (7.5)	7,410/35,177 (21.1)	2,559/17,966 (14.2)	8,211/51,693 (15.9)	7,188/21,246 (33.8)	937/4,066 (23.0)	228/1,571 (14.5)
IV	2,816/13,267 (21.2)	-	-	-	-	-	2,480/10,909 (22.7)	332/2,346 (14.2)
Laterality								
Left	19,404/144,383 (13.4)	8,974/115,340 (7.8)	-	-	-	104,30/29,043 (35.9)	-	-
Right	22,817/149,329 (15.3)	8,189/108,849 (7.5)	-	-	-	14628/40,,480 (36.1)	-	-
Bilateral	322/2,341 (13.8)	274/2,219 (12.3)	-	-	-	48/122 (39.3)	-	-

Abbreviations: CVD: cardiovascular disease; NSCLC: non-small cell lung cancer; DLBCL: diffuse large B-cell lymphoma.

Table 5.5 – Unadjusted odds of hospitalisation with cardiovascular disease in the overall and individual tumour cohorts using logistic regression analysis.[1]

Variable	Full cohort N = 634,240	Breast N = 226,516	Colon N = 91,210	Rectal N = 39,688	Prostate N = 175,639	NSCLC N = 70,458	DLBCL N = 23,426	Hodgkin lymphoma N = 7,303
Total with prior CVD	102,834	17,452	201,61	6,699	27,123	25,458	5,091	850
Age at cancer diagnosis (years), OR (95% CI)								
25-34	0.05 (0.04, 0.07)	0.08 (0.06, 0.12)	0.04 (0.02, 0.08)	0.04 (0.01, 0.14)	N/A	0.08 (0.04, 0.19)	0.09 (0.06, 0.16)	0.03 (0.02, 0.06)
35-44	0.06 (0.06, 0.07)	0.10 (0.09, 0.12)	0.07 (0.05, 0.10)	0.12 (0.08, 0.18)	0.10 (0.04, 0.22)	0.07 (0.04, 0.11)	0.10 (0.07, 0.15)	0.06 (0.04, 0.10)
45-54	0.16 (0.15, 0.16)	0.21 (0.20, 0.23)	0.23 (0.20, 0.26)	0.23 (0.19, 0.27)	0.23 (0.20, 0.25)	0.24 (0.21, 0.27)	0.28 (0.24, 0.34)	0.22 (0.16, 0.29)
55-64	0.45 (0.44, 0.46)	0.45 (0.42, 0.47)	0.47 (0.44, 0.50)	0.51 (0.46, 0.55)	0.51 (0.49, 0.53)	0.55 (0.52, 0.58)	0.58 (0.52, 0.64)	0.53 (0.42, 0.67)
65-74	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
75-84	2.04 (2.01, 2.07)	2.66 (2.55, 2.77)	1.87 (1.80, 1.95)	1.95 (1.82, 2.08)	1.79 (1.74, 1.85)	1.61 (1.55, 1.67)	1.75 (1.62, 1.90)	1.79 (1.46, 2.18)
≥85	3.20 (3.13, 3.27)	5.32 (5.07, 5.58)	2.74 (2.61, 2.88)	2.75 (2.52, 3.00)	2.92 (2.75, 3.09)	2.07 (1.97, 2.18)	2.60 (2.35, 2.89)	2.46 (1.80, 3.36)
Sex, OR (95% CI)								
Male	1 (Reference)	-	1 (Reference)	1 (Reference)	-	1 (Reference)	1 (Reference)	1 (Reference)

[1] Numbers refer to tumour diagnoses (and not to patients).

Female	0.51 (0.51, 0.52)	-	0.63 (0.61, 0.65)	0.6 (0.57, 0.64)	-	0.62 (0.60, 0.64)	0.65 (0.61, 0.69)	0.70 (0.60, 0.82)
Ethnicity, OR (95% CI)								
White	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Mixed	0.53 (0.47, 0.60)	0.58 (0.45, 0.76)	0.64 (0.47, 0.89)	0.80 (0.49, 1.31)	0.70 (0.57, 0.88)	0.53 (0.37, 0.76)	0.48 (0.26, 0.87)	0.09 (0.01, 0.62)
Asian	0.88 (0.84, 0.92)	0.88 (0.8, 0.96)	0.87 (0.78, 0.98)	1.02 (0.87, 1.20)	1.44 (1.32, 1.57)	0.93 (0.82, 1.05)	1.12 (0.96, 1.31)	0.94 (0.71, 1.25)
Black	0.53 (0.50, 0.57)	0.65 (0.57, 0.74)	0.61 (0.52, 0.71)	0.70 (0.53, 0.94)	0.57 (0.53, 0.62)	0.65 (0.55, 0.78)	0.43 (0.31, 0.60)	0.52 (0.31, 0.86)
Other	0.57 (0.53, 0.61)	0.52 (0.44, 0.62)	0.57 (0.47, 0.69)	0.51 (0.37, 0.72)	0.73 (0.63, 0.84)	0.73 (0.61, 0.89)	0.73 (0.54, 0.98)	0.58 (0.32, 1.05)
Income domain of the Index of Multiple Deprivation[2], OR (95% CI)								
1 - Least	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
2	1.13 (1.11, 1.16)	1.13 (1.08, 1.19)	1.05 (1.01, 1.11)	1.02 (0.94, 1.11)	1.12 (1.08, 1.16)	1.13 (1.07, 1.19)	1.13 (1.02, 1.24)	0.97 (0.77, 1.23)
3	1.25 (1.22, 1.27)	1.31 (1.25, 1.38)	1.16 (1.11, 1.22)	1.15 (1.06, 1.25)	1.18 (1.13, 1.23)	1.13 (1.07, 1.19)	1.14 (1.04, 1.26)	0.95 (0.76, 1.21)
4	1.41 (1.38, 1.44)	1.47 (1.40, 1.55)	1.26 (1.20, 1.33)	1.30 (1.20, 1.42)	1.27 (1.21, 1.32)	1.21 (1.14, 1.27)	1.21 (1.09, 1.33)	1.15 (0.92, 1.44)
5 - Most	1.71 (1.67, 1.75)	1.73 (1.65, 1.82)	1.43 (1.36, 1.50)	1.46 (1.34, 1.59)	1.49 (1.43, 1.56)	1.29 (1.22, 1.36)	1.25 (1.13, 1.38)	1.11 (0.88, 1.40)

[2] Income domain of the Index of Multiple Deprivation derived in 2015 used for patients diagnosed with cancer in 2013 and Income domain of the Index of Multiple Deprivation derived in 2019 used for patients diagnosed with cancer after 2013.

Charlson comorbidity index[3], OR (95% CI)								
0	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
1	0.99 (0.97, 1.02)	0.98 (0.93, 1.04)	1.00 (0.94, 1.06)	1.02 (0.93, 1.13)	0.94 (0.90, 0.99)	1.06 (1.00, 1.12)	1.02 (0.90, 1.14)	1.18 (0.91, 1.53)
2	0.98 (0.97, 1.00)	1.00 (0.96, 1.04)	0.94 (0.90, 0.97)	1.00 (0.93, 1.06)	0.97 (0.94, 1.00)	1.02 (0.98, 1.06)	1.02 (0.95, 1.11)	1.11 (0.93, 1.32)
3	0.99 (0.97, 1.01)	1.00 (0.95, 1.06)	1.04 (0.98, 1.09)	0.98 (0.90, 1.07)	0.95 (0.91, 0.99)	0.99 (0.94, 1.05)	0.98 (0.88, 1.09)	1.06 (0.83, 1.36)
≥4	1.00 (0.97, 1.02)	0.98 (0.92, 1.03)	0.99 (0.94, 1.05)	0.95 (0.86, 1.04)	1.00 (0.96, 1.05)	1.01 (0.95, 1.06)	1.07 (0.96, 1.19)	1.21 (0.94, 1.55)
Screen-detected, OR (95% CI)								
Yes	-	0.41 (0.40, 0.43)	-	-	-	-	-	-
No	-	1 (Reference)	-	-	-	-	-	-
TNM stage, OR (95% CI)								
	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
II	0.90 (0.88, 0.91)	1.22 (1.19, 1.27)	0.96 (0.92, 1.00)	0.93 (0.87, 0.99)	0.85 (0.82, 0.88)	0.87 (0.83, 0.9)	0.90 (0.80, 1.00)	0.74 (0.57, 0.95)
III	1.17 (1.15, 1.19)	1.08 (1.02, 1.14)	0.88 (0.85, 0.92)	0.68 (0.64, 0.73)	0.99 (0.96, 1.02)	0.83 (0.8, 0.86)	1.15 (1.04, 1.28)	1.47 (1.15, 1.88)
IV	1.41 (1.35, 1.47)	-	-	-	-	-	1.13 (1.04, 1.23)	1.43 (1.13, 1.81)
Laterality, OR (95% CI)								

[3] 5 years before diagnosis and excluding cardiovascular disease.

Left	1 (Reference)	1 (Reference)	-	-	-	1 (Reference)	-	-
Right	1.16 (1.14, 1.19)	0.96 (0.93, 0.99)	-	-	-	1.01 (0.98, 1.04)	-	-
Bilateral	1.03 (0.91, 1.16)	1.67 (1.47, 1.90)	-	-	-	1.16 (0.80, 1.67)	-	-
Treatment modality ("No" reference for each treatment type)[4], OR (95% CI)								
Surgery	0.41 (0.41, 0.42)	0.16 (0.16, 0.17)	0.61 (0.58, 0.64)	0.45 (0.42, 0.47)	0.38 (0.37, 0.40)	0.49 (0.47, 0.50)	-	-
Radiotherapy	0.50 (0.50, 0.51)	0.31 (0.30, 0.32)	0.78 (0.71, 0.86)	0.91 (0.87, 0.96)	1.05 (1.02, 1.08)	1.08 (1.04, 1.11)	0.72 (0.67, 0.78)	0.60 (0.50, 0.72)
Chemotherapy	0.43 (0.42, 0.44)	0.25 (0.24, 0.26)	0.35 (0.33, 0.36)	0.37 (0.35, 0.40)	1.19 (1.12, 1.26)	0.41 (0.39, 0.42)	0.38 (0.35, 0.41)	0.41 (0.35, 0.49)

Abbreviations: OR: odds ratio; CI: confidence interval; CVD: cardiovascular disease; NSCLC: non-small cell lung cancer; DLBCL: diffuse large B-cell lymphoma.

[4] The three treatment modalities are not mutually exclusive, and reference includes either "No surgery" or "No chemotherapy" or "No radiotherapy".

Table 5.6 – Patient, tumour and treatment characteristics overall and with Cancer Alliances grouped in tertiles of CVD prevalence.

Cancer Alliance tertile	Minimum	Middle	Maximum	All
Total	213,332	209,560	211,348	634,240
Number of Cancer Alliances	7	5	8	20
CVD prevalence, n (%)	30,844 (14.5; 14.3, 14.6)	32,585 (15.5; 15.4, 15.7)	39,405 (18.6; 18.5, 18.8)	102,834 (16.2; 16.1, 16.3)
Cancer site, n %				
Breast	78,833 (37.0; 36.7, 37.2)	74,443 (35.5; 35.3, 35.7)	73,240 (34.7; 34.5, 34.9)	226,516 (35.7; 35.6, 35.8)
Colon	30,214 (14.2; 14.0, 14.3)	29,797 (14.2; 14.1, 14.4)	31,199 (14.8; 14.6, 14.9)	91,210 (14.4; 14.3, 14.5)
Rectal	12,956 (6.1; 6.0, 6.2)	12,885 (6.1; 6, 6.3)	13,847 (6.6; 6.4, 6.7)	39,688 (6.3; 6.2, 6.3)
Prostate	60,664 (28.4; 28.2, 28.6)	61,855 (29.5; 29.3, 29.7)	53,120 (25.1; 24.9, 25.3)	175,639 (27.7; 27.6, 27.8)
NSCLC	20,320 (9.5; 9.4, 9.6)	20,292 (9.7; 9.6, 9.8)	29,846 (14.1; 14.0, 14.3)	70,458 (11.1; 11.0, 11.2)
DLBCL	7,817 (3.7; 3.6, 3.7)	7,798 (3.7; 3.6, 3.8)	7,811 (3.7; 3.6, 3.8)	23,426 (3.7; 3.6, 3.7)
Hodgkin lymphoma	2,528 (1.2; 1.1, 1.2)	2,490 (1.2; 1.1, 1.2)	2,285 (1.1; 1.0, 1.1)	7,303 (1.2; 1.1, 1.2)
Age at cancer diagnosis (years), n (% of total)				
25-35	2,840 (1.3; 1.3, 1.4)	2,714 (1.3; 1.2, 1.3)	2,248 (1.1; 1.0, 1.1)	7,802 (1.2; 1.2, 1.3)
36-45	8,621 (4.0; 4.0, 4.1)	7,834 (3.7; 3.7, 3.8)	6,840 (3.2; 3.2, 3.3)	23,295 (3.7; 3.6, 3.7)
46-55	26,243 (12.3; 12.2, 12.4)	24,060 (11.5; 11.3, 11.6)	23,665 (11.2; 11.1, 11.3)	73,968 (11.7; 11.6, 11.7)
56-65	45,025 (21.1; 20.9, 21.3)	42,416 (20.2; 20.1, 20.4)	43,953 (20.8; 20.6, 21.0)	131,394 (20.7; 20.6, 20.8)
66-75	69,393 (32.5; 32.3, 32.7)	68,101 (32.5; 32.3, 32.7)	70,018 (33.1; 32.9, 33.3)	207,512 (32.7; 32.6, 32.8)
76-85	46,504 (21.8; 21.6, 22.0)	48,825 (23.3; 23.1, 23.5)	49,341 (23.3; 23.2, 23.5)	144,670 (22.8; 22.7, 22.9)
>85	14,706 (6.9; 6.8, 7.0)	15,610 (7.4; 7.3, 7.6)	15,283 (7.2; 7.1, 7.3)	45,599 (7.2; 7.1, 7.3)
Sex, n (% of total)				
Male	101,262 (47.5; 47.3, 47.7)	102,082 (48.7; 48.5, 48.9)	99,677 (47.2; 46.9, 47.4)	303,021 (47.8; 47.7, 47.9)
Female	112,070 (52.5; 52.3, 52.7)	107,478 (51.3; 51.1, 51.5)	111,671 (52.8; 52.6, 53.1)	331,219 (52.2; 52.1, 52.3)
Ethnicity, n (% of total),				

White	182,128 (85.4; 85.2, 85.5)	182,676 (87.2; 87.0, 87.3)	199,883 (94.6; 94.5, 94.7)	564,687 (89.0; 89.0, 89.1)
Mixed	1,151 (0.5; 0.5, 0.6)	1,068 (0.5; 0.5, 0.5)	475 (0.2; 0.2, 0.2)	2,694 (0.4; 0.4, 0.4)
Asian	7,139 (3.3; 3.3, 3.4)	6,708 (3.2; 3.1, 3.3)	3,076 (1.5; 1.4, 1.5)	16,923 (2.7; 2.6, 2.7)
Black	6,431 (3.0; 2.9, 3.1)	5,918 (2.8; 2.8, 2.9)	1,230 (0.6; 0.5, 0.6)	13,579 (2.1; 2.1, 2.2)
Other	3,426 (1.6; 1.6, 1.7)	2,749 (1.3; 1.3, 1.4)	949 (0.4; 0.4, 0.5)	7,124 (1.1; 1.1, 1.1)
Missing	13,057 (6.1; 6.0, 6.2)	10,441 (5.0; 4.9, 5.1)	5,735 (2.7; 2.6, 2.8)	29,233 (4.6; 4.6, 4.7)
Income domain of the Index of Multiple Deprivation				
1 - Least	57,878 (27.1; 26.9, 27.3)	44,453 (21.2; 21, 21.4)	38,542 (18.2; 18.1, 18.4)	140,873 (22.2; 22.1, 22.3)
2	52,368 (24.5; 24.4, 24.7)	49,513 (23.6; 23.4, 23.8)	43,030 (20.4; 20.2, 20.5)	144,911 (22.8; 22.7, 23.0)
3	45,246 (21.2; 21.0, 21.4)	46,360 (22.1; 21.9, 22.3)	40,017 (18.9; 18.8, 19.1)	131,623 (20.8; 20.7, 20.9)
4	36,685 (17.2; 17.0, 17.4)	38,788 (18.5; 18.3, 18.7)	38,758 (18.3; 18.2, 18.5)	114,231 (18.0; 17.9, 18.1)
5 - Most	21,155 (9.9; 9.8, 10.0)	30,446 (14.5; 14.4, 14.7)	51,001 (24.1; 23.9, 24.3)	102,602 (16.2; 16.1, 16.3)
Charlson comorbidity index[1], n (% of total)				
0	99,170 (46.5; 46.3, 46.7)	97,637 (46.6; 46.4, 46.8)	99,154 (46.9; 46.7, 47.1)	295,961 (46.7; 46.5, 46.8)
1	18,005 (8.4; 8.3, 8.6)	17674 (8.4; 8.3, 8.6)	17,976 (8.5; 8.4, 8.6)	53,655 (8.5; 8.4, 8.5)
2	52,636 (24.7; 24.5, 24.9)	51,,200 (24.4; 24.2, 24.6)	51,863 (24.5; 24.4, 24.7)	155,699 (24.5; 24.4, 24.7)
3	21,955 (10.3; 10.2, 10.4)	21,710 (10.4; 10.2, 10.5)	21,862 (10.3; 10.2, 10.5)	65,527 (10.3; 10.3, 10.4)
≥4	18,959 (8.9; 8.8, 9.0)	18,776 (9.0; 8.8, 9.1)	18,826 (8.9; 8.8, 9.0)	56,561 (8.9; 8.8, 9.0)
Missing[2]	2,607 (1.2; 1.2, 1.3)	2,563 (1.2; 1.2, 1.3)	1,667 (0.8; 0.8, 0.8)	6,837 (1.1; 1.1, 1.1)
TNM stage, n (% of total)				
I	86,447 (40.5; 40.3, 40.7)	83,715 (39.9; 39.7, 40.2)	85,158 (40.3; 40.1, 40.5)	255,320 (40.3; 40.1, 40.4)
II	70,817 (33.2; 33.0, 33.4)	72,778 (34.7; 34.5, 34.9)	67,721 (32.0; 31.8, 32.2)	211,316 (33.3; 33.2, 33.4)

[1] 5 years before diagnosis excluding cardiovascular disease.

[2] Missing if not linked to Hospital Episode Statistics.

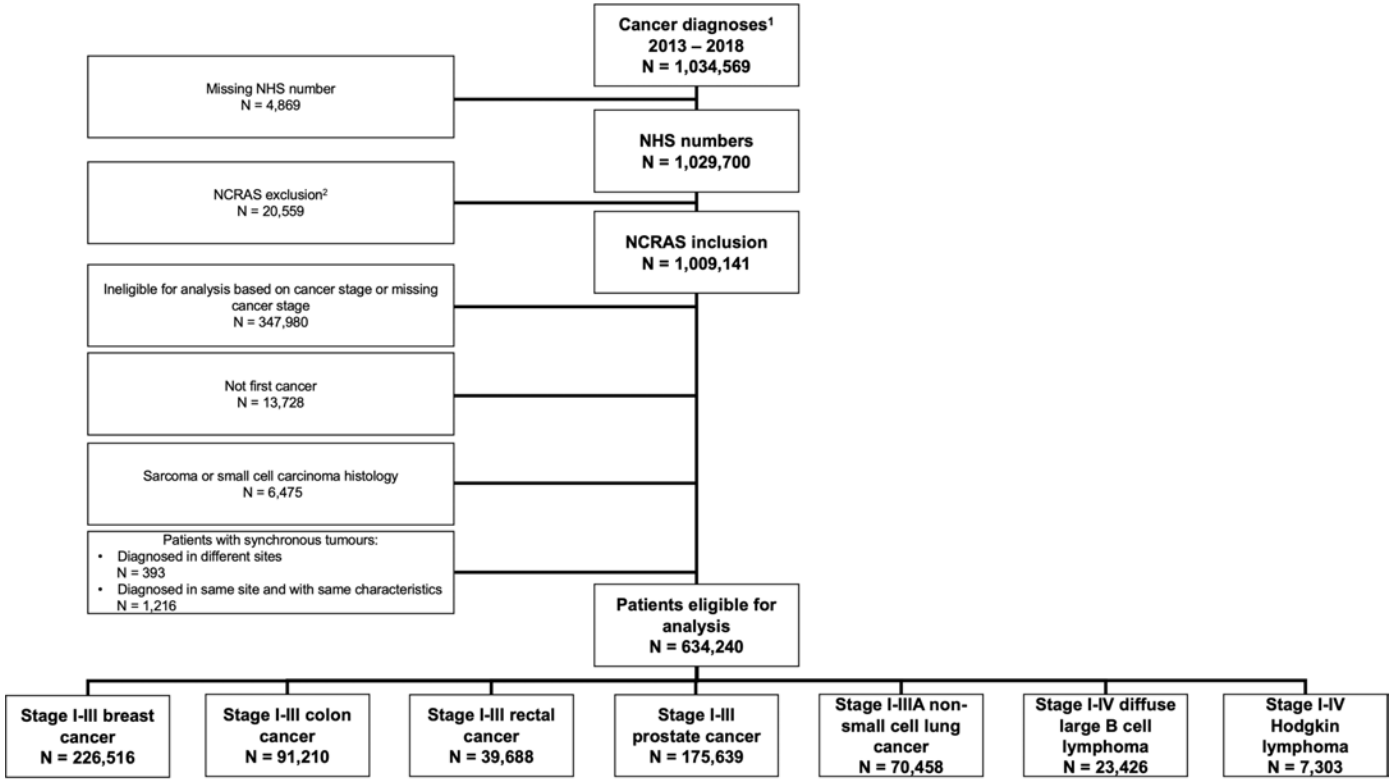
III	51,524 (24.2; 24.0, 24.3)	48,662 (23.2; 23.0, 23.4)	54,163 (25.6; 25.4, 25.8)	154,349 (24.3; 24.2, 24.4)
IV	4,544 (2.1; 2.1, 2.2)	4,405 (2.1; 2.0, 2.2)	4,306 (2.0; 2.0, 2.1)	13,255 (2.1; 2.1, 2.1)
Grade of differentiation, n (% of total)				
Well differentiated	66,348 (31.1; 30.9, 31.3)	67,431 (32.2; 32.0, 32.4)	67,126 (31.8; 31.6, 32.0)	200,905 (31.7; 31.6, 31.8)
Moderately differentiated	15,552 (7.3; 7.2, 7.4)	13,691 (6.5; 6.4, 6.6)	16,046 (7.6; 7.5, 7.7)	45,289 (7.1; 7.1, 7.2)
Poorly differentiated	82,908 (38.9; 38.7, 39.1)	79,586 (38.0; 37.8, 38.2)	82,080 (38.8; 38.6, 39.0)	244,574 (38.6; 38.4, 38.7)
Undifferentiated / anaplastic	42,895 (20.1; 19.9, 20.3)	43,221 (20.6; 20.5, 20.8)	41,311 (19.5; 19.4, 19.7)	12,7427 (20.1; 20, 20.2)
Not appropriate/ cannot be assessed	1,889 (0.9; 0.8, 0.9)	1,843 (0.9; 0.8, 0.9)	1,920 (0.9; 0.9, 0.9)	5,652 (0.9; 0.9, 0.9)
Missing	3,740 (1.8; 1.7, 1.8)	3,788 (1.8; 1.8, 1.9)	2,865 (1.4; 1.3, 1.4)	1,0393 (1.6; 1.6, 1.7)
Treatment modality[3], n (% of total)				
Surgery	128,160 (60.1; 59.9, 60.3)	123,649 (59; 58.8, 59.2)	126,677 (59.9; 59.7, 60.1)	378,486 (59.7; 59.6, 59.8)
Radiotherapy	89,141 (41.8; 41.6, 42)	85,108 (40.6; 40.4, 40.8)	90,016 (42.6; 42.4, 42.8)	264,265 (41.7; 41.5, 41.8)
Chemotherapy	55,759 (26.1; 26.0, 26.3)	55,042 (26.3; 26.1, 26.5)	57,847 (27.4; 27.2, 27.6)	168,648 (26.6; 26.5, 26.7)

Abbreviations: CVD: cardiovascular disease; NSCLC: non-small cell lung cancer; DLBCL: diffuse large B-cell lymphoma.

[3] All treatments identified using National Cancer Registration and Analysis Service treatment standard operating procedure (between 1 month before and 12 months after cancer diagnosis).

5.9. FIGURES

Figure 5.1 – CONSORT diagram showing the selection of cancer diagnoses for analysis.



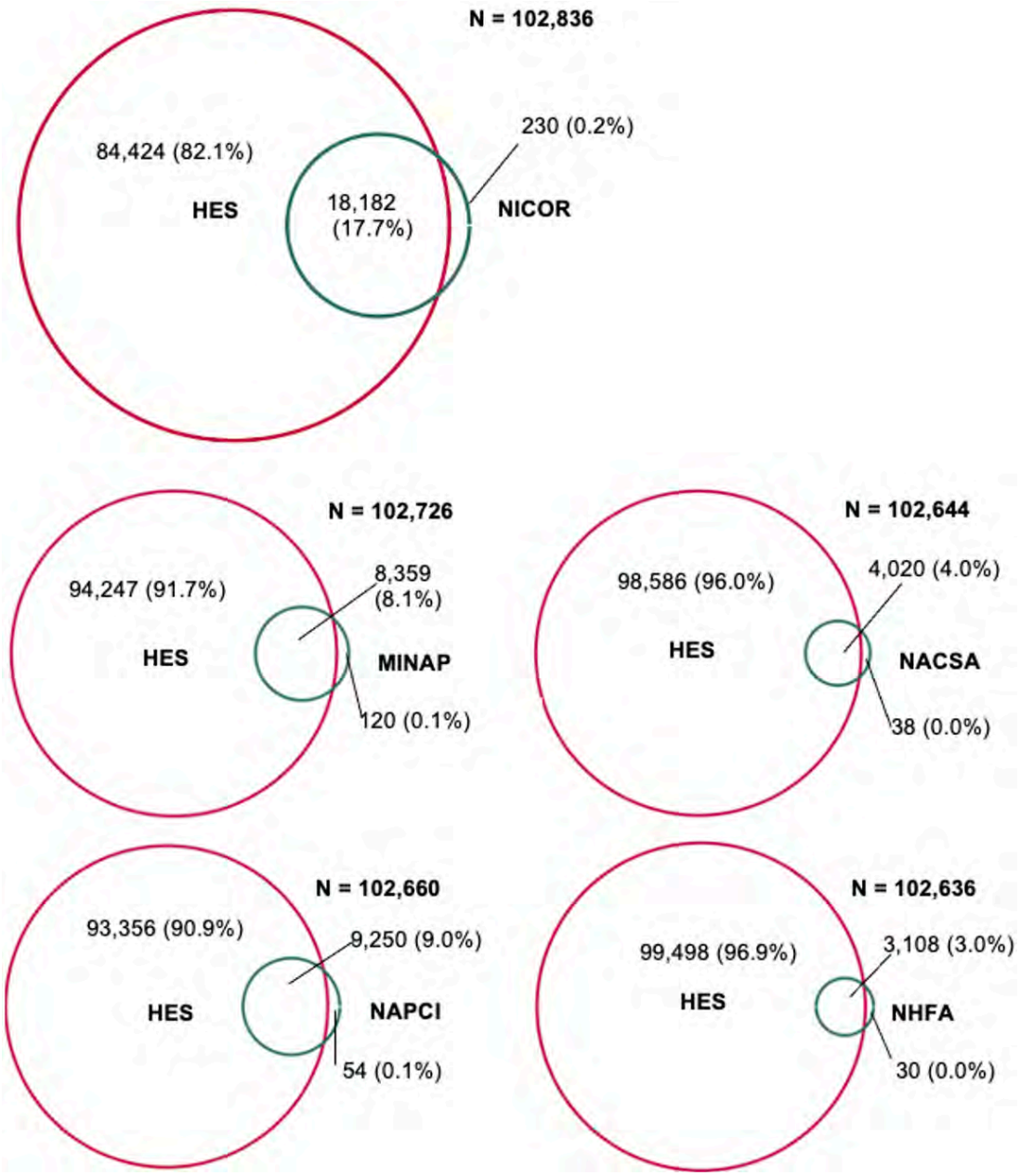
Abbreviations: NHS: National Health Service; NCRAS: National Cancer Registration and Analysis Service.

---

[1] ICD-10 codes: C50, C18, C19, C20, C61, C34 (excluding ICD-O-2 morphology codes 8041, 8042, 8043, 8044 or 8045), C83.3, C81.

[2] NCRAS exclusion criteria: age <18 years or >100 years at diagnosis; men diagnosed with breast cancer; women diagnosed with prostate cancer.

Figure 5.2 – Venn diagrams showing the overlap between tumours with hospitalised CVD categories identified using ICD-10 diagnosis code list in HES and a record found in a NICOR dataset.[1]

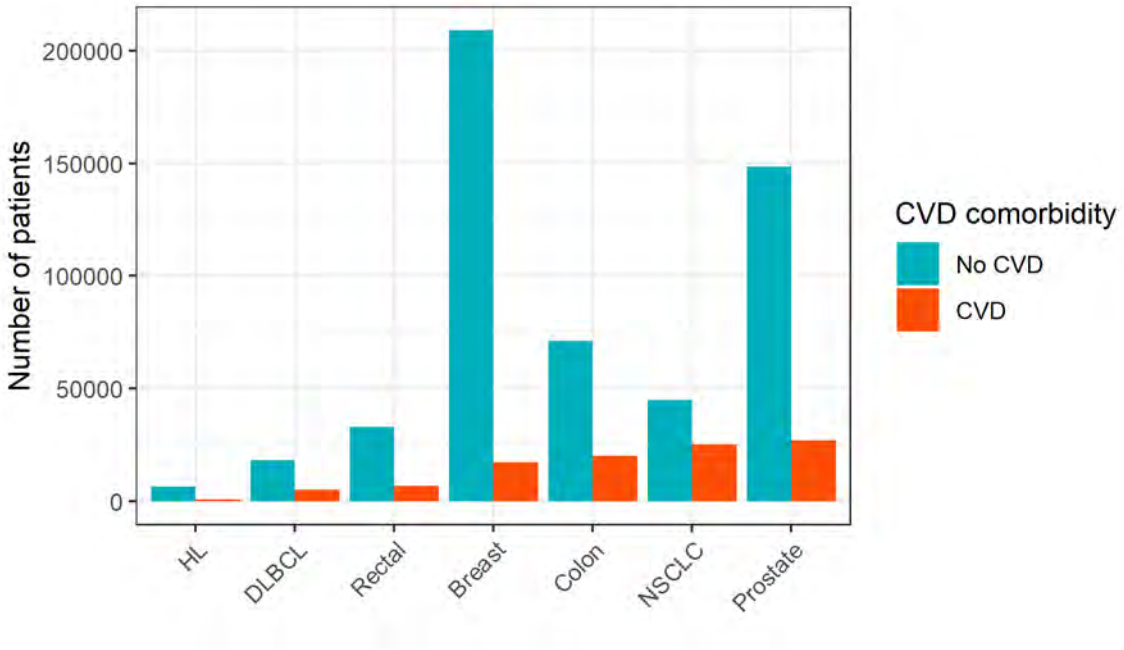


Abbreviations: CVD: cardiovascular disease; HES: Hospital Episode Statistics; NICOR: National Institute for Cardiovascular Outcomes Research; MINAP: Myocardial Ischaemia National Audit Project; NACSA: National Adult Cardiac Surgery Audit; NAPCI: National Audit of Percutaneous Coronary Intervention; NHFA: National Heart Failure Audit.

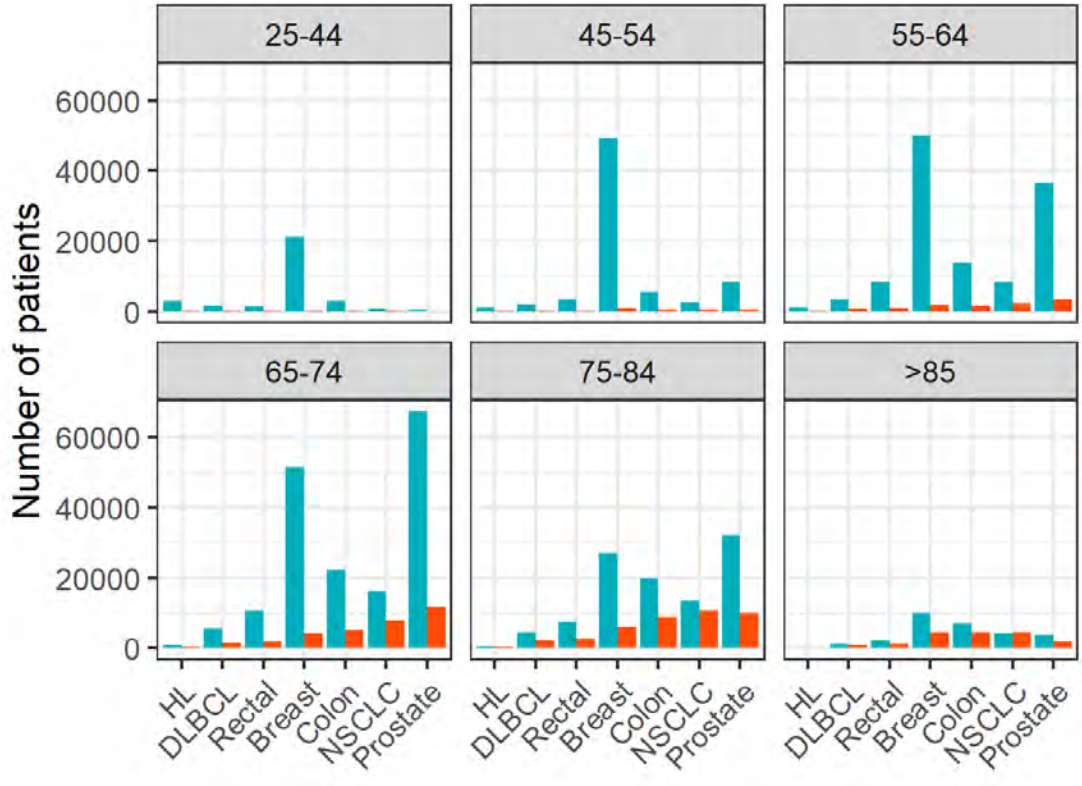
[1] Each Venn diagram includes patients in either HES or that dataset, so the totals are different across Venn diagram.

Figure 5.3 – Number of patients in each cancer site cohort with cardiovascular disease diagnosis, a) overall and b) by age-group.

a) overall



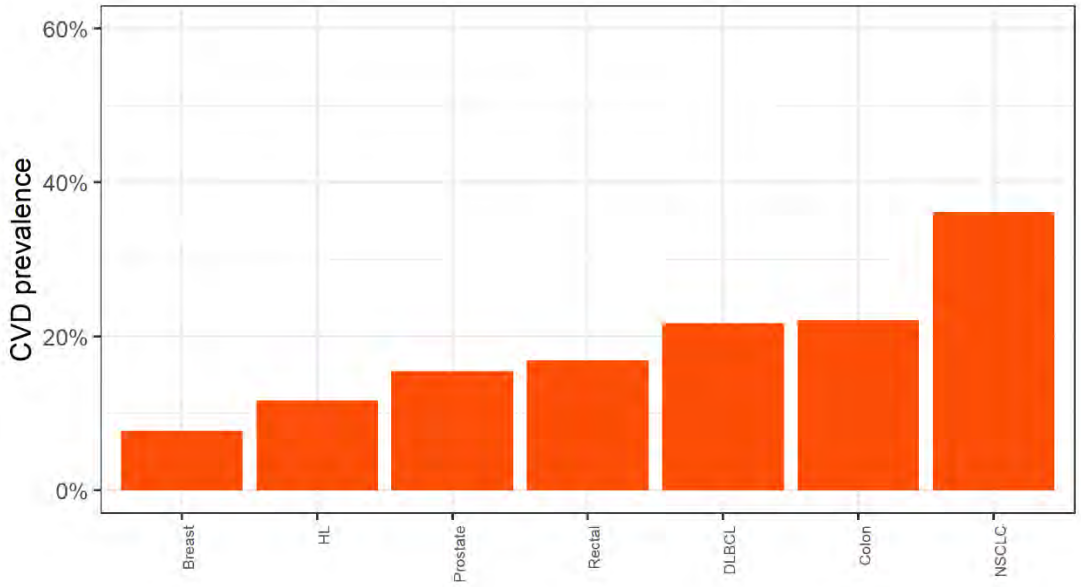
b) by age-group



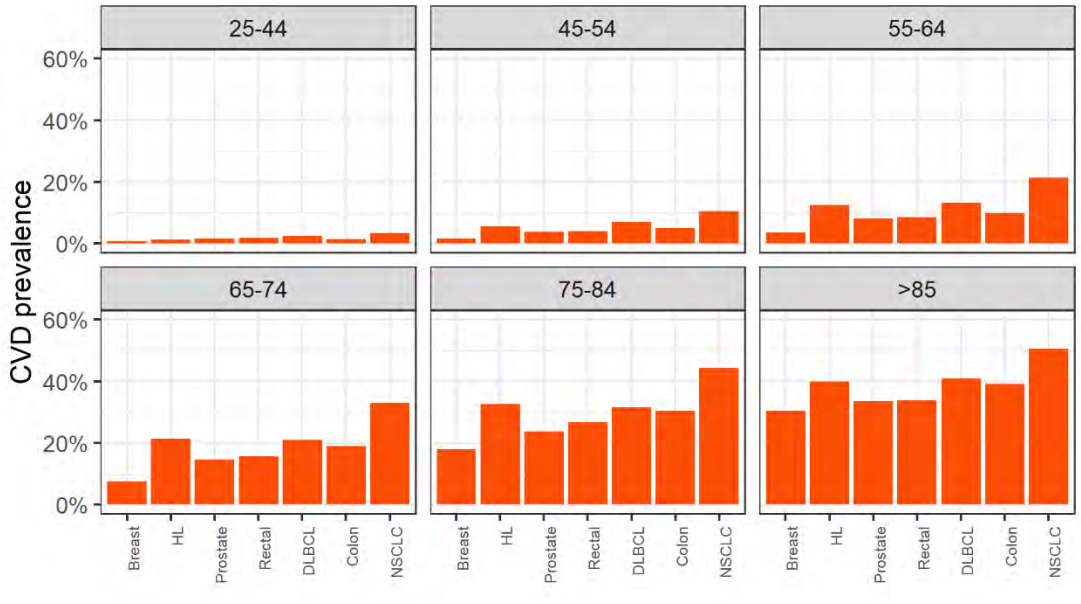
Abbreviations: NSCLC: non-small cell lung cancer; HL: Hodgkin lymphoma; DLBCL: diffuse large B-cell lymphoma.

Figure 5.4 – Overall proportion of patients with cardiovascular disease diagnosis in each cancer cohort.

a) overall

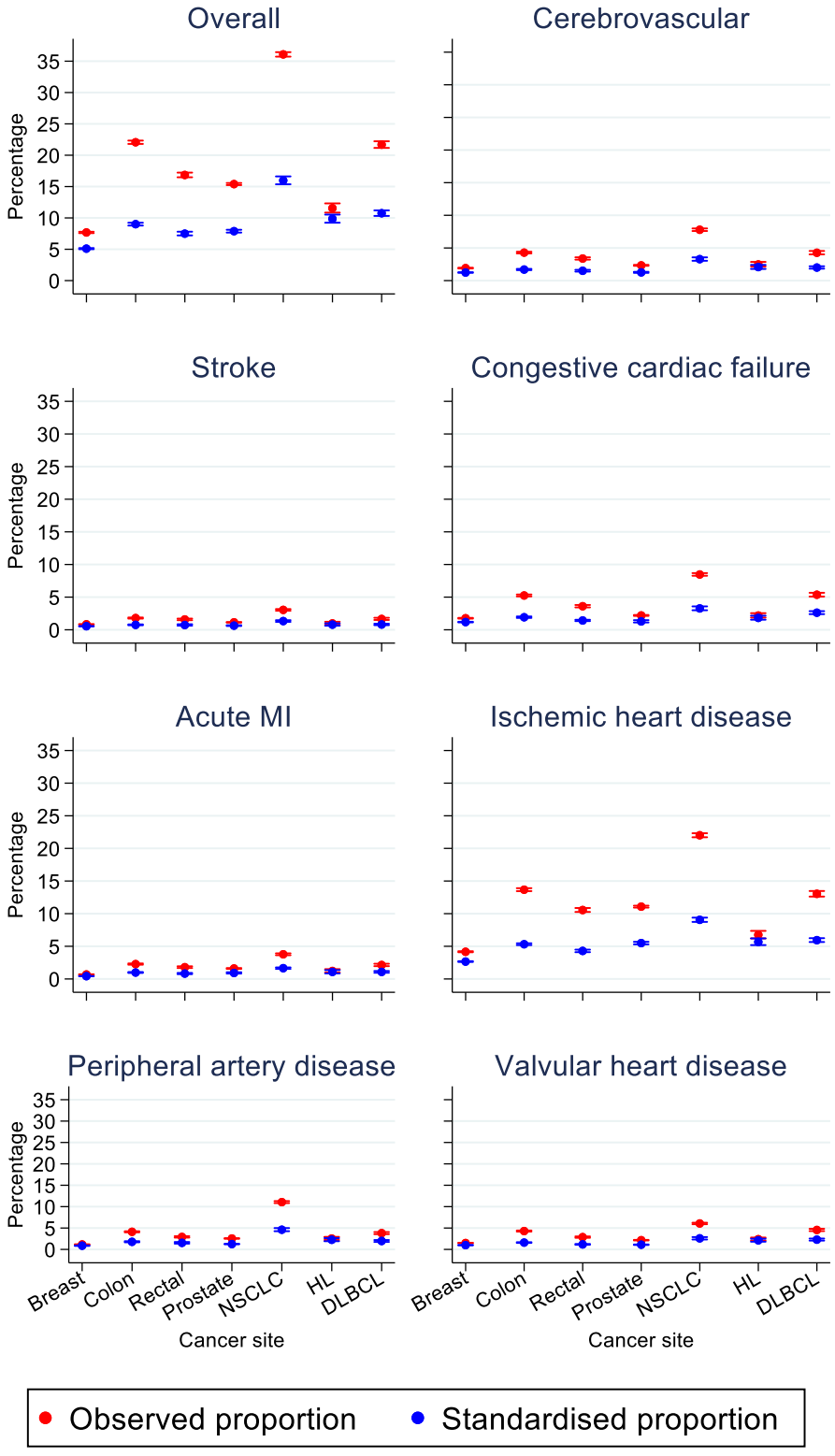


b) by age-group



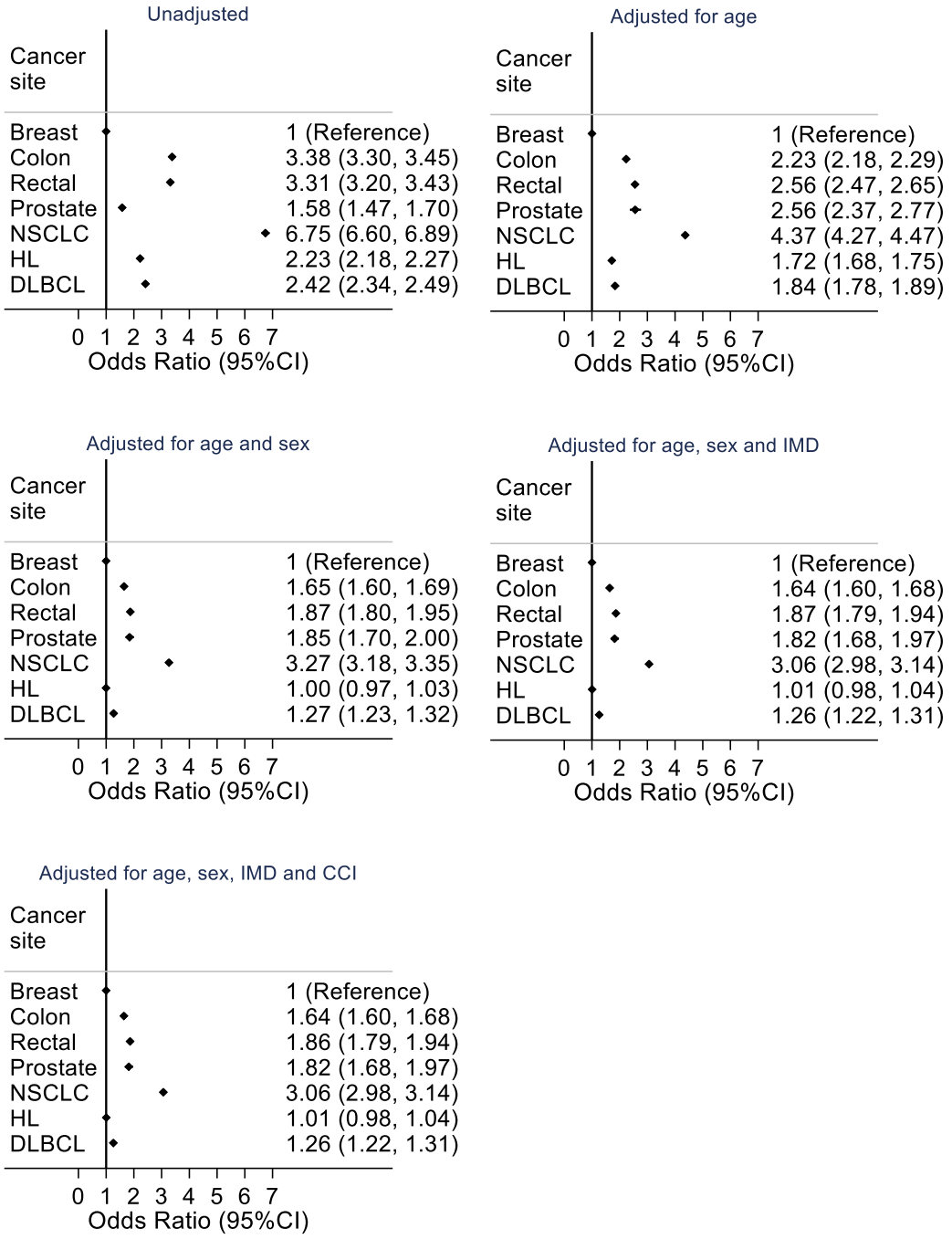
Abbreviations: NSCLC: non-small cell lung cancer; HL: Hodgkin lymphoma; DLBCL: diffuse large B-cell lymphoma.

Figure 5.5 – Observed and standardised prevalence (%) of cardiovascular disease in HES by cancer site (standardised by the age and sex stratum specific 2016 Office for National Statistics population estimates).



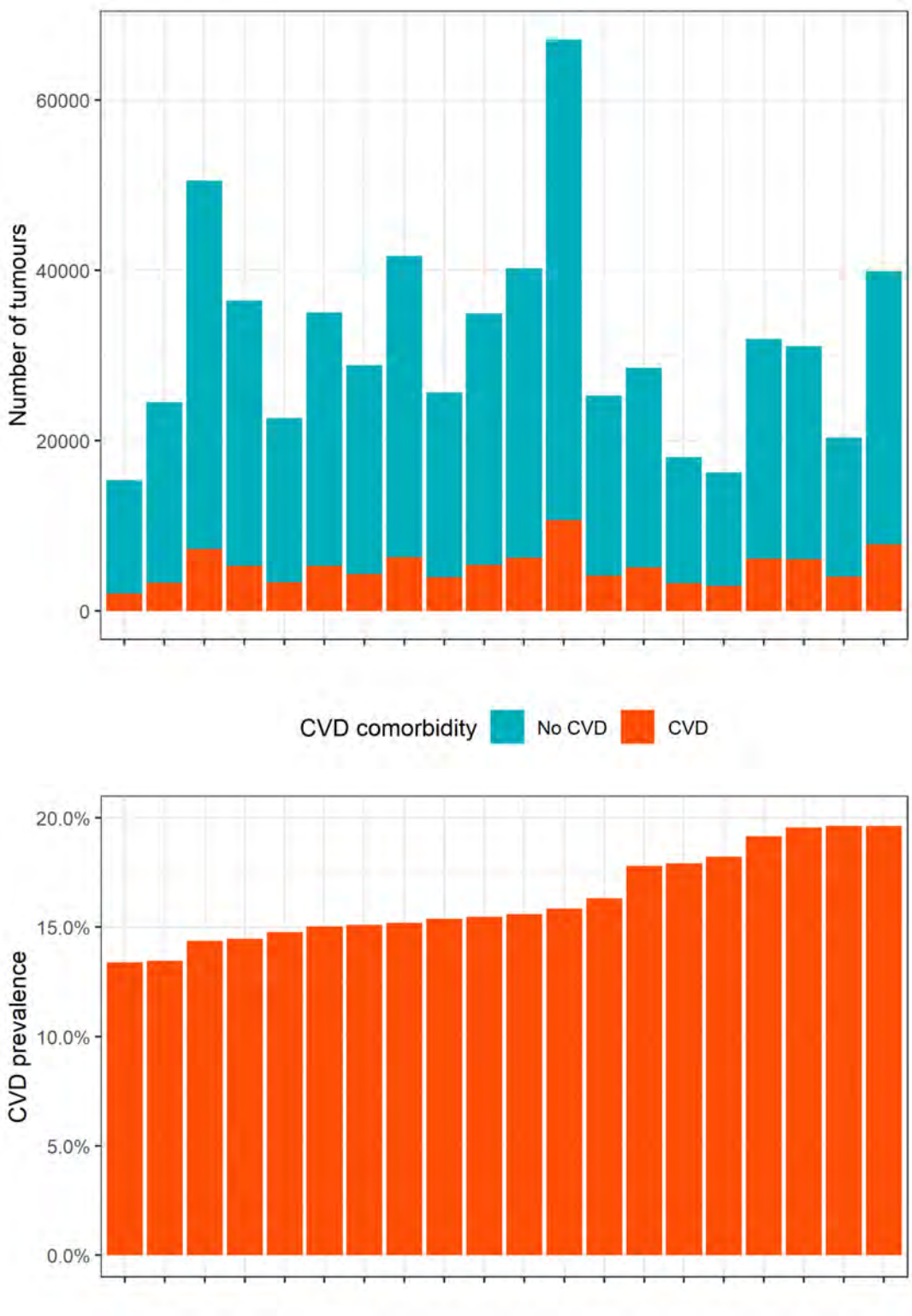
Abbreviations: MI: myocardial infarction; NSCLC: non-small cell lung cancer; HL: Hodgkin lymphoma; DLBCL: diffuse large B-cell lymphoma.

Figure 5.6 – Progressively adjusted logistic regression analysis reporting odds ratios of association between cardiovascular disease (HES and/or NICOR) comorbidity and cancer site (breast cancer reference).



Abbreviations: MI: myocardial infarction; NSCLC: non-small cell lung cancer; HL: Hodgkin lymphoma; DLBCL: diffuse large B-cell lymphoma; IMD: Index of Multiple Deprivation income domain; CCI: Charlson comorbidity index (5 years before diagnosis and excluding cardiovascular disease); HES: Hospital Episode Statistics; NICOR: National Institute for Cardiovascular Outcomes Research.

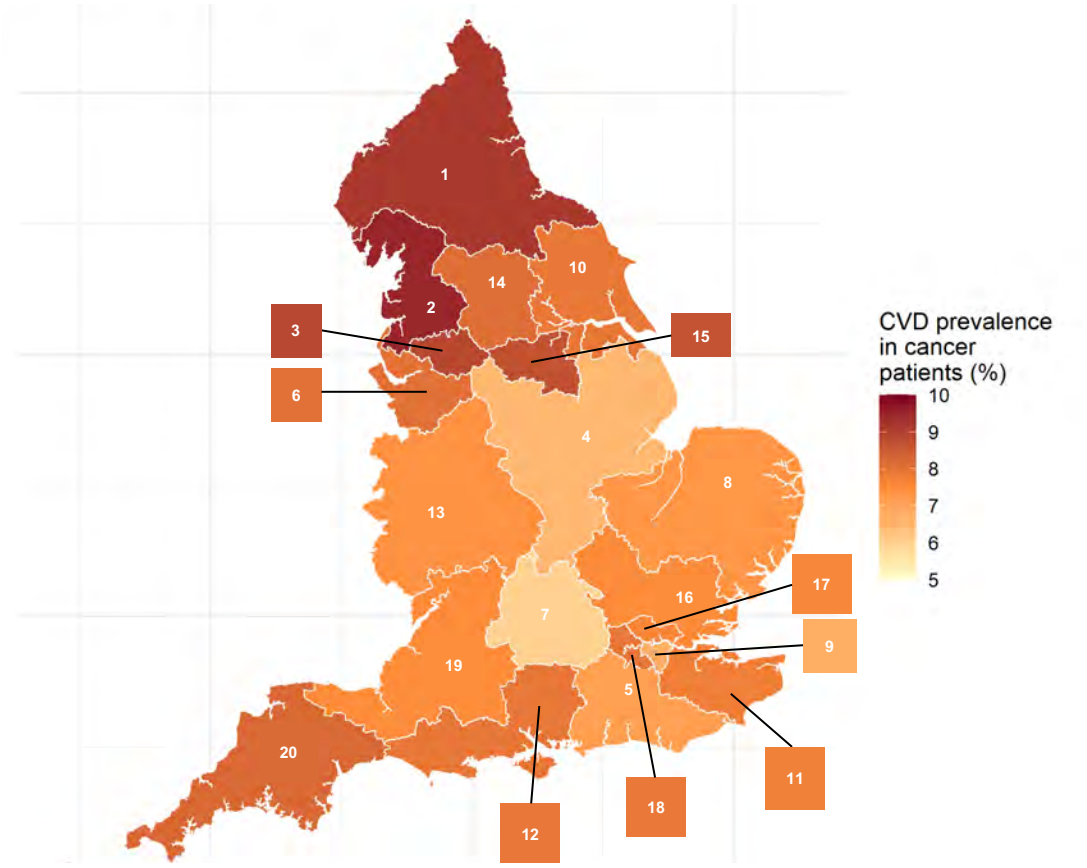
Figure 5.7 – Number of patients with any cardiovascular disease diagnosis code and prevalence for each Cancer Alliance.[1]



Abbreviations: CVD: cardiovascular disease.

[1] Both figures ordered by CVD prevalence, so Cancer Alliances are in the same order.

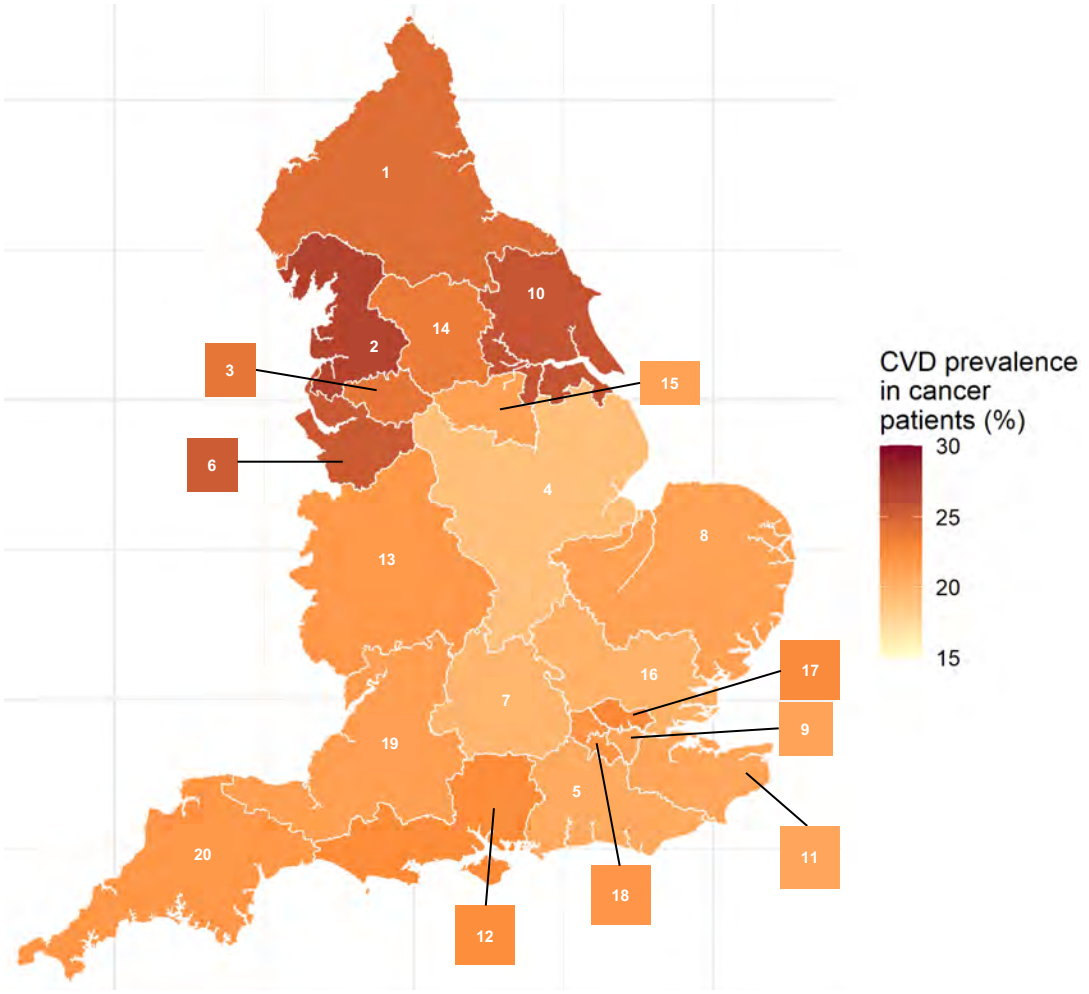
Figure 5.8 – Prevalence of cardiovascular disease in the breast cancer cohort according to Cancer Alliance.[1]



Abbreviations: CVD: cardiovascular disease.

[1] List of Cancer Alliances reported in Table 5.2.

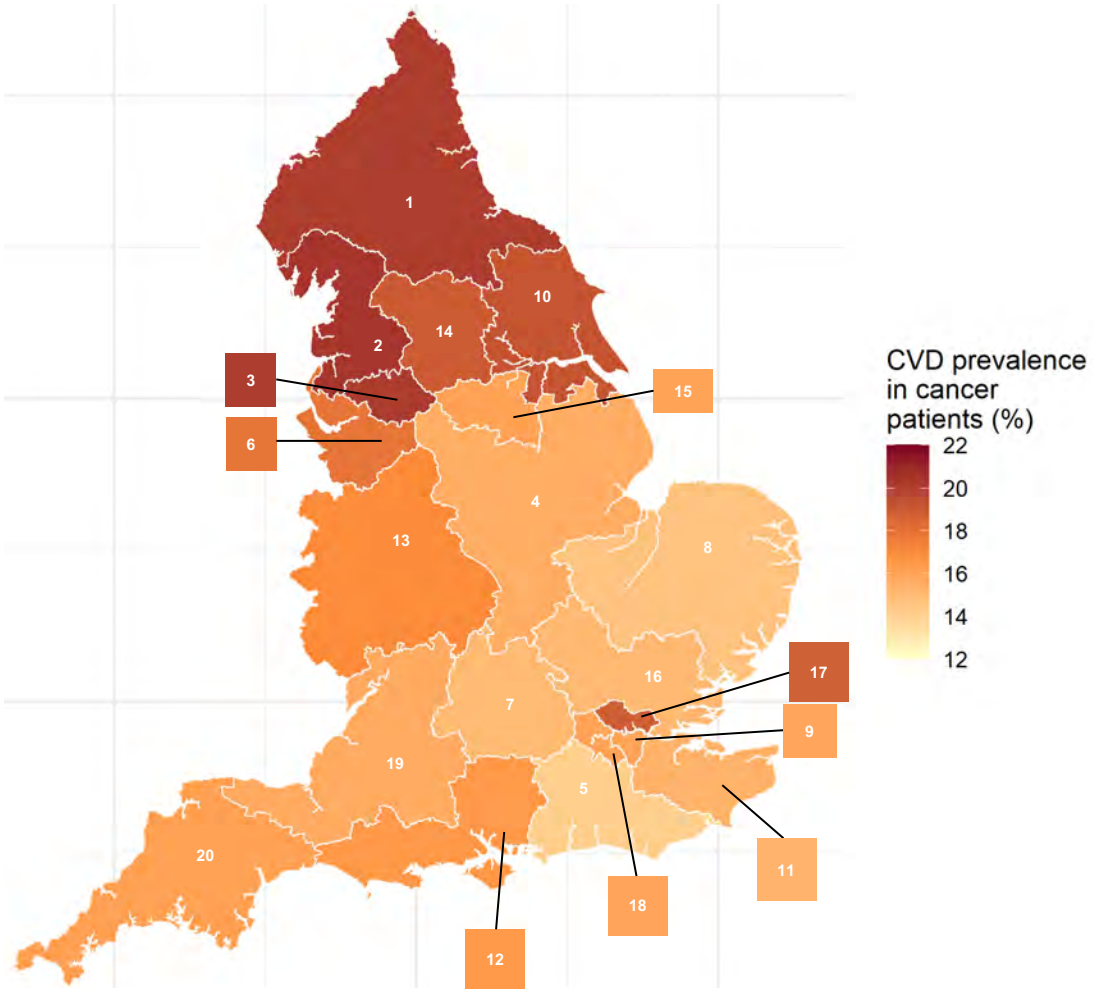
Figure 5.9 – Prevalence of cardiovascular disease in the colon cancer cohort according to Cancer Alliance.[1]



Abbreviations: CVD: cardiovascular disease.

[1] List of Cancer Alliances reported in Table 5.2.

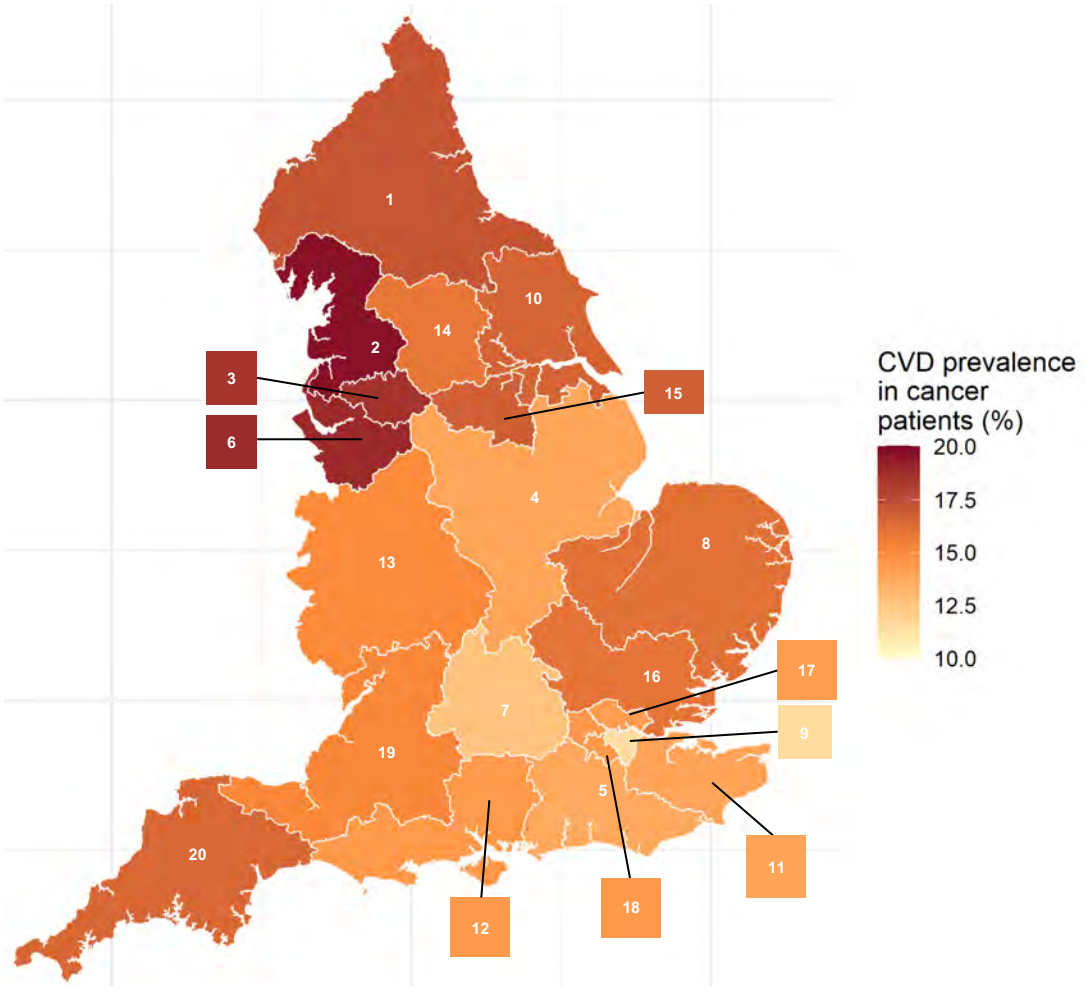
Figure 5.10 – Prevalence of cardiovascular disease in the rectal cancer cohort according to Cancer Alliance.[1]



Abbreviations: CVD: cardiovascular disease.

[1] List of Cancer Alliances reported in Table 5.2.

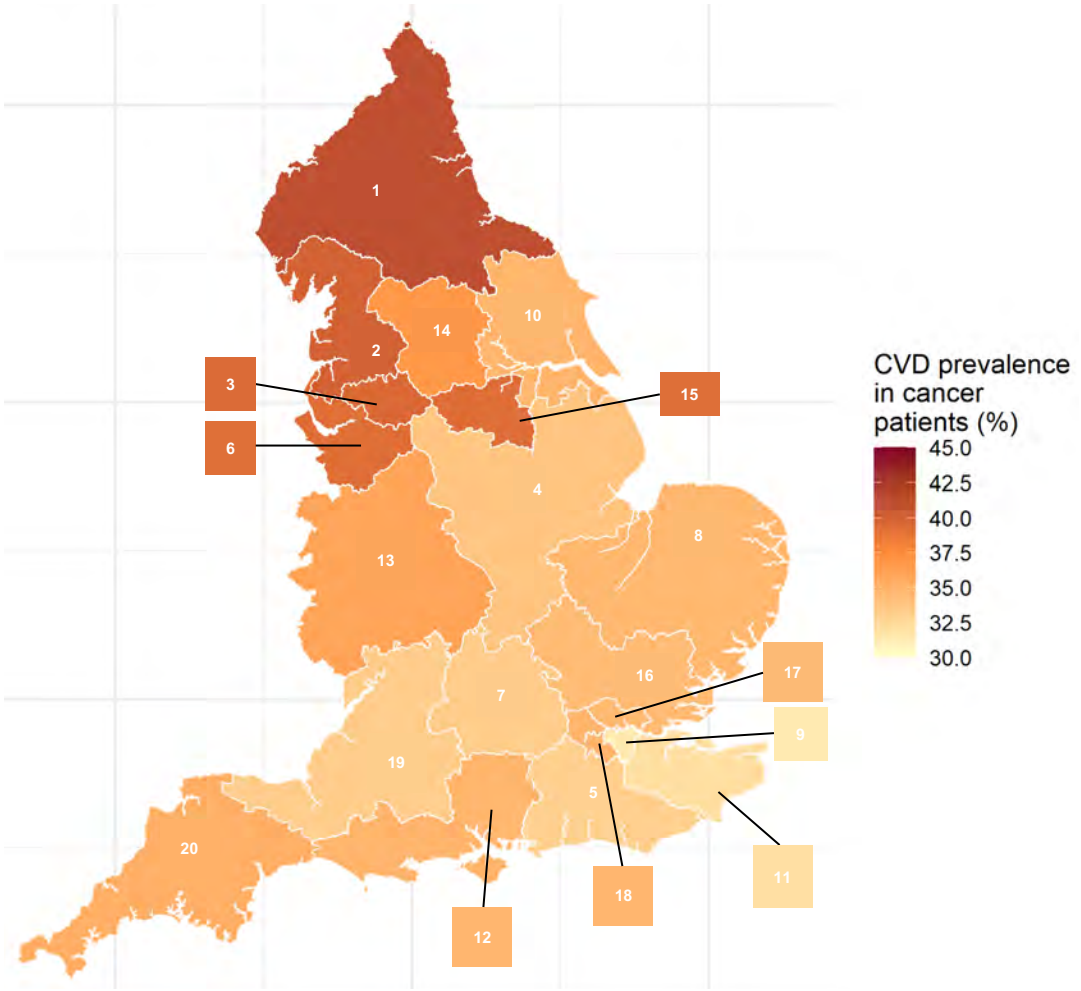
Figure 5.11 – Prevalence of cardiovascular disease in the prostate cancer cohort according to Cancer Alliance.[1]



Abbreviations: CVD: cardiovascular disease.

[1] List of Cancer Alliances reported in Table 5.2.

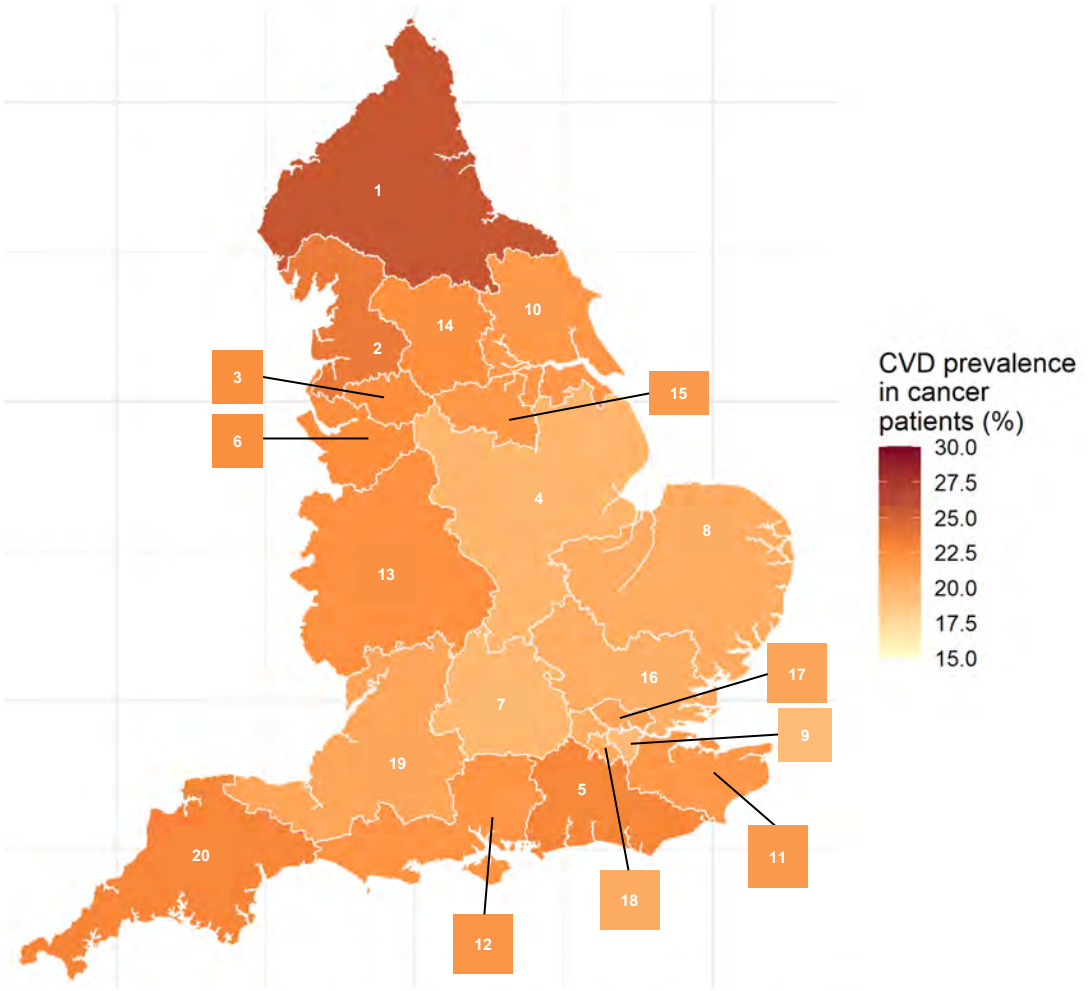
Figure 5.12 – Prevalence of cardiovascular disease in the non-small cell lung cancer cohort according to Cancer Alliance.[1]



Abbreviations: CVD: cardiovascular disease.

[1] List of Cancer Alliances reported in Table 5.2.

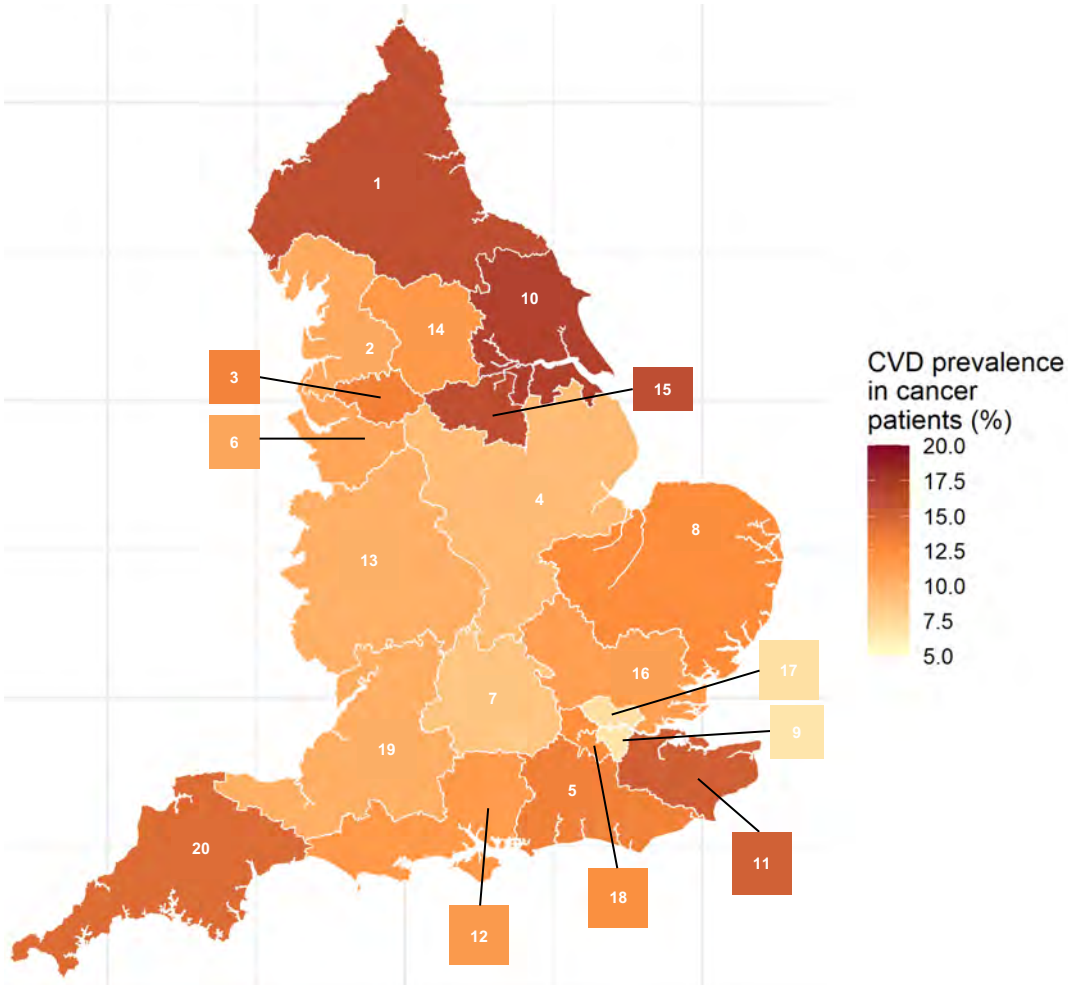
Figure 5.13 – Prevalence of cardiovascular disease in the diffuse large B-cell lymphoma cohort according to Cancer Alliance.[1]



Abbreviations: CVD: cardiovascular disease.

[1] List of Cancer Alliances reported in Table 5.2.

Figure 5.14 – Prevalence of cardiovascular disease in the Hodgkin lymphoma cohort according to Cancer Alliance.[1]

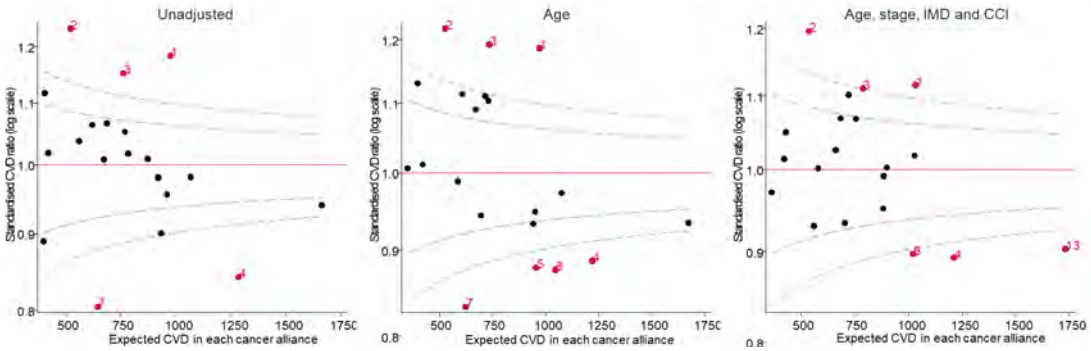


Abbreviations: CVD: cardiovascular disease.

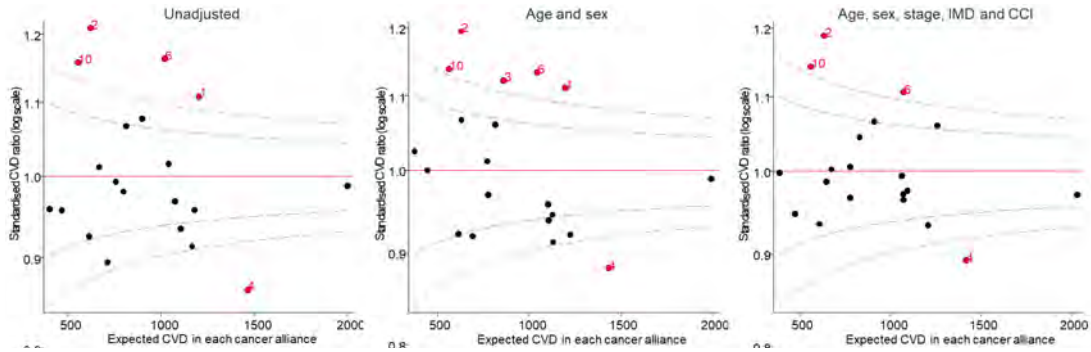
[1] List of Cancer Alliances reported in Table 5.2.

Figure 5.15 – Standardised CVD ratio for each Cancer Alliance by cancer type and adjusting for variables listed in the title of each graph.

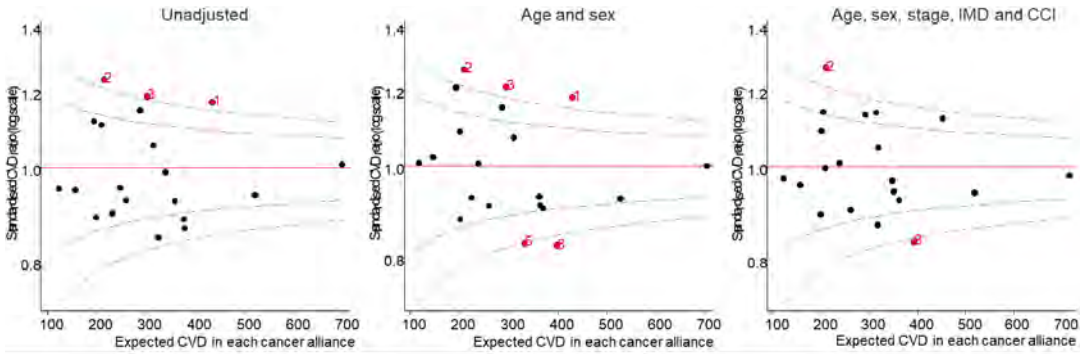
Breast cancer



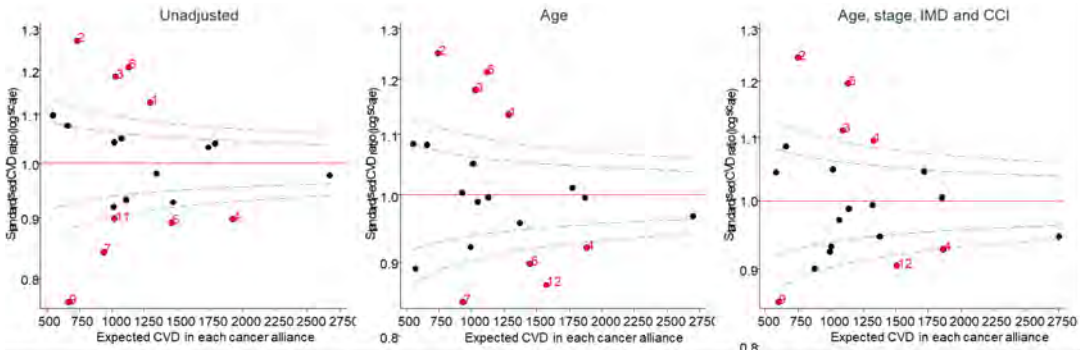
Colon cancer



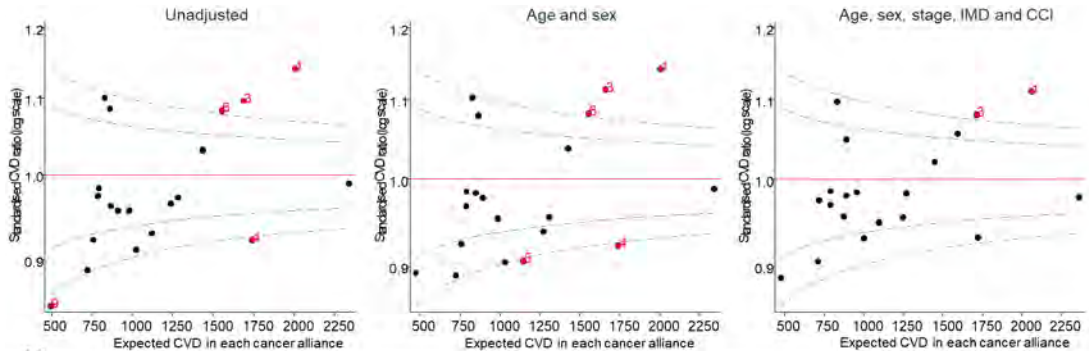
Rectal cancer



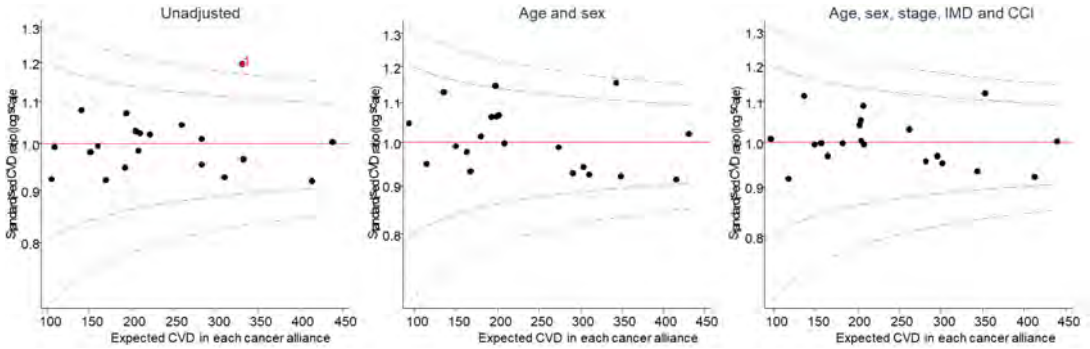
Prostate cancer



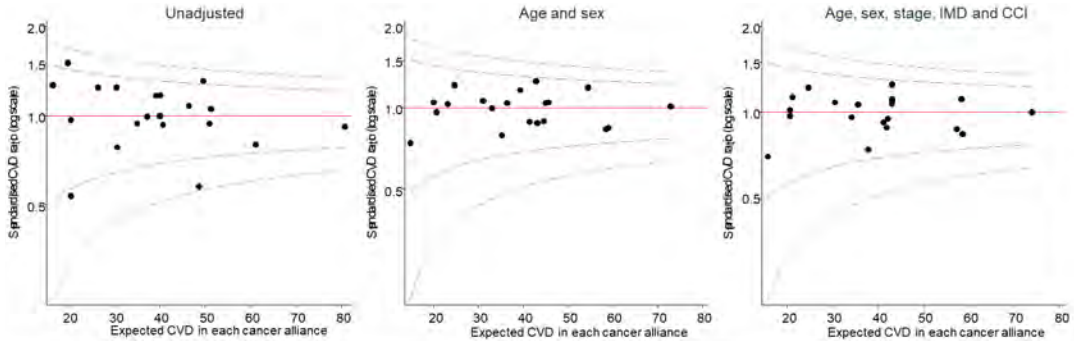
Non-small cell lung cancer



Diffuse large B-cell lymphoma



Hodgkin lymphoma



Abbreviations: CVD: cardiovascular disease; IMD: Index of Multiple Deprivation income domain; CCI: Charlson comorbidity index (5 years before diagnosis and excluding cardiovascular disease)

CHAPTER 6. INCIDENCE OF CARDIOTOXICITY AND VALIDATION OF THE HEART FAILURE ASSOCIATION-INTERNATIONAL CARDIO-ONCOLOGY SOCIETY RISK STRATIFICATION TOOL IN PATIENTS TREATED WITH TRASTUZUMAB FOR HER2-POSITIVE EARLY BREAST CANCER

6.1. ABSTRACT

Trastuzumab improves survival in patients with human epidermal growth factor receptor 2 (HER2)-positive early breast cancer (EBC). However, cardiotoxicity remains a concern, particularly in the curative setting, and there are limited data on its incidence outside of clinical trials. We retrospectively evaluated the cardiotoxicity rates (left ventricular ejection fraction [LVEF] decline, congestive heart failure [CHF], cardiac death or trastuzumab discontinuation) and assessed the performance of a proposed model to predict cardiotoxicity in routine clinical practice.

Patients receiving curative trastuzumab between 2011-2018 were identified. Demographics, treatments, assessments and toxicities were recorded. Fisher's exact test, chi-squared and logistic regression were used.

931 patients were included in the analysis. Median age was 54 years (range 24-83) and Charlson comorbidity index (CCI) 0 (0-6), with 195 patients (20.9%) aged 65 or older. 228 (24.5%) were smokers. Anthracyclines were given in 608 (65.3%). Median number of trastuzumab doses was 18 (1-18). The Heart Failure Association (HFA)-International Cardio-Oncology Society (ICOS) cardiovascular risk was low in 401 patients (43.1%), medium in 454 (48.8%), high in 70 (7.5%) and very high in 6 (0.6%).

Overall, 155 (16.6%) patients experienced cardiotoxicity: LVEF decline≥10% in 141 (15.1%), falling below 50% in 55 (5.9%), CHF New York Heart Association (NYHA) class II in 42 (4.5%) and class III-IV in 5 (0.5%) and discontinuation due to cardiac reasons in 35 (3.8%). No deaths were observed. Cardiotoxicity rates increased with HFA-ICOS score (14.0% low, 16.7% medium, 30.3% high/very high; p=0.002).

Cardiotoxicity was relatively common (16.6%), but symptomatic heart failure on trastuzumab was rare in our cohort. The HFA-ICOS score identifies patients at high risk of cardiotoxicity.

6.2. INTRODUCTION

In Chapter 5, we highlighted the issue of concomitant cardiovascular disease (CVD) and its potential impact on cancer outcomes and treatment tolerance. Whilst the rates of concomitant CVD are lower in patients with breast cancer compared some other tumour types, they are still relevant, particularly in older patients and when cardio-toxic treatment regimens are being considered.

Trastuzumab is a monoclonal antibody targeting the human epidermal growth factor receptor 2 (HER2) and is the standard of care for the management of early-stage and advanced HER2-positive breast cancer.[1] However, treatment with HER2-directed agents is associated with a risk of cardiotoxicity. This most frequently involves an asymptomatic decrease in the left ventricular ejection fraction (LVEF) detected during surveillance before presentation with symptomatic heart failure. Less frequently, rapid development of congestive heart failure (CHF) despite surveillance may develop.[2, 3] Cardiotoxicity associated with anti-HER2 agents is usually reversible with cessation of trastuzumab treatment and cardiac medication, but this may compromise optimal breast cancer treatment.[4] Factors associated with a higher risk of cardiotoxicity in patients receiving trastuzumab include older age, previous or concurrent anthracycline use, pre-existing cardiac dysfunction, pre-existing significant cardiovascular disease, high body mass index (BMI), antihypertensive therapy and, in older patients, diabetes mellitus.[5-11]

A metanalysis of adjuvant trials reported a risk of advanced heart failure (New York Heart Association [NYHA] class III-IV) of 0.4-2.5% in patients receiving trastuzumab.[12] Even when anthracyclines are not given, a trial investigating the use of trastuzumab along with taxane-based chemotherapy showed an incidence of cardiotoxicity of 3% although this was severe only in 0.5% of trial participants.[13] In contrast, previous real-world experiences have reported a rate of cardiovascular complications in 10-15% of patients receiving this agent in the curative setting.[14]

Age is a predictor of impaired cardiac function with trastuzumab treatment. This is a concern due to the higher burden of comorbidities and increased risk of adverse outcomes in older individuals.[15] Nonetheless, trastuzumab improves survival and reduces risk of recurrence and is otherwise well tolerated in older patients. The rate of cardiac events in a systematic review of randomized studies including data on patients aged over 60 years was 5%.[16] However, the incidence is unclear outside of clinical trials, which tend to recruit patients who are younger, with normal baseline cardiac function and who have a lower burden of co-morbidities including pre-existing CVD.

Therefore, predicting the cardiotoxicity of anti-HER2 agents is of considerable importance. Cardiac risk scores have been developed based on prospective trial(12) and retrospective registry data.(14) However, independent validation is needed before they can be considered for general use. The Heart Failure Association (HFA) of the European Society of Cardiology together with the International Cardio-Oncology Society (ICOS) have recently developed a risk stratification tool (HFA-ICOS Risk Tool) to evaluate the likelihood of cardiotoxicity at baseline for patients receiving HER2-directed treatments (Table 6.1).[17] In this study we investigated the rates of cardiotoxicity secondary to trastuzumab for HER2-positive early breast cancer (EBC) in a breast cancer service, comparing rates in older versus younger patients, and assessed the performance of HFA-ICOS cardiovascular risk prediction tool in this population.

6.3. METHODS

This analysis is a retrospective study of patients who received trastuzumab for HER2-positive EBC between 01/01/2011 and 31/12/2018 at the Royal Marsden Hospital NHS Foundation Trust. Eligible patients had curable disease (TNM stages: T1-4, N0-3, M0) and received trastuzumab in the neoadjuvant or adjuvant setting. Patients who received part of the course of treatment elsewhere or those with advanced-stage breast cancer were not eligible for the analysis. This analysis was approved as a service evaluation (SE842) at the Royal Marsden NHS Foundation Trust.

6.3.1. Baseline data collection

Baseline patient characteristics at initiation of trastuzumab were collected and included: date of birth, age at diagnosis, date of last follow-up, date of death, weight, BMI, comorbidities, smoking history, obesity, alcohol consumption, concurrent medications, Eastern Cooperative Oncology Group (ECOG) Performance Status (PS), menopausal status. Specifically, data on cardiovascular comorbidities and risk factors were collected and included: diabetes mellitus, hypertension, hypercholesterolemia, coronary artery disease, cerebrovascular disease, peripheral artery disease, heart failure and NYHA classification, rheumatic heart disease, arrhythmias, congenital heart disease, valvular heart disease, cardiomyopathy, aortic aneurysm, thromboembolic disease, pulmonary hypertension, pericardial disease and chronic kidney disease. A non-age adjusted Charlson Comorbidity Index (CCI) was calculated for each patient based on comorbidities at baseline. Specific data on medications relevant to cardiovascular risk were recorded and included: beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, mineralocorticoid receptor blockers, diuretics, digitalis, calcium channel blockers, antiplatelets, anticoagulants and statins. Blood tests results including haemoglobin, white blood count and creatinine measurements and LVEF measured on multiple-gated acquisition (MUGA) scan or echocardiogram as per local practice were also recorded at baseline.

Baseline data were collected regarding the primary tumour including: date of diagnosis, histology, grade, oestrogen receptor (ER) status and Allred score, progesterone receptor (PR) status and Allred score, HER2 testing method, best stage (i.e., the worst stage between clinical stage and pathological stage) and laterality.

Radiotherapy and systemic therapy data were collected. These included use of chemotherapy, anthracyclines, taxanes, platinum compounds, pertuzumab, radiotherapy, endocrine agents, along with setting (adjuvant versus neoadjuvant), cumulative dose of anthracyclines, number of chemotherapy cycles and number of doses of trastuzumab.

The baseline cardiovascular risk of these patients was classified as low/medium/high/very high based on the recommendations of the HFA-ICOS risk tool developed for HER2-targeted agents (Table 6.1).[17]

6.3.2. Follow-up and outcomes

Data on LVEF from MUGA scan or echocardiogram performed as per National Cancer Research Institute recommendations in the UK[18] until trastuzumab completion or discontinuation were recorded (i.e., baseline, 16 and 23 weeks for patients receiving taxanes alone and before and after anthracycline use for those receiving sequential chemotherapy regimens). Cardiac adverse outcomes were defined as: death due to cardiac reasons, LVEF decline of ≥10%, LVEF decline to below 50%, CHF (NYHA class II and III-IV) and trastuzumab discontinuation (temporary or permanent) due to cardiac toxicity. Reasons for discontinuing trastuzumab not related to cardiotoxicity and management of cardiac events with specialist referrals and medications were also recorded.

6.3.3. Statistical analysis

Analyses were performed in Stata/MP 16.0.[19] A $p<0.05$ was considered statistically significant. Baseline patients and breast cancer characteristics

were tabulated and compared among age groups (≥65 years and <65 years) and HFA-ICOS cardiovascular risk groups (low versus medium versus high versus very high) by using chi-squared, Fisher's statistics, two-sample t tests and 3-way ANOVA. Similarly, exposure to anticancer treatments was compared among age and HFA-ICOS cardiovascular risk groups. An age cut-off of 65 years was used to be consistent with previous analyses[15] and since individuals aged ≥65 years were under-represented in the pivotal trials of adjuvant trastuzumab.[20] Baseline LVEF measurements were compared with those at trastuzumab completion in the overall population and according to age group for those patients undergoing a MUGA scan or an echocardiogram at treatment initiation and specifically for those undergoing a baseline echocardiogram.

Cardiac event rates occurring at any time during the course of trastuzumab and subsequent follow-up were estimated and compared according to age (≥65 versus <65years) and HFA-ICOS cardiovascular risk (low versus medium versus high/very high). These rates were also compared based on menopausal status and use of statins at baseline. Reasons for trastuzumab discontinuation and management of cardiac events were also compared among these patient groups.

Logistic regression was used to calculate the odds of cardiac events based on HFA-ICOS risk category. The performance of the HFA-ICOS Risk Tool to predict cardiotoxicity was evaluated by calculating sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). We also composed receiver-operating characteristic (ROC) curves and calculated the area under the curve for the prediction model.

6.4. RESULTS

6.4.1. Population characteristics

Between January 2011 and December 2018, 1,094 patients initiated trastuzumab in the curative setting for HER2-positive EBC at The Royal Marsden NHS Foundation Trust. The analysis was restricted to 931 patients who completed the entire course of trastuzumab at our Institution for whom cardiac assessments were available (CONSORT diagram [Figure 6.1]).

Patient characteristics and tumour characteristics are shown in Table 6.2. No significant differences in patient and tumour characteristics were observed in those aged ≥65 years compared with their younger counterparts. Comorbidities and cardiovascular risk factors are outlined in Table 6.3. Patients aged 65 years and older had a higher prevalence of diabetes mellitus, hypertension and hypercholesterolemia compared with the younger patients (<65 years old). At trastuzumab initiation, a higher proportion of patients aged ≥65 years were on cardioprotective medications including beta-blockers, ACE inhibitors, angiotensin receptor blockers and mineralocorticoid receptor blockers (<65 years: 86/736 [11.7%]; ≥65 years: 60/195 [30.8%]; p=0.001) (Table 6.3).

Of the 931 patients, based on the HFA-ICOS risk stratification tool 401 (43.1%) had a low baseline cardiovascular risk, 454 patients (48.8%) were medium risk, 70 patients (7.5%) were high risk, and 6 patients (0.6%) were very high risk.

6.4.2. Treatment characteristics and cardiac assessments

Trastuzumab was given in the adjuvant setting only in 584 patients (62.7%), whereas 347 (37.3%) received trastuzumab neoadjuvantly and continued treatment in the adjuvant setting. The median number of doses given was 18 (range 1-18). The majority of patients received a sequential combination of anthracyclines and taxanes (594 [63.8%]), whilst 288 (30.9%) received taxanes alone. Pertuzumab was added to trastuzumab in 158 patients (17.0%)

and adjuvant radiotherapy was given to 689 patients (74.0%). Among 638 patients with ER-positive disease, tamoxifen was initially prescribed for 379 patients (59.4%) and an aromatase inhibitor for 226 (35.4%).

Table 6.4 report the treatments given in the overall population and based on age and HFA-ICOS risk category. Anthracyclines were added to a taxane less frequently in older patients (≥65 years 68 [34.9%] versus <65 years 526 [71.5%]; p=0.001) and in those with increasing HFA-ICOS risk score (low 271 [67.6%] versus medium 291 [64.1%] versus high 31 [44.3%] versus very high 1 [16.7%]; p=0.001). Similarly, older patients and those with higher cardiovascular risk were more likely to receive trastuzumab only in the adjuvant setting rather than in the neoadjuvant setting.

LVEF at baseline and upon trastuzumab completion in the overall population and according to age group are reported in Figure 6.2 and 6.3.

6.4.3. Cardiac events and their management

Cardiac adverse events occurred in 155 patients (16.6%) (Table 6.5 and Figure 6.4 and 6.5). No cardiac deaths were observed in this cohort. One hundred and forty-one patients (15.1%) experienced a LVEF decline ≥10% and 55 (5.9%) below 50%. Forty-seven patients (5.0%) developed symptomatic heart failure. In this cohort, 42 patients (4.5%) had mild symptoms (NYHA class II) and 5 patients (0.5%) had more severe symptomatic heart failure (NYHA class III-IV). No differences in cardiac events were observed based on tumour laterality (right: 71/450 [15.8%]; left: 81/467 [17.3%]; bilateral: 3/14 [21.5%]; p=0.726). The median time to cardiac toxicity was 19.9 weeks (mean: 21.9 weeks; range: 1-120 weeks).

Trastuzumab was discontinued due to cardiotoxicity in 35 patients (3.8%). No significant differences in cardiotoxicity were seen according to age group.

Supplementary table 6.1 outlines the management of cardiotoxicity events. One hundred and seventeen patients (12.6%) required a referral to a

cardiologist provided by a specialist cardio-oncology service. Beta-blockers (preferably carvedilol) were prescribed in 57 patients (6.1%), ACE inhibitors or angiotensin receptor blockers in 99 (10.6%), mineralocorticoid receptor blockers (eplerenone) in 5 patients (0.5%), diuretics in 16 patients (1.7%) and statins were started in 17 patients (1.8%) either by the treating oncologist or by the cardiologist. No significant differences were observed in the management of cardiac events based on age. In the older age group, cardioprotective medications (including beta-blockers, ACE inhibitors, angiotensin receptor blockers or mineralocorticoid receptor blockers) were prescribed in 37 patients out of 39 developing cardiac toxicity (94.9%). The use of cardioprotective medications following this specific toxicity increased with increasing HFA-ICOS risk category.

6.4.4. Performance of the HFA-ICOS risk prediction model

Increasing cardiovascular risk based on the HFA-ICOS category correlated with increasing rates of cardiac events on trastuzumab: the overall rates of cardiotoxicity was 14.0% in patients classified as low risk versus 16.7% with medium risk versus 30.3% classified as baseline as high or very high risk (p=0.002) (Figure 6.6).

The HFA-ICOS score also correlated with increasing rates of cardiac toxicity: 7.6% for low-risk patients with a score of 0 (n=66); 15.2% for low-risk patients with a score of 1 (n=335); 16.0% for medium-risk patients with a score of 2 (n=263); 18.3% for medium-risk patients with a score of 3 (n=120); 16.9% for medium-risk patients with a score of 4 (n=71); 30.3% for high- to very high-risk patients with a score ≥5 (n=76) (p=0.0147) (Figure 6.7).

The HFA-ICOS Risk Tool had a sensitivity of 14.8%, a specificity of 93.2%, a PPV of 30.3% and a NPV of 84.6% when predicting any cardiac event on trastuzumab in patients classified as low/medium risk versus those classified as high/very high risk. Area under the ROC curve for the predictive model for any cardiac toxicity was 0.56.

6.5. DISCUSSION

This is a large retrospective single centre study analysing cardiotoxicity incidence and outcomes for patients receiving trastuzumab for curable HER2-positive breast cancer, with a particular focus on outcomes for the older age group and according to baseline HFA-ICOS Risk. A significant proportion of these patients (43.1%) had a low cardiovascular risk profile based on the HFA-ICOS assessment tool. Nonetheless, more than a half had medium, high or very high risk and establishing the rates of cardiotoxicity in the real world is crucial especially in the curative setting.

A key result of our analysis is that the incidence of clinically serious symptomatic heart failure in patients receiving curative trastuzumab outside clinical trials is low (5.0%), with no fatal cardiotoxicity, although various degrees of cardiac toxicity may occur in up to 16.6% of patients on this treatment. These results are comparable to a recent pooled analysis of the trastuzumab registration trials which showed a small to modest risk of cardiotoxicity ranging between 5.5% and 19.4%.[20] The importance of this analysis is that it includes a real-world population of patients not enrolled in clinic trials and therefore may be particularly useful to inform routine clinical practice.

Benchmarking the incidence of cardiac events for patients receiving trastuzumab in the curative setting is also important in the context of the studies investigating de-escalation strategies. In our series one third of patients received taxanes alone and in a similar population with node-negative EBC, the APT study reported even lower rates of cardiac toxicity, with 0.5% of patients experiencing grade 3 left ventricular systolic dysfunction and 3% reporting asymptomatic LVEF decline.[13] In our series only 3.8% of patients did not complete a full one-year course of trastuzumab due to cardiac toxicity. The PERSEPHONE study suggested non-inferior efficacy of 6 months of treatment compared with 12 months along with a substantial reduction in cardiac events from 12% to 9%.[21]

This study suggests that there are no differences in the rates of cardiac adverse events according to age. This is consistent with previous analyses showing that most patients aged ≥66 years are able to complete a one-year course of trastuzumab without complications,[22] although comorbidities remain critical in determining the risk of cardiotoxicity.[23] One variable that may explain the lack of effect of age alone is the rate of anthracycline chemotherapy which was significantly lower in the patients ≥65 years (34.9%) versus the younger patients <65 years (71.5%). Therefore, the increased risk portended by increasing age may be balanced by the higher anthracycline chemotherapy use in the younger patients.

Our analysis also included a substantial proportion of patients with medium/high cardiovascular risk (56.9%). The registration trials of trastuzumab mandated stringent cardiac monitoring, limited the cumulative dose of anthracyclines to 300mg/m^2 and excluded subjects with abnormal baseline cardiac function. This consideration makes real-world experiences useful since the risk of cardiac toxicity on trastuzumab varies according to the use of previous chemotherapy, pre-existing heart disease and cardiovascular risk factors.[24] Therefore, identifying the baseline cardiovascular risk and developing prediction models able to identify those patients at higher risk of experiencing cardiac events remains particularly valuable.[17]

The HFA-ICOS risk score had a good correlation with the incidence of cardiotoxicity in our analysis, with 30.3% of patients with a high- to very high-risk score experiencing any cardiac event compared with 16.7% of those with medium risk and 14.0% of those with low risk. We documented a similar pattern also for specific types of cardiac adverse events, including LVEF decline, CHF and trastuzumab discontinuations. Importantly, the HFA-ICOS score had a high NPV (86.0%) which is highly desirable to identify those patients who are not at lower risk of cardiac toxicity in this setting. The score did not discriminate between the low and medium risk cohorts who had similar event rates and did not identify the cohort at absolute low risk (<5%). In practical terms the low sensitivity of the HFA-ICOS score would suggest that this should not be used to de-escalate cardiac monitoring in patients with lower

cardiovascular risk (as a 14% risk of cardiovascular events is still an appreciable rate in a curative setting). On the other hand, our findings might imply that enhanced monitoring (for example involving natriuretic peptides measurements, blood pressure control and earlier cardiology reviews if indicated) could be an appropriate strategy in those deemed at higher risk of cardiac toxicity. These findings would benefit from prospective validation in a larger cohort of patients.

This study has a number of limitations. At our institution, the measurement of cardiac biomarkers such as troponin and natriuretic peptides is not routine practice; therefore, despite their desirability where available,[17] they have not been included in the model. In this series, baseline cardiac assessments involved either MUGA scans or echocardiograms to measure LVEF which may have introduced bias. Measuring the global longitudinal strain (GLS) using speckle tracking echocardiography has become standard practice in our hospital only since 2016 and therefore this parameter has not been captured in our cohort. GLS has recently emerged as a new marker of subclinical ventricular dysfunction demonstrating a stronger association with prognosis compared with LVEF in patients with cardiac conditions not related to cancer.[25] Various observational studies suggested its potential role accurately to predict the cardiotoxicity of anticancer agents and guide cardioprotective treatment.[26, 27] Our analysis is retrospective and therefore may be subject to selection bias as we included patients who were deemed fit to receive trastuzumab. Finally, excluding patients who did not receive a full course of trastuzumab at our institution may have also contributed to selection bias.

This analysis has some major strengths as well. We have demonstrated within a large cohort that overall rates of serious cardiotoxicity associated with trastuzumab are low, but absolute rate of all cardiotoxicity is clinically significant (16.6%), and dependent on the individual cardiovascular risk profile at baseline. Our study provides evidence that rates of cardiotoxicity on trastuzumab do not differ based on age in a real-world population. Furthermore, we have included patients receiving contemporary

chemotherapy and targeted treatment regimens which make our findings applicable to current practice. Our study fills a gap of knowledge by providing evidence of external validation of a prediction model of cardiac toxicity in a population receiving treatment with substantial chances of cure.[1] This aspect is particularly valuable in the older patient population where competing risks of morbidity and mortality are more relevant.

These data should be considered when discussing risks and benefits of trastuzumab in older patients with HER2-positive EBC and prospective validation of the use of the HFA-ICOS risk tool is warranted.

6.6. PROGRESS TO PRESENTATION AND PUBLICATION

This analysis was performed in collaboration with Dr Alexander Lyon (Royal Brompton & Harefield NHS Foundation Trust). I have worked on the statistical analysis autonomously. I have presented these findings at the 2020 European Society for Medical Oncology Congress.[28] I have published this study manuscript in Breast Cancer Research and Treatment (impact factor 4.872) as first author.[29]

6.7. REFERENCES

1. Hayes, D.F., HER2 and Breast Cancer - A Phenomenal Success Story. N Engl J Med, 2019. 381(13): p. 1284-1286.
2. Perez, E.A. and R. Rodeheffer, Clinical cardiac tolerability of trastuzumab. J Clin Oncol, 2004. 22(2): p. 322-9.
3. Keefe, D.L., Trastuzumab-associated cardiotoxicity. Cancer, 2002. 95(7): p. 1592-600.
4. Eiger, D., et al., Long-term cardiac outcomes of patients with HER2-positive breast cancer treated in the adjuvant lapatinib and/or trastuzumab Treatment Optimization Trial. Br J Cancer, 2020. 122(10): p. 1453-1460.
5. Bowles, E.J., et al., Risk of heart failure in breast cancer patients after anthracycline and trastuzumab treatment: a retrospective cohort study. J Natl Cancer Inst, 2012. 104(17): p. 1293-305.
6. Ewer, S.M. and M.S. Ewer, Cardiotoxicity profile of trastuzumab. Drug Saf, 2008. 31(6): p. 459-67.
7. Guenancia, C., et al., Obesity As a Risk Factor for Anthracyclines and Trastuzumab Cardiotoxicity in Breast Cancer: A Systematic Review and Meta-Analysis. J Clin Oncol, 2016. 34(26): p. 3157-65.
8. Romond, E.H., et al., Seven-year follow-up assessment of cardiac function in NSABP B-31, a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel (ACP) with ACP plus trastuzumab as adjuvant therapy for patients with node-positive, human epidermal growth factor receptor 2-positive breast cancer. J Clin Oncol, 2012. 30(31): p. 3792-9.
9. Russell, S.D., et al., Independent adjudication of symptomatic heart failure with the use of doxorubicin and cyclophosphamide followed by trastuzumab adjuvant therapy: a combined review of cardiac data from the National Surgical Adjuvant breast and Bowel Project B-31 and the North Central Cancer Treatment Group N9831 clinical trials. J Clin Oncol, 2010. 28(21): p. 3416-21.
10. Slamon, D.J., et al., Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med, 2001. 344(11): p. 783-92.
11. Suter, T.M., et al., Trastuzumab-associated cardiac adverse effects in the herceptin adjuvant trial. J Clin Oncol, 2007. 25(25): p. 3859-65.

12. Moja, L., et al., Trastuzumab containing regimens for early breast cancer. Cochrane Database Syst Rev, 2012. 2012(4): p. Cd006243.
13. Dang, C., et al., Cardiac Outcomes of Patients Receiving Adjuvant Weekly Paclitaxel and Trastuzumab for Node-Negative, ERBB2-Positive Breast Cancer. JAMA Oncol, 2016. 2(1): p. 29-36.
14. Tarantini, L., et al., Trastuzumab adjuvant chemotherapy and cardiotoxicity in real-world women with breast cancer. J Card Fail, 2012. 18(2): p. 113-9.
15. Reeder-Hayes, K.E., et al., Comparative Toxicity and Effectiveness of Trastuzumab-Based Chemotherapy Regimens in Older Women With Early-Stage Breast Cancer. J Clin Oncol, 2017. 35(29): p. 3298-3305.
16. Brollo, J., et al., Adjuvant trastuzumab in elderly with HER-2 positive breast cancer: a systematic review of randomized controlled trials. Cancer Treat Rev, 2013. 39(1): p. 44-50.
17. Lyon, A.R., et al., Baseline cardiovascular risk assessment in cancer patients scheduled to receive cardiotoxic cancer therapies: a position statement and new risk assessment tools from the Cardio-Oncology Study Group of the Heart Failure Association of the European Society of Cardiology in collaboration with the International Cardio-Oncology Society. Eur J Heart Fail, 2020.
18. Jones, A.L., et al., Management of cardiac health in trastuzumab-treated patients with breast cancer: updated United Kingdom National Cancer Research Institute recommendations for monitoring. Br J Cancer, 2009. 100(5): p. 684-92.
19. StataCorp, Stata Statistical Software: Release 16. 2019.
20. de Azambuja, E., et al., A pooled analysis of the cardiac events in the trastuzumab adjuvant trials. Breast Cancer Res Treat, 2020. 179(1): p. 161-171.
21. Earl, H.M., et al., 6 versus 12 months of adjuvant trastuzumab for HER2-positive early breast cancer (PERSEPHONE): 4-year disease-free survival results of a randomised phase 3 non-inferiority trial. Lancet, 2019. 393(10191): p. 2599-2612.
22. Vaz-Luis, I., et al., Duration and toxicity of adjuvant trastuzumab in older patients with early-stage breast cancer: a population-based study. J Clin Oncol, 2014. 32(9): p. 927-34.
23. Serrano, C., et al., Trastuzumab-related cardiotoxicity in the elderly: a role for cardiovascular risk factors. Ann Oncol, 2012. 23(4): p. 897-902.

24. Henry, M.L., et al., Cardiotoxicity and Cardiac Monitoring Among Chemotherapy-Treated Breast Cancer Patients. JACC Cardiovasc Imaging, 2018. 11(8): p. 1084-1093.
25. Laufer-Perl, M., et al., The Role of Speckle Strain Echocardiography in the Diagnosis of Early Subclinical Cardiac Injury in Cancer Patients-Is There More Than Just Left Ventricle Global Longitudinal Strain? J Clin Med, 2021. 10(1).
26. Čelutkienė, J., et al., Role of cardiovascular imaging in cancer patients receiving cardiotoxic therapies: a position statement on behalf of the Heart Failure Association (HFA), the European Association of Cardiovascular Imaging (EACVI) and the Cardio-Oncology Council of the European Society of Cardiology (ESC). Eur J Heart Fail, 2020.
27. Thavendiranathan, P., et al., Strain-Guided Management of Potentially Cardiotoxic Cancer Therapy. J Am Coll Cardiol, 2021. 77(4): p. 392-401.
28. Battisti, N.M.L., et al., Rates of cardiac adverse events in older versus younger adults receiving trastuzumab for HER2-positive early breast cancer: results from 931 patients treated at The Royal Marsden (#2756), in European Society for Medical Oncology (ESMO) Virtual Congress. 2020.
29. Battisti, N.M.L., et al., Incidence of cardiotoxicity and validation of the Heart Failure Association-International Cardio-Oncology Society risk stratification tool in patients treated with trastuzumab for HER2-positive early breast cancer. Breast Cancer Res Treat, 2021.

6.8. TABLES

Table 6.1 – Heart Failure Association-International Cardio-Oncology Society baseline cardiovascular risk stratification tool for anti-HER2 therapies.

Domain class	Risk factor	Score	Risk categorisation
Previous cardiovascular disease	Heart failure or cardiomyopathy	VERY HIGH	LOW RISK = no risk factor OR one MEDIUM1 risk factor MEDIUM RISK = MEDIUM risk factors with a total of 2-4 points HIGH RISK = MEDIUM risk factors with a total of ≥5 points OR any HIGH risk factor VERY HIGH RISK = any VERY HIGH risk factor
	Myocardial infarction or CABG	HIGH	
	Stable angina	HIGH	
	Severe valvular heart disease	HIGH	
	Baseline LVEF <50%	HIGH	
	Borderline LVEF 50-54%	MEDIUM-2	
	Arrhythmia[1]	MEDIUM-2	
Cardiac biomarkers (where available)[2]	Elevated baseline troponin[3]	MEDIUM-2	
	Elevated baseline BNP or NT-proBNP[1]	MEDIUM-2	
Demographic and cardiovascular risk factors	Age ≥80 years	HIGH	
	Age 65-79 years	MEDIUM-2	
	Hypertension[4]	MEDIUM-1	

[1] Atrial fibrillation, atrial flutter, ventricular tachycardia or ventricular fibrillation.

[2] Baseline cardiac biomarkers have been measured in 27 patients: elevated troponin has not documented in any patients and elevated BNP or NT-proBNP have been documented in 7 patients (0.75%).

[3] Elevated above the upper limit of normal for local laboratory reference range.

[4] Systolic blood pressure (BP) >140mmg Hg or diastolic BP >90mm Hg, or on treatment.

	Diabetes mellitus[5]	MEDIUM-1	
	Chronic kidney disease[6]	MEDIUM-1	
Current cancer treatment regimen	Includes anthracycline before HER2-targeted therapy[7]	MEDIUM-1	
Previous cardiotoxic cancer treatment	Prior trastuzumab cardiotoxicity	VERY HIGH	
	Prior (remote) anthracycline exposure[8]	MEDIUM-2	
	Prior radiotherapy to left chest or mediastinum	MEDIUM-2	
Lifestyle risk factors	Current smoker or significant smoking history	MEDIUM-1	
	Obesity (BMI>30)	MEDIUM-1	

Abbreviations: HER2: human epidermal growth factor receptor 2; LVEF: left ventricular ejection fraction; CABG: coronary artery bypass graft; BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro b-type natriuretic peptide; BMI: body mass index.

[5] HbA1c >7.0% or >53mmol/mol or on treatment.

[6] Estimated glomerular filtration rate <60ml/min/1.73m^2.

[7] HIGH risk if anthracycline chemotherapy and trastuzumab delivered concurrently.

[8] Previous malignancy (not current treatment protocol).

Table 6.2 – Patient and tumour characteristics at baseline in the overall population and according to age group.

Characteristics		Overall N = 931	Age group		p value
			<65 years N = 736	≥65 years N = 195	
Continuous variables					
Age (years)	Median	54	50	69	-
	IQR	46-63	43-56	67-73	
	Mean	54.3	50.0	70.9	
	Standard deviation	11.9	9.0	4.6	
	Range	24-83	24-64	65-83	
Weight (kg)[1]	Median	69	69.0	68.8	0.555
	IQR	60.8-78.9	60.6-79.0	61.5-77.7	
	Mean	71.0	71.3	70.1	
	Standard deviation	14.8	15.4	12.4	
	Range	42.5-140.0	42.5-140.0	43.7-106.6	
BMI (kg/m^2)[2]	Median	25.4	25.4	26.7	0.073
	IQR	22.7-30.0	22.0-30.0	23.8-30.2	
	Mean	26.8	26.7	27.2	
	Standard deviation	5.50	5.70	4.7	

[1] Recorded in 929/931 patients.

[2] Recorded in 928/931 patients.

Characteristics		Overall N = 931		Age group <65 years N = 736		≥65 years N = 195		p value
	Range	15.9-51.8		15.9-51.8		17.3-42.2		
Charlson comorbidity index	Median	0		0		0		0.259
	IQR	0-2		0-0		0-1		
	Mean	0.9		0.9		1.0		
	Standard deviation	1.1		1.0		1.1		
	Range	0-6		0-5		0-6		
Categorical variables		N	%	N	%	N	%	
Sex	Female	930	99.9	736	100.00	194	99.5	-
	Male	1	0.1	0	0.00	1	0.5	-
ECOG PS	0	826	88.7	679	92.3	147	75.4	0.001
	1	102	11.0	57	7.7	45	23.1	0.001
	2	3	0.3	0	0.0	3	1.5	0.009
Menopausal status	Pre/perimenopausal	427	45.9	427	58.0	0	0.0	-
	Postmenopausal	504	54.1	309	42.0	195	100.0	0.001
Status (on 13/05/2020)	Dead	51	5.5	36	4.9	15	7.7	0.155
	Alive	880	94.5	700	95.1	180	92.3	-
Previous (remote) use of chemotherapy		45	4.8	35	4.8	10	5.1	0.851
Previous (remote) use of anthracyclines		29	3.1	23	3.1	6	3.1	0.999

Characteristics		Overall N = 931		Age group				p value
				<65 years N = 736		≥65 years N = 195		
Previous (remote) use of trastuzumab		9	1.0	9	1.2	0	0.0	0.217
Histology	Ductal	885	95.1	706	95.9	179	91.8	0.022
	Lobular	38	4.1	25	3.4	13	6.7	0.064
	Mixed ductal/lobular	5	0.5	3	0.4	2	1.0	0.282
	Other	2	0.2	1	0.1	1	0.5	0.376
	Missing	1	0.1	1	0.1	0	0.0	-
Grade	1	15	1.6	12	1.6	3	1.5	0.999
	2	332	35.7	263	35.7	69	35.4	0.867
	3	570	61.2	448	60.9	122	62.6	0.868
	Missing	14	1.5	13	1.8	1	0.5	-
ER status	Negative	293	31.5	226	30.7	67	34.4	0.341
	Positive	638	68.5	510	69.3	128	65.6	0.341
PR status	Negative	447	48.0	340	46.2	107	54.9	0.017
	Positive	452	48.5	373	50.7	79	40.5	0.017
	Missing	32	3.4	23	3.1	9	4.6	-
HER2 testing method	IHC	611	65.6	494	67.1	117	60.0	-
	ISH	201	21.6	146	19.9	55	28.2	-
	Unknown	119	12.8	96	13.0	23	11.8	-

Characteristics		Overall N = 931		Age group				p value
				<65 years N = 736		≥65 years N = 195		
Best stage[3]	I	212	22.8	163	22.1	49	25.1	0.386
	II	551	59.2	442	60.0	109	55.9	0.324
	III	162	17.4	127	17.3	35	17.9	0.831
	Missing	6	0.6	4	0.5	2	1.0	-
Laterality	Right	450	48.3	355	48.2	95	48.7	0.936
	Left	467	50.2	370	50.3	97	49.7	0.936
	Bilateral[4]	14	1.5	11	1.5	3	1.5	0.999

Abbreviations: BMI: Body Mass Index; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ER: oestrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2; ISH: in situ hybridisation; IHC: immunohistochemistry.

[3] Corresponds to the “worst” stage between clinical stage (for patients receiving neoadjuvant systemic therapy) or pathological stage (for those receiving only adjuvant systemic therapy).

[4] Includes patients with bilateral HER2-positive disease (and not patients with monolateral HER2-positive disease plus contralateral HER2-negative disease).

Table 6.3 – Comorbidities, cardiovascular risk factors and concurrent medications at baseline in the overall population and according to age group.

Comorbidities and cardiovascular risk factors			Overall N = 931		Age group <65 years N = 736		≥65 years N = 195		p value
			N	%	N	%	N	%	
Diabetes mellitus			44	4.7	28	3.8	16	8.2	0.014
Hypertension			176	18.9	96	13.0	80	41.0	0.001
Hypercholesterolemia			91	9.8	44	6.0	47	24.1	0.001
Coronary artery disease			12	1.3	5	0.7	7	3.6	0.005
Cerebrovascular disease			4	0.4	2	0.2	2	1.0	0.195
Peripheral artery disease			1	0.1	0	0.0	1	0.5	0.209
Heart failure	Overall		2	0.21	1	0.14	1	0.51	0.375
	NYHA class	1	1	0.11	1	0.14	0	0.00	-
		3	1	0.11	0	0.00	1	0.51	-
Rheumatic heart disease			1	0.1	1	0.1	0	0.0	0.999
Abnormal heart rhythm			23	2.5	12	1.6	11	5.6	0.003
Congenital heart disease			7	0.7	5	0.7	2	1.0	0.641
Valvular heart disease			9	1.0	6	0.8	3	1.5	0.406
Cardiomyopathy			4	0.4	4	0.5	0	0.0	0.585
Aortic aneurysm			1	0.1	0	0.0	1	0.5	0.209
Thromboembolic disease			9	01.0	7	0.9	2	1.0	0.999
Venous thromboembolism			6	0.6	5	0.7	1	0.5	0.999
Pulmonary hypertension			1	0.1	0	0.0	1	0.5	0.209
Pericardial disease			1	0.1	1	0.1	0	0.0	0.999

Comorbidities and cardiovascular risk factors		Overall N = 931		Age group <65 years N = 736		≥65 years N = 195		p value
		N	%	N	%	N	%	
Chronic kidney disease		5	0.5	3	0.4	2	1.0	0.282
Cigarette smoking	Overall	228	24.5	179	24.3	49	24.5	0.851
	Current	42	4.5	38	5.2	4	2.0	-
	Past	186	20.0	141	19.2	45	23.1	-
Regular alcohol consumption		385	41.3	299	40.6	86	44.1	0.414
Concurrent medications		N	%	N	%	N	%	
Cardioprotective medications[1]		146	15.7	86	11.7	60	30.8	0.001
Beta-blockers		54	5.8	30	4.1	24	12.3	0.001
ACE inhibitors		77	8.3	47	6.4	30	15.4	0.001
Angiotensin receptor blockers		38	4.1	18	2.4	20	10.3	0.001
Mineralocorticoid receptor blockers		1	0.1	0	0.0	1	0.5	0.209
Diuretics		50	5.4	25	3.4	25	12.8	0.001
Digitalis		3	0.3	1	0.1	2	1.0	0.113
Calcium channel blockers		82	8.8	46	6.2	36	18.5	0.001
Antiplatelets		33	3.5	20	2.7	13	6.7	0.014
Anticoagulants		12	1.3	7	0.9	5	2.6	0.143
Statins		83	8.9	38	5.2	45	23.1	0.001

Abbreviations: NYHA: New York Heart Association; ACE: angiotensin-converting enzyme.

[1] Cardioprotective medications include beta-blockers, ACE inhibitors, angiotensine receptor blockers and mineralcorticoid receptor blockers.

Table 6.4 – Treatment characteristics and exposure in the overall population and according to age and Heart Failure Association-International Cardio-Oncology Society risk group.

		Overall N = 931		Age group <65 years N = 736		Age group ≥65 years N = 195		p value	HFA-ICOS risk group Low N = 401		Medium N = 454		High N = 70		Very high N = 6		p value
Treatment characteristics	Category	N	%	N	%	N	%		N	%	N	%	N	%	N	%	
Concurrent chemotherapy	No chemotherapy	10	1.1	7	0.9	3	1.5	0.445	3	0.7	6	1.3	0	0.0	1	16.7	0.002
	Anthracycline + taxanes	594	63.8	526	71.5	68	34.9	0.001	271	67.6	291	64.1	31	44.3	1	16.7	0.001
	Taxanes alone	288	30.9	174	23.6	114	58.5	0.001	111	27.7	141	31.1	33	47.1	3	50.0	0.001
	Anthracyclines alone	14	1.5	13	1.8	1	0.5	0.323	6	1.5	8	1.8	0	0.0	0	0.0	0.714
	Including carboplatin	29	3.1	25	3.4	4	2.0	0.486	12	3.0	14	3.1	2	2.9	1	16.7	0.297
	Other regimen	25	2.7	16	2.2	9	4.6	0.078	10	2.5	8	1.8	6	8.6	1	16.7	0.002
Epirubicin dose ≥450mg/m^2		21	2.3	18	2.4	3	1.5	0.721	6	2.2	13	4.3	2	6.2	0	0.0	0.416
Pertuzumab use		158	17.0	143	19.4	15	7.7	0.001	74	18.4	74	16.3	9	12.9	1	16.7	0.657
Setting	Adjuvant only	584	62.7	434	59.0	150	76.9	0.001	235	58.6	291	64.1	54	77.1	4	66.7	0.023
	Neoadjuvant + adjuvant	347	37.3	302	41.0	45	23.1	0.001	166	41.4	163	35.9	16	22.9	2	33.3	0.023
Radiotherapy use	No	242	26.0	179	24.3	63	32.3	0.027	106	26.4	111	24.4	24	34.3	1	16.7	0.337
	Yes	689	74.0	557	75.7	132	67.7	0.027	295	73.6	343	75.5	46	65.7	5	83.3	0.337

Endocrine therapy	No endocrine therapy	326	35.0	255	34.6	71	36.4	0.673	125	31.2	176	38.8	24	34.3	1	16.7	0.097
	Tamoxifen[51]	379	40.7	338	45.9	41	21.0	0.001	212	52.9	149	32.8	14	20.0	4	66.7	0.001
	Aromatase inhibitor[1]	226	24.3	143	19.4	83	42.6	0.001	64	16.0	129	28.4	32	45.7	1	16.7	0.001
Chemotherapy cycles	Median	6		6		4		0.001	6		6		5		5		0.001
	IQR	4-8		4-8		4-6			4-8		4-8		4-6		4-6		
	Mean	5.9		6.2		4.9			6.1		5.9		5.1		4.7		
	SD	1.9		1.8		2.0			1.9		1.9		2.0		2.7		
	Range	0-10		0-10		0-10			0-10		0-10		1-8		0-8		
Epirubicin cumulative dose (mg/m^2)[52]	Median	360		360		360		0.798	360		360		360		360		0.852
	IQR	300-360		300-360		300-360			300-360		300-360		300-360		360-360		
	Mean	333.4		333.1		335.4			329.7		336.0		338.9		360.0		
	SD	67.8		67.7		69.6			61.5		73.4		66.7		0.0		
	Range	90-600		90-600		90-600			90-600		90-600		180-600		360-360		
Trastuzumab doses	Median	18		18		18		0.001	18		18		18		18		0.193
	IQR	18-18		18-18		17-18			18-18		18-18		17-18		14-18		
	Mean	17.3		17.5		16.8			17.6		17.3		16.4		15.0		
	SD	2.1		1.7		3.1			1.4		2.2		3.7		5.6		
	Range	1-18		3-18		1-18			3-18		1-18		4-18		4-18		

Abbreviations: HFA: Heart Failure Association; ICOS: International Cardio-Oncology Society

[51] Initial choice of endocrine agent (regardless of subsequent changes based on menopausal status and tolerance).

[52] Two patients who received doxorubicin instead of epirubicin have been excluded from this analysis.

Table 6.5 – Rates of cardiac events at any time following trastuzumab initiation in the overall population and according to age group and Heart Failure Association-International Cardio-Oncology Society risk group.

Cardiac events (not mutually exclusive)		Overall N = 931		Age group <65 years N = 736		Age group ≥65 years N = 195		p value	HFA-ICOS risk category Low N = 401		Medium N = 454		High N = 70		Very high N = 6		p value
		N	%	N	%	N	%		N	%	N	%	N	%	N	%	
Overall		155	16.6	116	15.8	39	20.0	0.161	56	14.0	76	16.7	20	28.57	3	50.0	0.003
LVEF decline ≥10%		141	15.1	106	14.4	35	17.9	0.218	51	12.	70	15.42	17	24.3	3	50.0	0.007
LVEF decline below 50%		55	5.9	43	5.8	12	6.1	0.865	18	4.5	29	6.4	6	8.6	2	33.3	0.014
CHF	NYHA class II	42	4.5	34	4.6	8	4.1	0.757	12	3.0	24	5.3	4	5.7	2	33.3	0.002
	NYHA class III-IV	5	0.5	3	0.4	2	1.0	0.294	0	0.0	4	0.9	1	1.4	0	0.0	0.236
Trastuzumab discontinuation due to cardiotoxicity	Overall	35	3.8	26	3.5	9	4.6	0.040	9	2.2	17	3.7	7	10.0	2	33.3	0.001
	Temporary	23	2.5	18	2.4	5	2.6	0.999	5	1.2	12	2.6	4	5.7	2	33.3	0.001
	Permanent	12	1.3	8	1.1	4	2.0	0.289	4	1.0	5	1.1	3	4.3	0	0.0	0.144

Abbreviations: HFA: Heart Failure Association; ICOS: International Cardio-Oncology Society; LVEF: left ventricular ejection fraction; CHF: congestive heart failure; NYHA: New York Heart Association.

6.9. FIGURES

Figure 6.1 – CONSORT diagram.

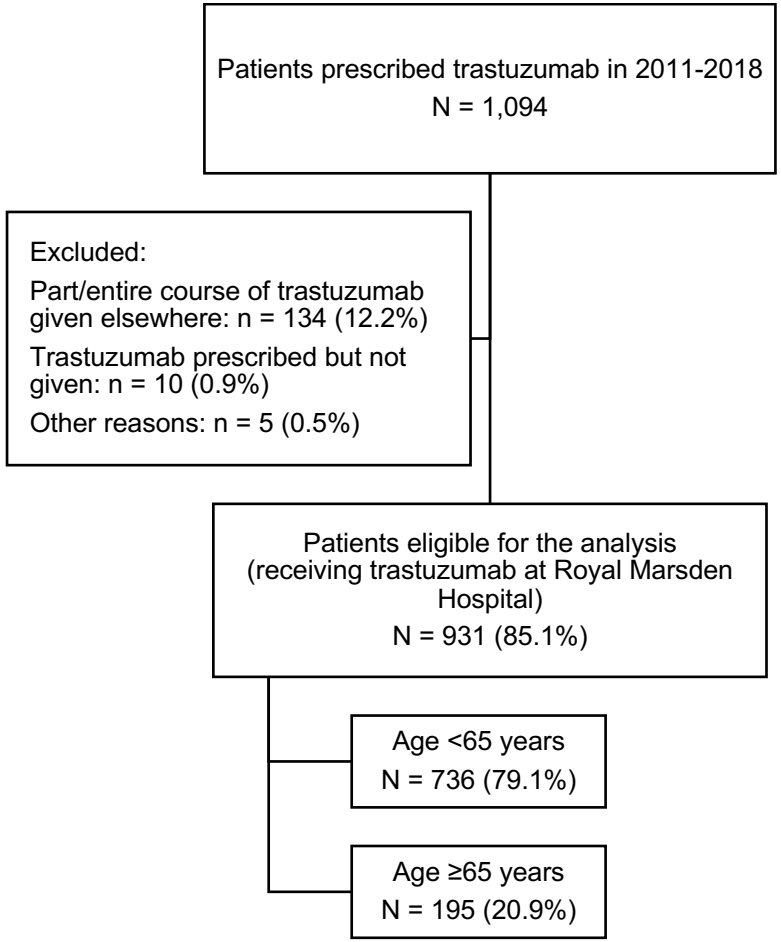


Figure 6.2 – Left ventricular ejection fraction at baseline and upon trastuzumab completion in the overall population.

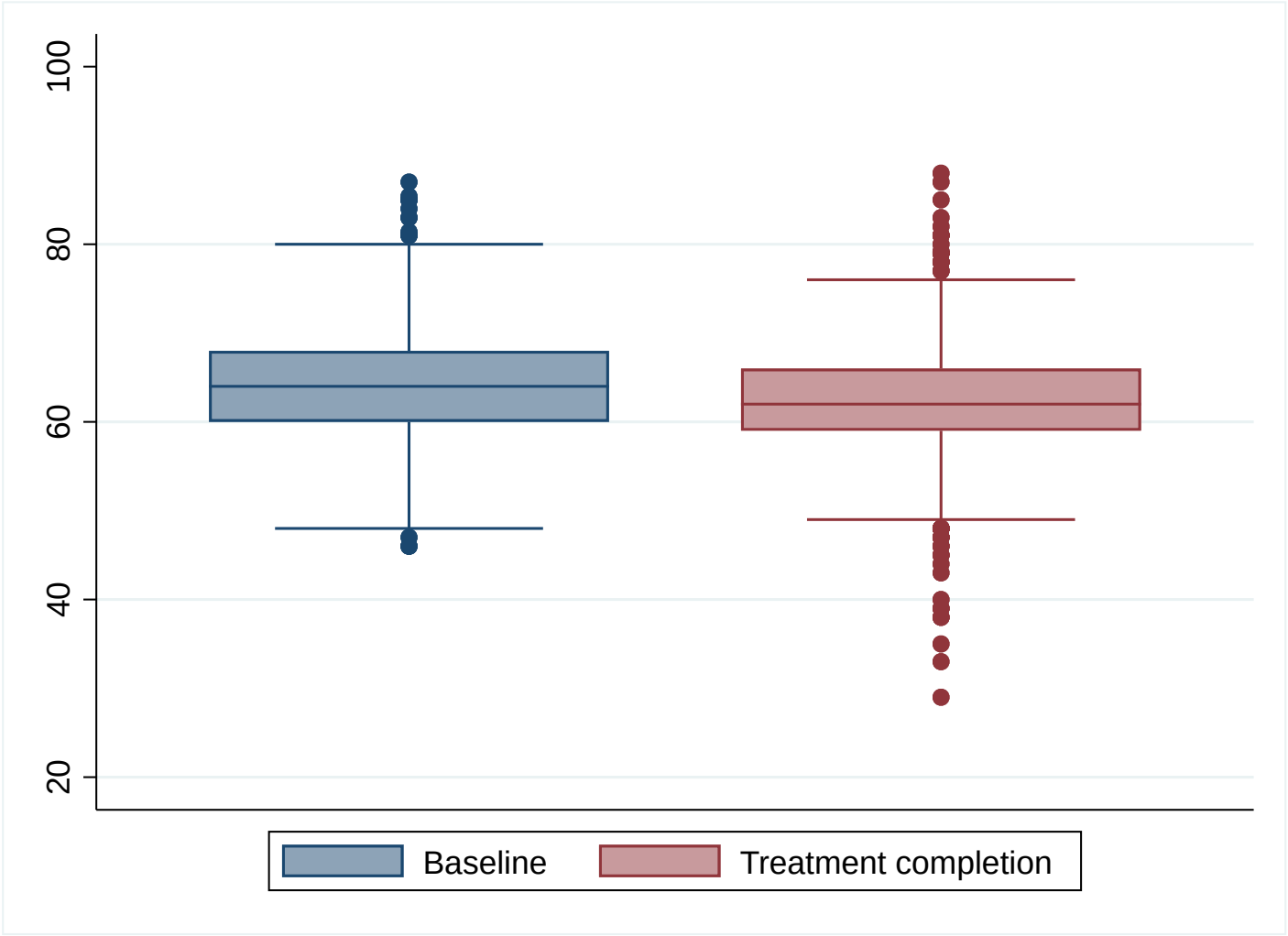


Figure 6.3 – Left ventricular ejection fraction at baseline and upon trastuzumab completion according to age group.

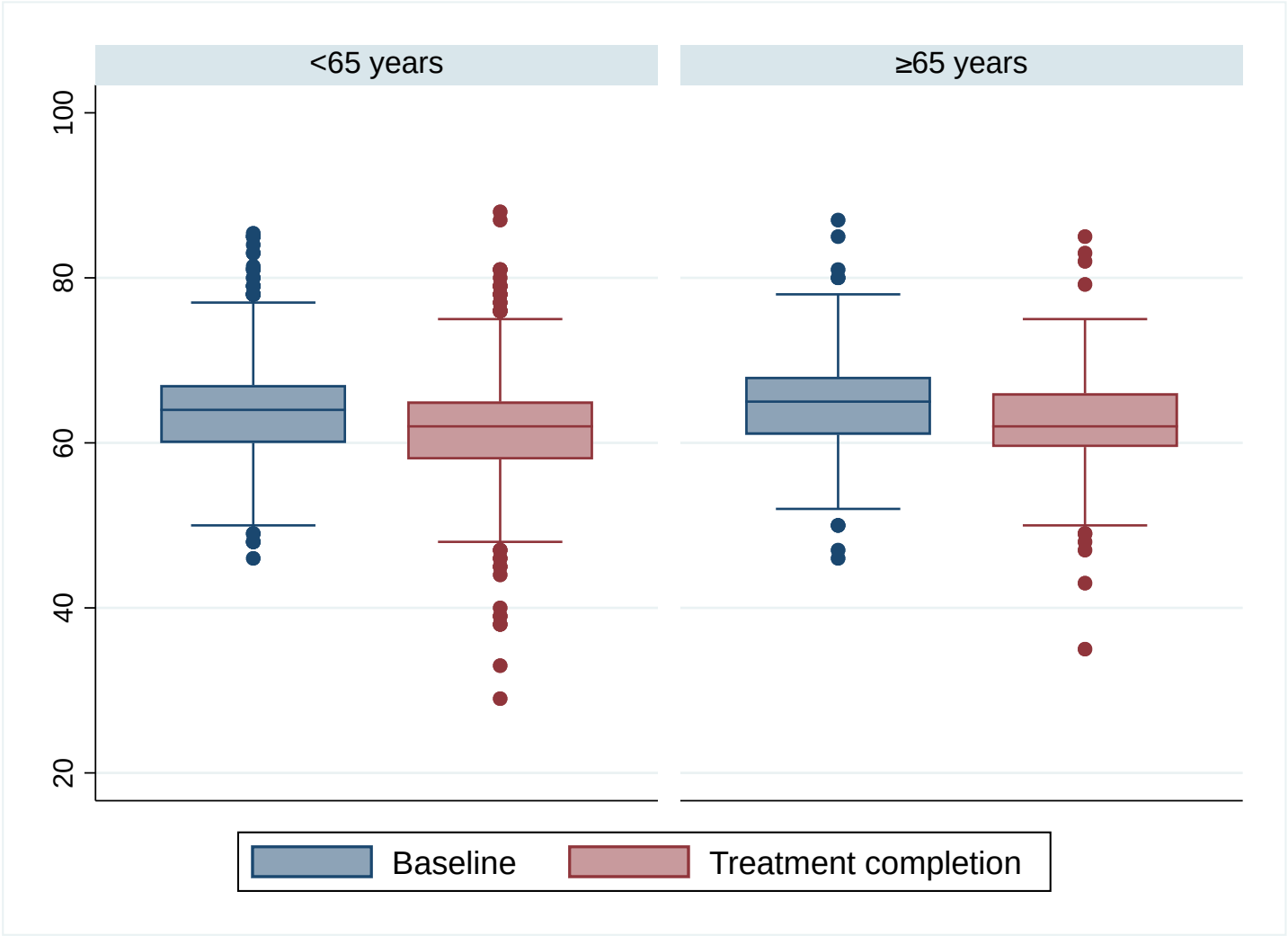
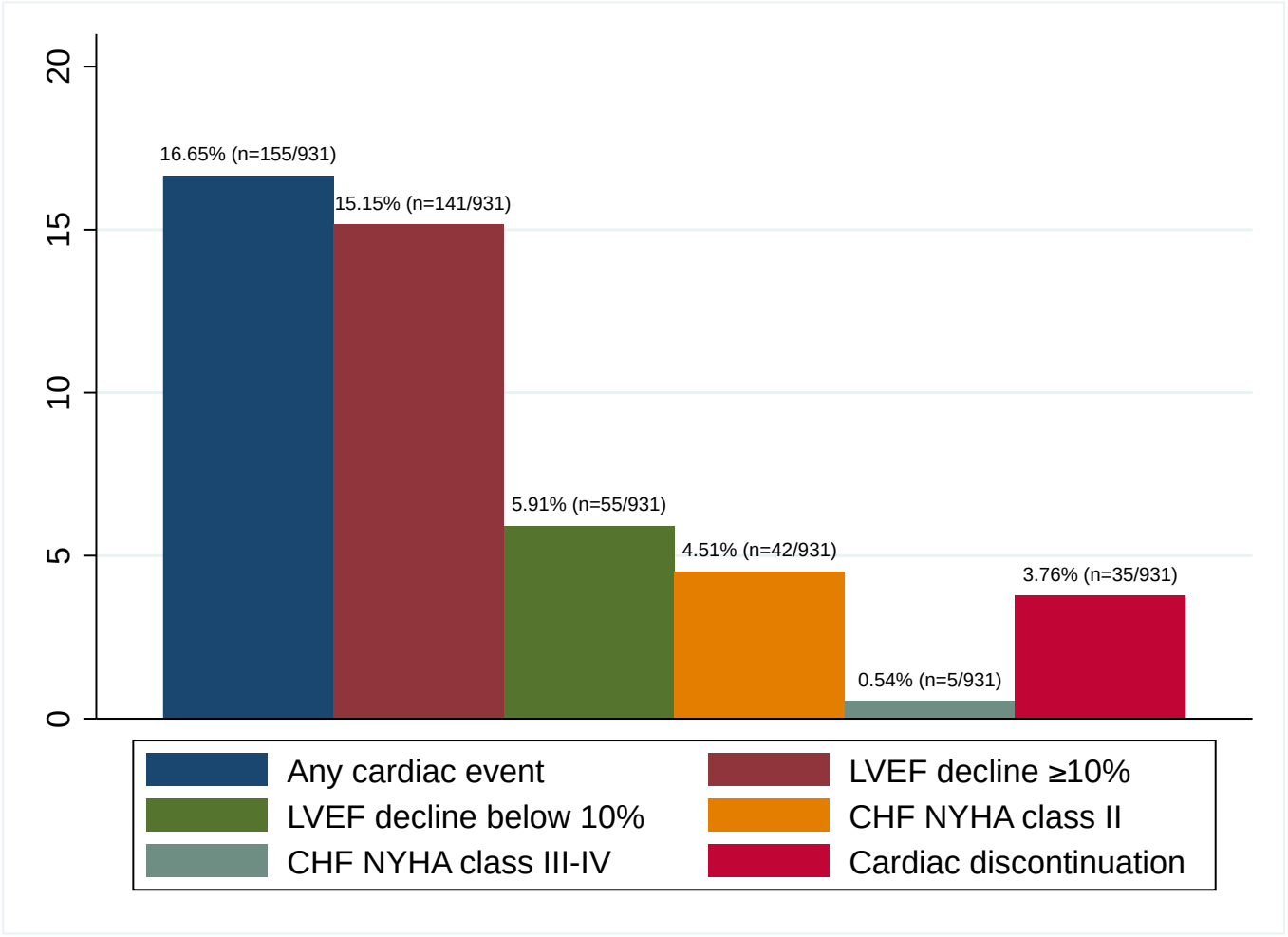
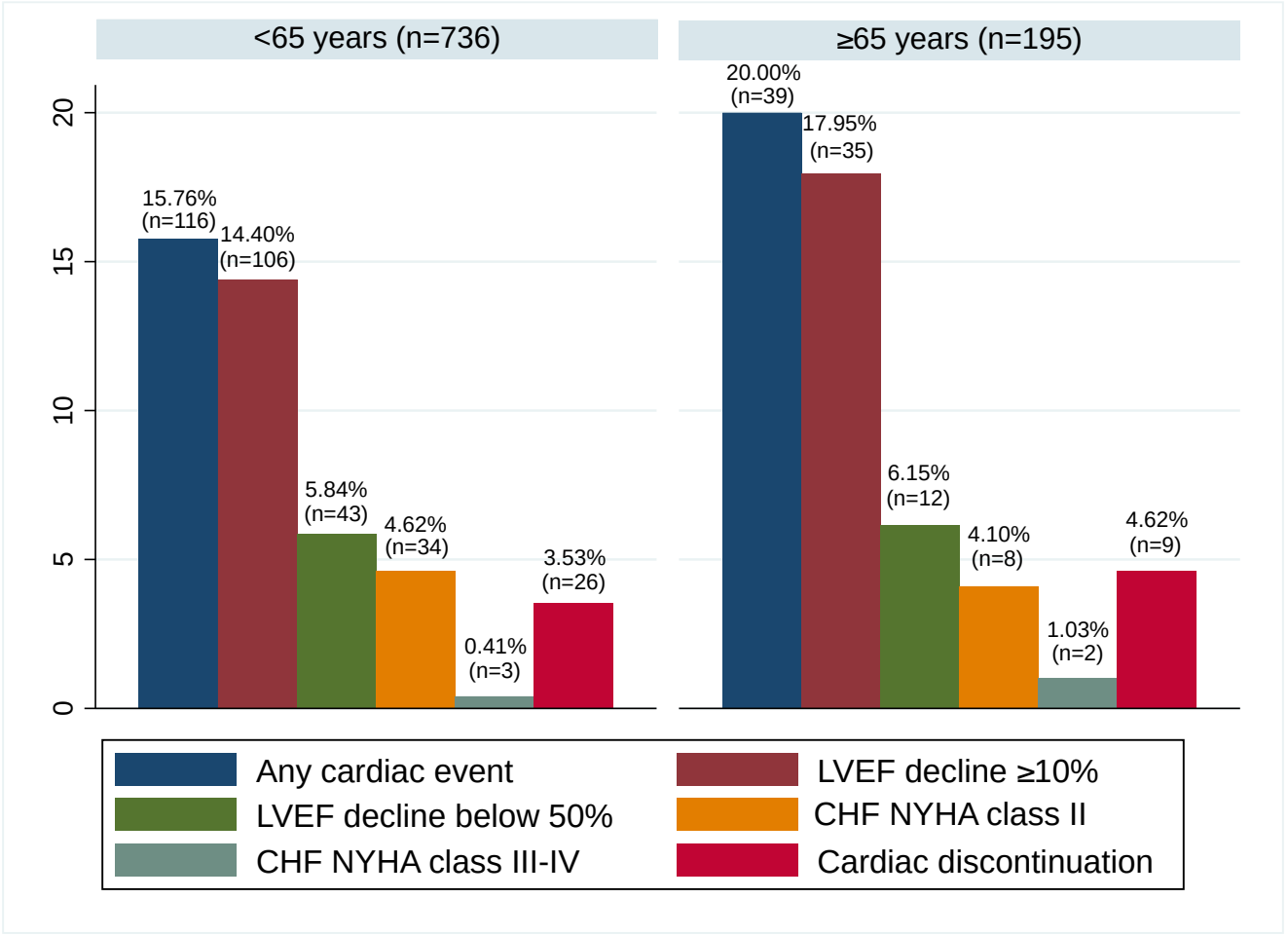


Figure 6.4 – Rates of cardiac events at any time following trastuzumab initiation in the overall population.



Abbreviations: LVEF: left ventricular ejection fraction; CHF: congestive heart failure; NYHA: New York Heart Association.

Figure 6.5 – Rates of cardiac events at any time following trastuzumab initiation according to age group.



Abbreviations: LVEF: left ventricular ejection fraction; CHF: congestive heart failure; NYHA: New York Heart Association.

Figure 6.6 – Rates of overall cardiac events by Heart Failure Association-International Cardio-Oncology Society risk category.

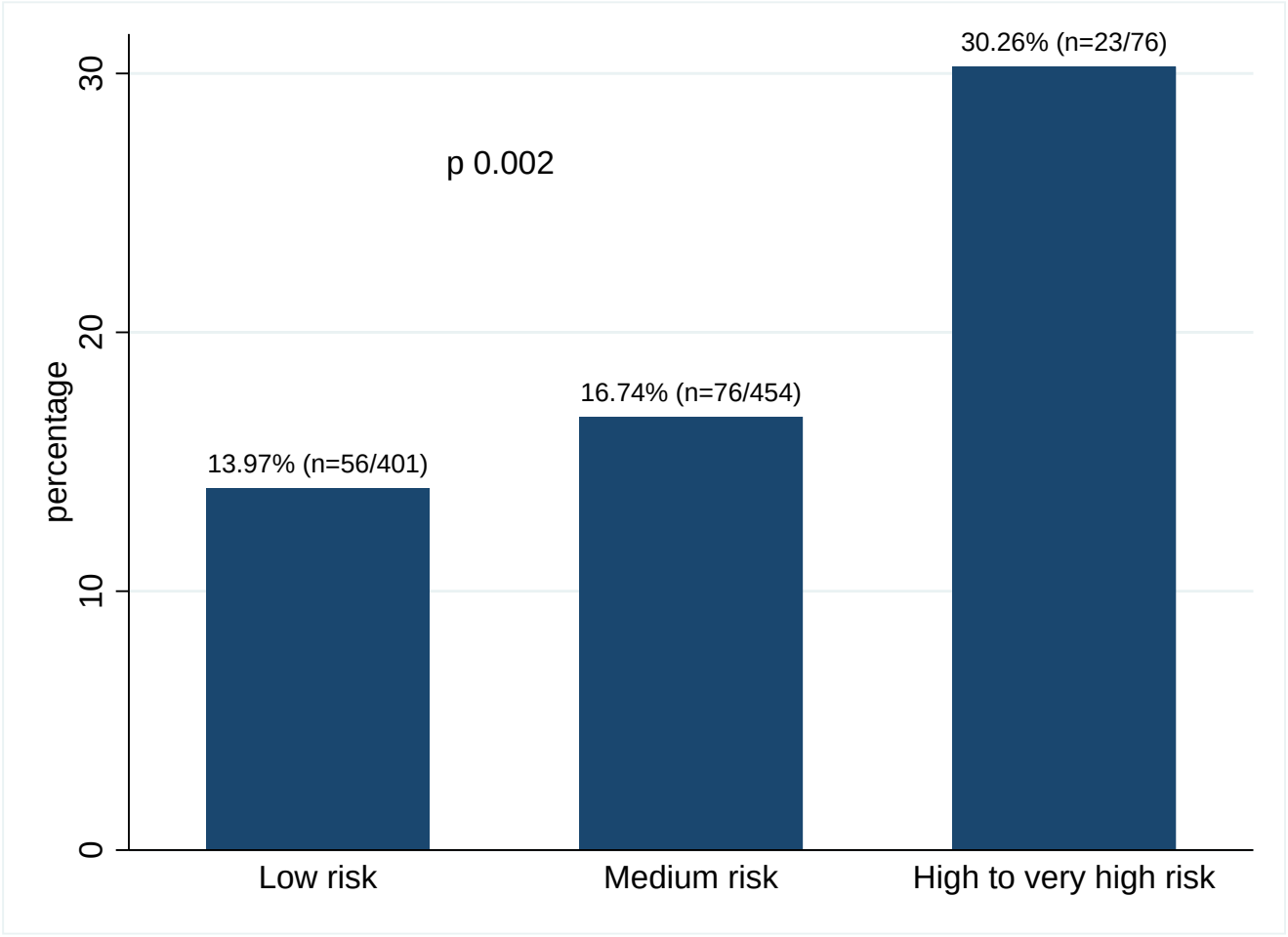
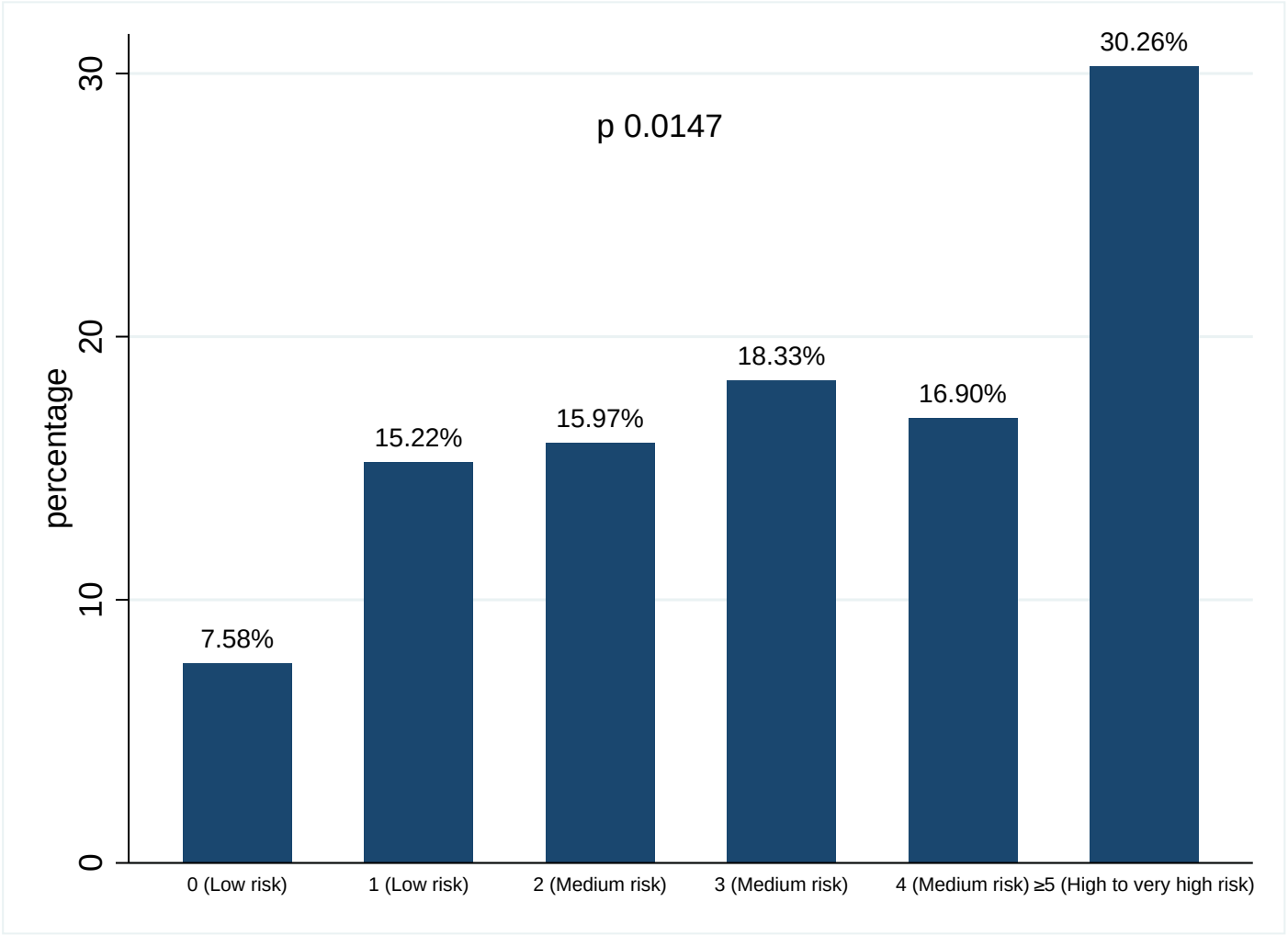


Figure 6.7 – Rates of overall cardiac events by Heart Failure Association-International Cardio-Oncology Society risk score.



GENERAL SUMMARY AND CONCLUSIONS

This thesis describes the impact of age and comorbidities on different aspects of the management of breast cancer and other common malignancies in five closely related research projects.

The first study aimed to describe the age- and risk-stratified patterns of receipt of adjuvant systemic therapy in older patients with early breast cancer (EBC) enrolled in the Bridging the Age Gap study, with propensity score-matched analysis of disease recurrence and survival outcomes to determine which patients might benefit from treatment.[1] We analysed data from a multicentre, prospective, observational study to determine the use of chemotherapy (with or without trastuzumab) and survival outcomes in patients aged ≥70 years diagnosed with EBC. Propensity score-matching adjusted for variation in baseline age, fitness and tumour stage. The study recruited 3,416 women in 56 UK centres between 2013 and 2018. We analysed data on 2,811 patients (82%) who underwent surgery. Among these, 1,520/2,811 (54%) had high-risk EBC and 2,059/2,811 (73%) were fit. Chemotherapy was given to 306/1,100 (27.8%) fit patients with high-risk EBC. Unmatched comparison of chemotherapy versus no chemotherapy demonstrated a reduction in the risk of metastatic risk in high-risk patients (hazard ratio [HR] 0.36 [95% CI 0.19–0.68]) and in 541 age, stage and fitness-matched patients (adjusted HR 0.43 [95% CI 0.20–0.92]). However, we did not document any benefit in overall survival (OS) or breast cancer-specific survival (BCSS) in either group. Chemotherapy improved survival in women with oestrogen receptor (ER)-negative cancer (OS: HR 0.20 [95% CI 0.08–0.49]; BCSS: HR 0.12 [95% CI 0.03–0.44]). Therefore, chemotherapy was associated with reduced risk of metastatic recurrence, but survival benefits were only seen in patients with ER-negative cancer. This analysis is a large prospective cohort study and provides valuable data on tumour characteristics and fitness in this specific population. Importantly, we integrated considerations on tumour recurrence risk and fitness and demonstrated low chemotherapy uptake even in fit, older

patients with high-risk EBC. Consistently with previous evidence, we did not observe a survival benefit on chemotherapy in the overall patient population, but this was limited to those with ER-negative tumours. Nonetheless, based on previous retrospective evidence showing survival benefits for older patients with node-positive EBC, the burden of nodal disease should also be considered for chemotherapy decision-making in this population.[2] Future research should focus on the integration of measures of fitness in predictors of treatment benefits, the use of alternative (and potentially safer) systemic treatment options and the impact of patient and clinician education approaches to better inform systemic treatment decisions for this population.

Quality of life (QoL) is also a critical endpoint for older individuals with cancer in the context of the more limited life expectancy and less pronounced benefits observed on standard anticancer therapeutic approaches in this population. Therefore, the second study aimed to investigate the impact of curative chemotherapy on the QoL of older patients with EBC enrolled in the Bridging the Age Gap study.[3] We analysed data from the Bridging the Age Gap study that included data on demographics, patient, tumour characteristics, treatments and adverse events. The study also included data on QoL assessed with the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaires (QLQ) C30, BR23 and ELD15 and the Euroqol-5D (EQ-5D) over 24 months. These outcomes were analysed at each time point using baseline adjusted linear regression analysis and propensity score-matching. Among 3,416 patients enrolled in the study, we restricted the analysis to 1,520 individuals undergoing surgery and who had high-risk EBC for whom we would typically consider chemotherapy. 376/1,520 (24.7%) received chemotherapy. At 6 months, chemotherapy had a significant negative impact in several EORTC-QLQ-C30 domains, including global health score, physical, role, social functioning, cognition, fatigue, nausea/vomiting, dyspnoea, appetite loss, diarrhoea and constipation. Similar trends were documented on other scales (EORTC-QLQ-BR23, EORTC-QLQ-ELD15 and EQ-5D-5L). Its impact was no longer significant at 18-24 months in unmatched and matched cohorts. Therefore, the negative impact of chemotherapy on QoL is clinically and statistically significant at 6 months but resolves by 18 months,

which is crucial to inform decision-making for older patients with EBC contemplating chemotherapy. This is a key aspect to better inform treatment decisions and to improve discussions with older patients with EBC that may have different preferences on the trade-off between quantity and quality of life. Importantly, by expanding the knowledge on effects of chemotherapy on QoL may provide further reassurance to the concerns of clinicians and patients that contribute to the existing variation in the use of chemotherapy in this population. However, more research is warranted on the differential impact of different systemic treatment options on QoL and the effect of geriatric assessment-driven interventions on this metric in this population.

Radiotherapy is an important treatment approach for EBC for older patients associated with a reduction of the risk of breast recurrence in this population. Nonetheless, this benefit should be balanced against a holistic patient assessment and its impact on QoL and evidence on radiotherapy patterns in this population is sparce. The third study aimed to describe the age- and risk-stratified patterns of receipt of adjuvant radiotherapy following breast conserving surgery or mastectomy and its impact on QoL in older patients with EBC enrolled in the Bridging the Age Gap study.[4] We analysed data from the Bridging the Age Gap study that and determined associations between radiotherapy use, surgery, clinico-pathological parameters, fitness based on geriatric parameters and treatment centre. QoL was measured using the EORTC questionnaires. Among 3,416 women recruited in the study, we analysed data on 2,811 patients who underwent surgery with a median follow-up of 52 months. On multivariable analysis, age and tumour risk predicted radiotherapy use. Among healthier patients with high-risk tumours (where fitness was defined based on geriatric assessments), 534/613 (87.1%) having breast-conserving surgery and 185/341 (54.2%) having mastectomy received radiotherapy. In less fit individuals with low-risk tumours undergoing breast-conserving surgery, 149/207 (72.0%) received radiotherapy. We observed radiotherapy effects on QoL domains, including breast symptoms and fatigue, although these resolved by 18 months. Therefore, radiotherapy use in EBC patients ≥70 years is affected by age and recurrence risk, whereas geriatric parameters have limited impact regardless of the type of surgery. We also

detected geographical variation in the use of radiotherapy, with some fit older women with high-risk tumours not receiving it and some older patients with low-risk EBC patients receiving it after BCS despite evidence of limited benefit. Importantly, the impact of radiotherapy on QoL was transient. This analysis is critical to identify older patients with EBC at risk of over- or under-treatment and those suitable for radiotherapy de-escalation strategies. Geriatric assessments represent a unique opportunity to minimise these risks and further personalise also the use of radiotherapy in this population. This study is also important to inform the allocation of resources in radiotherapy service provision across England and Wales. Nevertheless, more evidence is needed on the impact of geriatric assessments on radiotherapy benefits and toxicities and on the integration of biomarkers with measures of fitness to tailor the management of EBC in this age group.

Cardiovascular disease (CVD) is a common challenge for clinicians when managing older individuals with cancer, especially when treatment intent is curative. This is a key component of patient fitness that may contribute to treatment variation in older adults with cancer. The fourth study, included in the Virtual Cardio-Oncology Research Institute initiative, aimed to determine the prevalence of pre-existing CVD in patients with a new diagnosis of potentially curable cancer on the UK National Cancer Registration and Analysis Service (NCRAS) and the National Institute for Cardiovascular Outcomes Researcher (NICOR) datasets.[5] Within this study, we retrieved data on patients diagnosed in England with stage I-III breast cancer, stage I-III colon/rectal cancer, stage I-III prostate cancer, stage I-IIIA non-small cell lung cancer (NSCLC), stage I-IV diffuse large B cell lymphoma (DLBCL) and stage I-IV Hodgkin lymphoma from 2013 to 2018 from cancer registry data. Linked hospital records and national cardiovascular disease databases identified prior presentations with CVD. We investigated the rates of CVD presentations in each tumour cohort and the association between patient and disease characteristics and CVD presentations. Among 634,240 patients included, 102,834 (16.2%) had prior CVD. Men, older patients and those living in deprived areas had higher prior CVD presentation rates. Rates were highest for NSCLC (36.1%) and lowest for breast cancer (7.7%). After adjustment for

age, sex, Index of Multiple Deprivation (IMD) and Charlson Comorbidity Index (CCI), CVD rates remained higher in the other tumour cohorts compared to breast cancer patients. Therefore, we observed a significant overlap between cancer and CVD burden. This is essential to consider CVD when comparing national and international treatment patterns and cancer outcomes. By examining a key component of fitness for treatment, this study provides context to where over or under-treatment of older patients of cancer may occur. This information is important to inform the management of individual patients with cancer. At population level, this analysis provides useful insight to inform cancer policy strategies and resource allocation. However, future research will need to investigate the impact of CVD on specific anticancer treatments in this setting, while comparisons with data derived in other countries might prove useful to interpret international variation in their uptake.

Estimating the individual risk of cardiac toxicity is particularly relevant in the older age group in the context of the increased burden of competing risks of morbidity and mortality, the more limited life expectancy and the less pronounced benefits observed on curative treatments. In the fifth study, we therefore evaluated the risk of cardiac toxicity in older versus younger patients with human epidermal growth factor receptor 2 (HER2)-positive EBC receiving trastuzumab and validated the performance of the Heart Failure Association-International Cardio-Oncology Society (HFA-ICOS) risk stratification tool. In this population, we retrospectively evaluated the rates of cardiac toxicity defined as: left ventricular ejection fraction (LVEF) decline, congestive heart failure (CHF), cardiac death or trastuzumab discontinuation.[6] We also evaluated the performance of a proposed model to predict cardiac toxicity in routine clinical practice. We retrieved data on patients receiving curative trastuzumab between 2011 and 2018 at The Royal Marsden NHS Foundation Trust of London, UK. We recorded demographics, treatments, cardiac function assessments and toxicities and used Fisher's exact test, Chi-squared and logistic regression. We included data on 931 patients in the analysis. Median age was 54 years (range 24–83) and Charlson comorbidity index 0 (0–6), with 195 patients (20.9%) aged ≥65 years. Two hundred and twenty-eight patients (24.5%) were smokers. Anthracyclines

were given in 608 patients (65.3%). Trastuzumab was given for a median number of 18 cycles. The HFA-ICOS cardiovascular risk was low in 401 patients (43.1%), medium in 454 (48.8%), high in 70 (7.5%) and very high in 6 (0.6%). Overall, 155 (16.6%) patients experienced cardiac toxicity, including: LVEF decline ≥ 10% in 141 patients (15.1%), LVEF decline below 50% in 55 patients (5.9%), CHF New York Heart Association (NYHA) class II in 42 patients (4.5%) and class III–IV in 5 patients (0.5%) and discontinuation due to cardiac reasons in 35 patients (3.8%). No deaths were observed. Cardiac toxicity rates increased with HFA-ICOS score (14.0% low, 16.7% medium, 30.3% high/very high; p = 0.002). In this study, cardiac toxicity was relatively common (16.6%), but symptomatic heart failure on trastuzumab was rare. The HFA-ICOS score identifies patients at high risk of cardiac toxicity. This study confirms that the rate of serious cardiac toxicity associated with trastuzumab in this population is low and not associated with age; on the other hand, the absolute rate of any cardiac adverse events remains clinically significant and dependent on baseline cardiovascular risk profile. These findings provide further rationale for the routine use of the HFA-ICOS tool to predict adverse cardiovascular outcomes in patients with HER2-positive breast cancer, which proves particularly useful in the older age group. Nonetheless, future research should involve the validation of the HFA-ICOS tool in a prospective cohort of patients and its integration with considerations on patient fitness and tumour risk of recurrence to enhance opportunities for treatment personalisation.

These studies highlight the importance of geriatric assessments to inform treatment decision-making more accurately for older adults with cancer and to drive oncologic and non-oncologic interventions addressing their individual needs in the context of their preferences and goals and the prediction of treatment benefits and potential complications. Consensus recommendations from the American Society of Clinical Oncology (ASCO), the International Society of Geriatric Oncology (SIOG) and the National Comprehensive Cancer Network (NCCN) are available to guide geriatric assessments and driven recommendations in this population.[7-9] Importantly, in order to positively impact on outcomes for older adults with cancer, geriatric assessments should trigger tailored interventions to support them and improve their health before,

during and after cancer treatment. Therefore, comprehensive geriatric assessment (CGA) is not only a diagnostic, but also a therapeutic process which is typically delivered in a multidisciplinary setting in order to fully address the complex care needs of this population.

These recommendations rely on increasing evidence showing significant benefits associated with integrating CGA in the routine care of this population. Recent trials documented that CGA is associated with reduced severe toxicities, reduced unplanned hospitalisations, increased rates of advance care planning and improved quality of life (QoL) for older individuals with cancer receiving systemic anticancer therapy.[10-12] While some initial evidence suggests that CGA is also cost-effective,[13] more research is needed on the economic evaluation of integrated oncogeriatric care models in order to support their sustainability in the long term.

The practicalities of implementing CGA in the management of older adults with cancer should take into account the type of care setting and the availability of specific professions including geriatricians, nurses, allied healthcare professionals and pharmacists.[14] Nevertheless, key geriatric domains that might impact on the delivery and outcomes of anticancer treatments and warranting routine assessment should always include comorbidities, polypharmacy, functional status and physical performance, cognition, mood, nutritional status and geriatric syndromes. Since CGA may be time-consuming, geriatric screening tools have been developed to predict its outcomes and identify older patients warranting a CGA versus those that can be safely (and effectively) managed similarly to their younger counterparts. The use of geriatric screening tools is also endorsed by consensus from the SIOG and the NCCN.[9, 15] Selecting the most adequate geriatric screening tool to implement in routine clinical practice should also take into considerations specific aspects inherent to the care setting and model.[14]

No evidence is available to inform the timing and the need to repeat geriatric assessments and more research is warranted on these aspects. Nonetheless, pragmatically these should be carried out before systemic therapy initiation or

surgery to allow more accurate and goal-concordant treatment decision-making and opportunities to optimise patients' health and support them during and after cancer interventions.

Figure 1 outlines the geriatric assessments currently in use as part of the ongoing implementation of the Senior Adult Oncology Programme, a consultative multidisciplinary oncogeriatric service for patients with cancer aged 70 years and older being considered for a new line of systemic anticancer therapy at The Royal Marsden NHS Foundation Trust, a large cancer centre in London, United Kingdom, without geriatrics input available. Patients being considered for systemic anticancer therapy (with curative or palliative intent) by medical oncology teams undergo geriatric screening with Senior Adult Oncology Programme Screening Questionnaire (SAOP3),[16, 17] a pragmatic tool developed at the H. Lee Moffitt Cancer Center of Tampa, Florida, United States (Table 1). SAOP3 is a patient-reported geriatric screening tool including questions on polypharmacy, functional status, falls, nutrition, speech and language domains, welfare, mood, social support, spiritual aspects, hearing, vision, QoL, self-perceived health and goals of care combined with Mini-Cog,[18] a validated brief cognitive screening tool that can be administered by any healthcare professional.

Patients with at least one need identified on SAOP3 are offered a referral to the Senior Adult Oncology Programme multidisciplinary clinic. This multidisciplinary team includes a dedicated Advanced Nurse Practitioner, Physiotherapist, Pharmacist, Occupational Therapist and Dietitian. The team carries out a targeted form of CGA based on SAOP3 geriatric screening outcomes (Figure 1).

CGA includes assessment of comorbidities (Charlson Comorbidity Index [CCI][19]), physical performance (Sit to stand test[20]) and sarcopenia (SARC-F[21]) for all patients referred to the team. All patients are also offered blood tests to investigate thyroid function, HbA1c, vitamin B12 and D, folate and haematinics. Based on SAOP3 geriatric screening outcomes, patients may also require assessment of functional status (activities of daily living [ADL]

Katz Index,[22] instrumental activities of daily living [IADL] Lawton scale,[23] Timed Get Up and Go [TUG] test,[24] TUG-Cog test[25] and Godin questionnaire[26]), incontinence (3 Incontinence Questionnaire [3IQ][27]), nutrition (Mini Nutritional Assessment [MNA][28]), polypharmacy (drug history, interaction check, patient-centred assessment and medication review based on STOPP/START criteria[29] and 2019 Beers American Geriatrics Society criteria[30]), sleep (Pittsburgh Sleep Quality Index [PSQI][31]), social support and activity (Medical Outcomes Study [MOS] Social Activity and Social Support questionnaires[32, 33]), mood (Psychological Health Questionnaire 9 [PHQ9][34]) and QoL (EQ-5D-5L). For patients being considered for cytotoxic therapy, the Cancer and Aging Research Group (CARG) chemotherapy toxicity prediction tool[35, 36] (or the CARG-Breast Cancer [CARG-BC] chemotherapy toxicity prediction tool[37] for those with early breast cancer [EBC]) is administered.

Subsequently, based on CGA outcomes, the multidisciplinary team issues patients personalised non-oncologic recommendations addressing individual geriatric impairments and feedbacks them to the referring medical oncology team (responsible for the systemic anticancer treatment) and to general practitioners. While these tools have been validated to inform the management of cancer in older adults, alternative geriatric assessments have also been validated and may be more easily to implement or more appropriate in different care settings and models.

Overall, the aims of these studies have been met. These findings expand the evidence base on the management of cancer and common malignancies in older adults and provide additional insight on benefits and impacts on QoL and more opportunities to inform treatment personalisation and discussions with patients.

REFERENCES

1. Ring, A., et al., Bridging The Age Gap: observational cohort study of effects of chemotherapy and trastuzumab on recurrence, survival and quality of life in older women with early breast cancer. Br J Cancer, 2021. 125(2): p. 209-219.
2. Battisti, N.M.L., et al., Systemic therapy for older patients with early breast cancer. Cancer Treat Rev, 2021. 100: p. 102292.
3. Battisti, N.M.L., et al., Bridging the Age Gap in breast cancer: Impact of chemotherapy on quality of life in older women with early breast cancer. Eur J Cancer, 2021. 144: p. 269-280.
4. Battisti, N.M.L., et al., Observational cohort study in older women with early breast cancer: Use of radiation therapy and impact on health-related quality of life and mortality. Radiother Oncol, 2021. 161: p. 166-176.
5. Battisti, N.M.L., et al., Prevalence of Cardiovascular Disease in Patients With Potentially Curable Malignancies: A National Registry Dataset Analysis. JACC CardioOncol, 2022. 4(2): p. 238-253.
6. Battisti, N.M.L., et al., Incidence of cardiotoxicity and validation of the Heart Failure Association-International Cardio-Oncology Society risk stratification tool in patients treated with trastuzumab for HER2-positive early breast cancer. Breast Cancer Res Treat, 2021. 188(1): p. 149-163.
7. Mohile, S.G., et al., Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Chemotherapy: ASCO Guideline for Geriatric Oncology. J Clin Oncol, 2018. 36(22): p. 2326-2347.
8. Wildiers, H., et al., International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. J Clin Oncol, 2014. 32(24): p. 2595-603.
9. Older Adult Oncology (Version 2.2022). 2022.
10. Mohile, S.G., et al., Evaluation of geriatric assessment and management on the toxic effects of cancer treatment (GAP70+): a cluster-randomised study. Lancet, 2021.
11. Soo, W.-K., et al., Integrated geriatric assessment and treatment (INTEGERATE) in older people with cancer planned for systemic anticancer therapy. Journal of Clinical Oncology, 2020. 38(15_suppl): p. 12011-12011.
12. Li, D., et al., Geriatric Assessment-Driven Intervention (GAIN) on Chemotherapy-Related Toxic Effects in Older Adults With Cancer: A Randomized Clinical Trial. JAMA Oncol, 2021.

13. Alibhai, S.M.H., et al., Economic Evaluation of a Geriatric Oncology Clinic. Cancers (Basel), 2022. 14(3).
14. Chapman, A.E., et al., Models of Care in Geriatric Oncology. J Clin Oncol, 2021. 39(19): p. 2195-2204.
15. Decoster, L., et al., Screening tools for multidimensional health problems warranting a geriatric assessment in older cancer patients: an update on SIOG recommendations†. Ann Oncol, 2015. 26(2): p. 288-300.
16. Senior Adult Oncology Program Tools: SAOP3 screening questionnaire. [cited 2022 21/07/2022]; Available from: https://moffitt.org/media/10947/senior-adult-supplement-screening-questionnaire-saop3.pdf.
17. Extermann, M., Evaluation of the Senior Cancer Patient: Comprehensive Geriatric Assessment and Screening Tools for the Elderly. Handbook of Cancer in the Senior Patient, ed. D. Schrijvers, et al. 2010, New York: Informa Healthcare.
18. Ketelaars, L., et al., Use of the Freund clock drawing test within the Mini-Cog as a screening tool for cognitive impairment in elderly patients with or without cancer. J Geriatr Oncol, 2013. 4(2): p. 174-82.
19. Charlson, M.E., et al., A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis, 1987. 40(5): p. 373-83.
20. Bohannon, R.W. and R. Crouch, 1-Minute Sit-to-Stand Test: SYSTEMATIC REVIEW OF PROCEDURES, PERFORMANCE, AND CLINIMETRIC PROPERTIES. Journal of Cardiopulmonary Rehabilitation and Prevention, 2019. 39(1): p. 2-8.
21. Malmstrom, T.K. and J.E. Morley, SARC-F: a simple questionnaire to rapidly diagnose sarcopenia. J Am Med Dir Assoc, 2013. 14(8): p. 531-2.
22. Katz, S., et al., Progress in development of the index of ADL. Gerontologist, 1970. 10(1): p. 20-30.
23. Lawton, M.P., Scales to measure competence in everyday activities. Psychopharmacol Bull, 1988. 24(4): p. 609-14.
24. Shumway-Cook, A., S. Brauer, and M. Woollacott, Predicting the probability for falls in community-dwelling older adults using the Timed Up & Go Test. Phys Ther, 2000. 80(9): p. 896-903.
25. Cardon-Verbecq, C., et al., Predicting falls with the cognitive timed up-and-go dual task in frail older patients. Annals of Physical and Rehabilitation Medicine, 2017. 60(2): p. 83-86.

26. Amireault, S., et al., The use of the Godin-Shephard Leisure-Time Physical Activity Questionnaire in oncology research: a systematic review. BMC Med Res Methodol, 2015. 15: p. 60.
27. Brown, J.S., et al., The sensitivity and specificity of a simple test to distinguish between urge and stress urinary incontinence. Ann Intern Med, 2006. 144(10): p. 715-23.
28. Guigoz, Y., The Mini Nutritional Assessment (MNA) review of the literature--What does it tell us? J Nutr Health Aging, 2006. 10(6): p. 466-85; discussion 485-7.
29. O'Mahony, D., et al., STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age Ageing, 2015. 44(2): p. 213-8.
30. American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc, 2019. 67(4): p. 674-694.
31. Buysse, D.J., et al., The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res, 1989. 28(2): p. 193-213.
32. Sherbourne, C.D. and A.L. Stewart, The MOS social support survey. Soc Sci Med, 1991. 32(6): p. 705-14.
33. Hays, R.D., C.D. Sherbourne, and R.M. Mazel, User's manual for the Medical Outcomes Study (MOS) core measures of health-related quality of life. 1995: Rand Corporation Santa Monica.
34. Kroenke, K., R.L. Spitzer, and J.B. Williams, The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med, 2001. 16(9): p. 606-13.
35. Hurria, A., et al., Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. J Clin Oncol, 2011. 29(25): p. 3457-65.
36. Hurria, A., et al., Validation of a Prediction Tool for Chemotherapy Toxicity in Older Adults With Cancer. J Clin Oncol, 2016. 34(20): p. 2366-71.
37. Magnuson, A., et al., Development and Validation of a Risk Tool for Predicting Severe Toxicity in Older Adults Receiving Chemotherapy for Early-Stage Breast Cancer. J Clin Oncol, 2021. 39(6): p. 608-618.

TABLES

Table 1 – Senior Adult Oncology Programme Screening Questionnaire (SAOP3).

Questions		Please check one for each line		
Can we access your Summary Care Record (General Practitioner records)?		□ Yes	□ No	
Are you on 5 or more regular medications (prescribed by GP or other hospitals)?		□ Yes	□ No	
1	**Activities of Daily Living/Instrumental Activities of Daily Living (ADL/IADL)**			
A	Do you use a stick or a walking frame?	□ Yes	□ Occasionally	□ No
B	Have you noticed any changes to your walking recently (such as being able to walk less far or getting tired more quickly, feeling less steady or needing more support)?	□ Yes	□ Occasionally	□ No
C	Do you need help to get in/out of bed, on/off the toilet, on/off the chair, in/out the shower or bath?	□ Yes	□ Occasionally	□ No
D	Have you lost your balance, tripped or fallen in the past year?	□ Yes	□ No	
E	Do you find the stairs difficult to use?	□ Yes	□ No	
F	Have you noticed any changes to your fitness, stamina or activity levels recently (such as being able to do less around the house, going out and about less or finding normal activities more effortful)?	□ Yes	□ No	
G	Is your ability to exercise as you would like to affected by your cancer or your cancer treatment? Would you like to speak to the physiotherapist about this?	□ Yes but I do not need to speak to the physiotherapist	□ Yes and I would like to speak to the physiotherapist	□ No

H	Do you have problems holding your urines or stools (*more than small leaks controlled with a pad*)?	□ Yes	□ Occasionally	□ No
I	Can you shower or bathe yourself completely?	□ Yes	□ Yes, but with help	□ No
J	Can you dress yourself completely?	□ Yes	□ Yes, but with help	□ No
K	Can you feed yourself?	□ Yes	□ Yes, but with help	□ No
L	Are you able to prepare your own meals?	□ Yes	□ Yes, but with help	□ No
M	Are you able to drive or use public transport?	□ Yes	□ Yes, but with help	□ No
N	Are you able to go shopping?	□ Yes	□ Yes, but with help	□ No
O	Can you take care of your finances?	□ Yes	□ Yes, but with help	□ No
P	Do you remember to take your medicines?	□ Yes	□ Yes, but with help	□ No
Q	Do you get your medications delivered at home?	□ Yes	□ No (I collect them)	
R	Can you use a telephone?	□ Yes	□ Yes, but with help	□ No
2	**Have you lost 5 or more pounds/2.5 Kgs in the past 6 months <u>without dieting</u>?**		□ Yes	□ No
3	**Has your appetite decreased in the last 3 months?**		□ Yes	□ No
4	**Has there been a change in the types of foods you are able to eat?**		□ Yes	□ No
5	**Since your cancer diagnosis have you noticed any of the following:**			
A	Difficulty swallowing?		□ Yes	□ No
B	Difficulty chewing?		□ Yes	□ No

C	Being more aware of your swallowing?	□ Yes	□ No
D	Changes to how your voice sounds?	□ Yes	□ No
6	**Are you in receipt of any Allowances, Benefits or Pension credit?**	□ Yes	□ No
7	**Do you feel you are sleeping well?**	□ Yes	□ No
8	**Are you in a carer role for anyone at present?**	□ Yes	□ No
9	**If it was necessary, is there someone who could help take care of you?**	□ Yes	□ No
10	**Do you feel sad more days than not?**	□ Yes	□ No
11	**Have you lost interest in things you used to enjoy (hobbies, food, sex, being with friends/family)?**	□ Yes	□ No

12	**On a scale of 1 to 10, rate your present quality of life (10 is the best life, 1 is the worst)**	□ 1	□ 2	□ 3	□ 4	□ 5	□ 6	□ 7	□ 8	□ 9	□ 10
13	**On a scale of 1 to 10, rate your present overall health (10 is the best health, 1 is the worst)**	□ 1	□ 2	□ 3	□ 4	□ 5	□ 6	□ 7	□ 8	□ 9	□ 10
14	**On a scale of 1 to 10, have you had concerns about spirituality or faith? (10 is high level of concern, 1 is a low level of concern)**	□ 1	□ 2	□ 3	□ 4	□ 5	□ 6	□ 7	□ 8	□ 9	□ 10
15	**On a scale of 1 to 10, have you had concerns about your meaning or purpose of life? (10 is high level of concern, 1 is a low level of concern)**	□ 1	□ 2	□ 3	□ 4	□ 5	□ 6	□ 7	□ 8	□ 9	□ 10

16	**On a scale of 1 to 10, have you had concerns about feeling at odds with your culture, beliefs, or values? (10 is high level of concern, 1 is a low level of concern)**	□ 1	□ 2	□ 3	□ 4	□ 5	□ 6	□ 7	□ 8	□ 9	□ 10

HEARING AND VISION				
How do you rate your hearing?	□ Excellent	□ Good	□ Fair	□ Poor
Do you use hearing aids?	□ Yes		□ No	
If so, do they help in improving your hearing?	□ A great deal	□ Somewhat	□ Not at all	
How do you rate your eyesight?	□ Excellent	□ Good	□ Fair	□ Poor
Do you use eyeglasses?	□ Yes		□ No	
If so, do they help in improving your eyesight?	□ A great deal	□ Somewhat	□ Not at all	

WHAT MATTERS TO YOU?

The Mini-Cog Evaluation™

Step 1: Three Word Registration

Look directly at the patient and say, "Please listen carefully. I am going to say three words that I want you to repeat back to me now and try to remember. Please say them for me now." If the person cannot repeat them after 3 times, move on to Step 2.

Version 1	Version 2	Version 3	Version 4	Version 5
Banana	Leader	Village	River	Captain
Sunrise	Season	Kitchen	Nation	Garden
Chair	Able	Baby	Finger	Picture

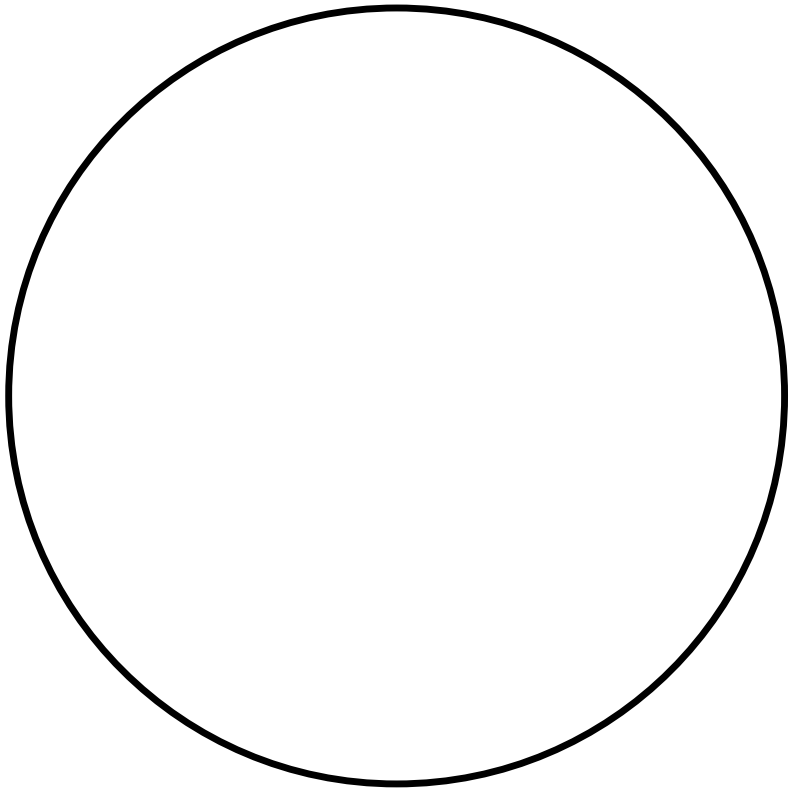
Step 2: Clock drawing

Say "Next I want you to draw a clock for me. First put the numbers where they go." When that is completed "Now set the hands to 10 past 11."

Step 3: Three Word Recall

Ask the person to recall the three words you stated in Step 1. Say "What were the three words I asked you to remember?"

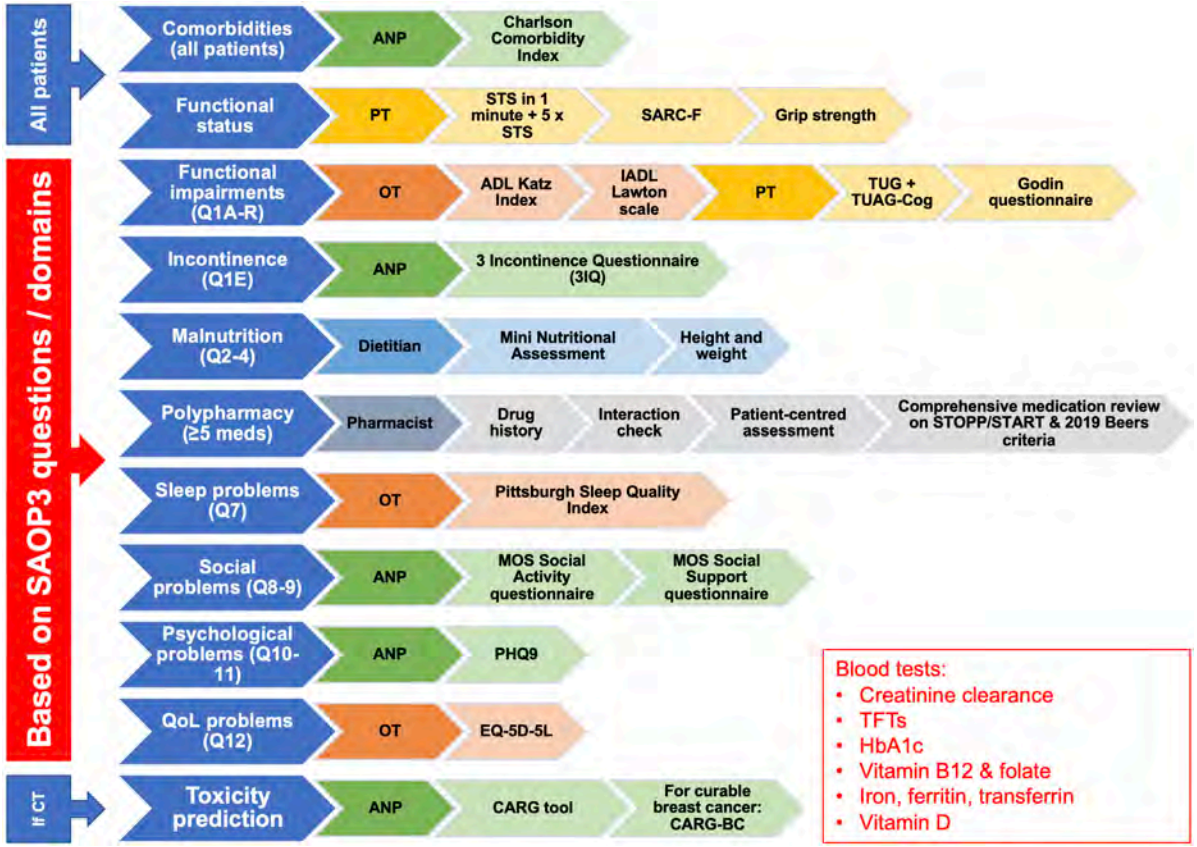
Patient's answers:

The Mini-Cog Evaluation™		
Mini-Cog™ © S Borson. All rights reserved. Reprinted with permission of the author solely for clinical and educational purposes. May not be modified or used for commercial marketing or research purposes without permission of the author (soob@uw.edu). V. 19.01.16		
		
MINI COG SCORING		
Number of correct items recalled: _____	**3 correct: Normal** **1-2 correct: see clock results** **0 correct: Abnormal**	
If 1-2, is clock drawing abnormal?	□ **Yes (Cognitive impairment)** □ **No (Normal)**	
SCORING PAGE		
1A-1H	**ADL/IADL mobility items:** If at least two **YES** responses, then refer to *If answer is **YES/OCCASIONALLY** to **1E**, administer the modified 3 Incontinence Questionnaire (3IQ)*	□ Physiotherapy □ Occupational therapy □ Welfare Rights Advisor □ Patient declined
1I-1R	**ADL/IADL items:**	□ Physiotherapy

	if more than one is **NO / OCCASIONALLY / YES, BUT WITH HELP** responses, then refer to	□ Occupational therapy □ *if 1F-1M involved*: Welfare Rights Advisor □ Patient declined
2-4	**Nutrition items:** if at least two **YES** responses, then refer to *Consider referral to Dietetics also if concerns regarding weight gain*	□ Dietetics □ Patient declined
5A-5D	If **YES**, refer to	□ Speech and language therapy □ Patient declined
6	If **YES**, refer to *Consider referrals also for patients answering **NO** if they need specific input*	□ Community Social worker □ Welfare Rights Advisor □ Patient declined
7-11	**Psychosocial items:** If response is **NO** to 7 or 9 and/or **YES** to 8, 10 or 11, then refer to *If response is **NO** to **7**, administer Pittsburg Sleep Quality Index (PSQI)*	□ Adult Psychological Support Service □ Occupational therapy □ Patient declined
12-13	**Quality of life and self-rated health items:** If score less than 8, then refer to	□ Adult Psychological Support Service □ SAOP MDT member: _____ □ Patient declined
14-16	**Spiritual items** **Discuss responses and make aware of support** If score 8 or more, then refer to	□ Pastoral care □ SAOP MDT member: _____ □ Patient declined
Mini-Cog: If positive for **cognitive impairment**, then refer to		□ Occupational therapy □ Speech and language therapy □ Patient declined
Number of **medications** 5 or greater, then refer to		□ Pharmacy □ Patient declined

FIGURES

Figure 1 – Example of comprehensive geriatric assessment in use as part of the Senior Adult Oncology Programme implementation project at The Royal Marsden NHS Foundation Trust.



Abbreviations: SAOP3: Senior Adult Oncology Programme Screening Questionnaire; CT: chemotherapy; ANP: advanced nurse practitioner; PT: physiotherapist; OT: occupational therapist; STS: sit to stand test; ADL: activities of daily living; IADL: instrumental activitis of daily living; MOS: Medical Outcomes Study; PHQ9: Psychological Health Questionnaire 9; EQ-5D-5L: 5-level Euroqol-5D; CARG: Cancer and Aging Research Group; CARG-BC: Cancer and Aging Research Group-Breast Cancer; TFTs: thyroid function tests.

PUBLICATIONS AND PRESENTATIONS

ORIGINAL RESEARCH RELATED TO THIS THESIS: PUBLICATIONS

Battisti NML, Reed MWR, Herbert E, Morgan JL, Collins KA, Ward SE, Holmes GR, Bradburn M, Walters SJ, Burton M, Lifford K, Edwards A, Robinson TG, Martin C, Chater T, Pemberton KJ, Shrestha A, Brennan A, Cheung KL, Todd A, Audisio RA, Wright J, Simcock R, Green T, Revell D, Gath J, Horgan K, Holcombe C, Winter MC, Naik J, Parmeshwar R, Gosney MA, Hatton MQ, Thompson AM, Wyld L, Ring A; Age Gap TMG. Bridging the Age Gap in breast cancer: Impact of chemotherapy on quality of life in older women with early breast cancer. Eur J Cancer. 2021 Feb;144:269-280. doi: 10.1016/j.ejca.2020.11.022. Epub 2020 Dec 26. PMID: 33373871; PMCID: PMC7896040.

Battisti NML, Andres MS, Lee KA, Ramalingam S, Nash T, Mappouridou S, Senthivel N, Asavisanu K, Obeid M, Tripodaki ES, Angelis V, Fleming E, Goode EF, John S, Rosen SD, Allen M, Stanway S, Lyon AR, Ring A. Incidence of cardiotoxicity and validation of the Heart Failure Association-International Cardio-Oncology Society risk stratification tool in patients treated with trastuzumab for HER2-positive early breast cancer. Breast Cancer Res Treat. 2021 Jul;188(1):149-163. doi: 10.1007/s10549-021-06192-w. Epub 2021 Apr 5. PMID: 33818652.

Ring A*, **Battisti NML***, Reed MWR, Herbert E, Morgan JL, Bradburn M, Walters SJ, Collins KA, Ward SE, Holmes GR, Burton M, Lifford K, Edwards A, Robinson TG, Martin C, Chater T, Pemberton KJ, Brennan A, Cheung KL, Todd A, Audisio RA, Wright J, Simcock R, Green T, Revell D, Gath J, Horgan K, Holcombe C, Winter MC, Naik J, Parmeshwar R, Gosney MA, Hatton MQ, Thompson AM, Wyld L; Age Gap TMG. Bridging The Age Gap: observational cohort study of effects of chemotherapy and trastuzumab on recurrence, survival and quality of life in older women with early breast cancer. Br J

Cancer. 2021 Jul;125(2):209-219. doi: 10.1038/s41416-021-01388-9. Epub 2021 May 10. PMID: 33972747; PMCID: PMC8292504.
* Contributed equally

Battisti NML, Hatton MQ, Reed MWR, Herbert E, Morgan JL, Bradburn M, Simcock R, Walters SJ, Collins KA, Ward SE, Holmes GR, Burton M, Lifford KJ, Edwards A, Robinson TG, Martin C, Chater T, Pemberton KJ, Brennan A, Leung Cheung K, Todd A, Audisio RA, Wright J, Green T, Revell D, Gath J, Horgan K, Holcombe C, Winter MC, Naik J, Parmeshwar R, Gosney MA, Thompson AM, Wyld L, Ring A; Bridging the Age Gap TMG. Observational cohort study in older women with early breast cancer: Use of radiation therapy and impact on health-related quality of life and mortality. Radiother Oncol. 2021 Aug;161:166-176. doi: 10.1016/j.radonc.2021.06.021. Epub 2021 Jun 17. PMID: 34146616.

Battisti NML, Welch CA, Sweeting M, de Belder M, Deanfield J, Weston C, Peake MD, Adlam D, Ring A. Prevalence of Cardiovascular Disease in Patients With Potentially Curable Malignancies: A National Registry Dataset Analysis. JACC CardioOncol. 2022 Jun 21;4(2):238-253. doi: 10.1016/j.jaccao.2022.03.004. PMID: 35818547; PMCID: PMC9270631.

ORIGINAL RESEARCH RELATED TO THIS THESIS: POSTERS AND PRESENTATIONS

Battisti NML, Herbert E, Bradburn M, Morgan J, Wyld L, Ring A. Impact of chemotherapy for early-stage breast cancer on quality of life in older adults: Results from 2811 women enrolled in the Bridging the Age Gap study. European Society for Medical Oncology 2020 Congress. Online. 19th-21st September 2020.

Battisti NML, Lee KA, Nash T, Mappouridou S, Senthivel N, Asavisanu K, Obeid M, Tripodaki E, Angelis V, Fleming E, Goode EF, John S. Andres MS, Allen M, Lyon A, Ring A. Rates of cardiac adverse events in older versus younger adults receiving trastuzumab for HER2-positive early breast cancer: Results from 931 patients treated at The Royal Marsden. European Society for Medical Oncology 2020 Congress. Online. 19th-21st September 2020.

Battisti NML, Ring A, Bradburn M, Wyld L on behalf of the Age Gap trial steering group
Use of systemic therapy for early-stage breast cancer in older adults: results from the Bridging the Age Gap study. San Antonio 2019 Breast Cancer Symposium. San Antonio, TX, USA. 10th-14th December 2019.

Battisti NML, Welch C, DeBelder M, Deanfield J, Weston C, Peake MD, Sweeting M, Adlam D, Ring A. Prevalence of cardiovascular disease in patients diagnosed with six common curable malignancies: A Virtual Cardio-Oncology Research Institute (VICORI) national registry dataset analysis. European Society for Medical Oncology 2021 Congress. Online. 16th-21st September 2021.

Battisti NML, Welch C, DeBelder M, Deanfield J, Weston C, Peake MD, Sweeting M, Adlam D, Ring A. Cardiovascular disease prevalence in patients diagnosed with six curable tumours: a VICORI national registry analysis. European Network of Cancer Registries 2021 Scientific Meeting. Online. 16th-18th November 2021.

EDITORIALS/REVIEWS/GUIDELINES ON TOPICS RELATED TO THIS THESIS

Guidelines

Biganzoli L, **Battisti NML**, Wildiers H, McCartney A, Colloca G, Kunkler IH, Cardoso MJ, Cheung KL, de Glas NA, Trimboli RM, Korc-Grodzicki B, Soto-Perez-de-Celis E, Ponti A, Tsang J, Marotti L, Benn K, Aapro MS, Brain EGC. Updated recommendations regarding the management of older patients with breast cancer: a joint paper from the European Society of Breast Cancer Specialists (EUSOMA) and the International Society of Geriatric Oncology (SIOG). Lancet Oncol. 2021 Jul;22(7):e327-e340. doi: 10.1016/S1470-2045(20)30741-5. Epub 2021 May 14. PMID: 34000244.

Reviews

Battisti NML, Decoster L, Williams GR, Kanesvaran R, Wildiers H, Ring A. Targeted Therapies in Older Adults With Solid Tumors. J Clin Oncol. 2021 Jul 1;39(19):2128-2137. doi: 10.1200/JCO.21.00132. Epub 2021 May 27. PMID: 34043448; PMCID: PMC8260907.

Battisti NML, Biganzoli L. Systemic therapy for early breast cancer in older adults: current status and prospects. Curr Opin Oncol. 2021 Nov 1;33(6):574-583. doi: 10.1097/CCO.0000000000000768. PMID: 34183493.

Battisti NML, Joshi K, Nasser MS, Ring A. Systemic therapy for older patients with early breast cancer. Cancer Treat Rev. 2021 Nov;100:102292. doi: 10.1016/j.ctrv.2021.102292. Epub 2021 Sep 11. PMID: 34536728.

Battisti NML, Liposits G, De Glas NA, Gomes F, Baldini C, Mohile S. Systemic Therapy of Common Tumours in Older Patients: Challenges and Opportunities. A Young International Society of Geriatric Oncology Review Paper. Curr Oncol Rep. 2020 Jul 28;22(10):98. doi: 10.1007/s11912-020-00958-z. PMID: 32725503.

Editorials

Battisti NML, Simcock R. Hindsight and Foresight: How Comorbidity Assessment Helps Us in Cancer Care. Clin Oncol (R Coll Radiol). 2022 Jul;34(7):480-482. doi: 10.1016/j.clon.2022.03.017. Epub 2022 Apr 19. PMID: 35450771.

Milton M, Jethwa J, **Battisti NML**. Elucidating the effect of geriatric parameters on COVID-19 outcomes for older adults with cancer. Lancet Healthy Longev. 2022 Mar;3(3):e122-e123. doi: 10.1016/S2666-7568(22)00026-5. Epub 2022 Feb 14. PMID: 35187515; PMCID: PMC8843064.

Battisti NML, McCartney A, Biganzoli L. The Conundrum of the Association of Chemotherapy With Survival Outcomes Among Elderly Patients With Curable Luminal Breast Cancer. JAMA Oncol. 2020 Oct 1;6(10):1535-1537. doi: 10.1001/jamaoncol.2020.2194. PMID: 32672797.

Biganzoli L, McCartney A, **Battisti NML**. Expanding the Scope of Geriatric Assessment for the Management of Cancer in Older Adults. JAMA Oncol. 2020 Feb 1;6(2):204-205. doi: 10.1001/jamaoncol.2019.4708. PMID: 31697305.

PRESENTATIONS DELIVERED ON TOPICS RELATED TO THIS THESIS

Geriatric oncology: Precision oncology for older adults with cancer. The Royal Marsden Senior Adult Oncology Study Day. 20th June 2022. The National Heart & Lung Institute Guy Scadding Building, London, UK

How can we use social media to address health inequities for older patients with advanced breast cancer? Pfizer event on "Health inequities for elderly patients with metastatic breast cancer". 11th May 2022. Online meeting

Geriatric oncology: Moving the needle towards an evidence-based precision approach for older adults with cancer. Chinese Conference on Oncology. 6th May 2022. Online meeting

Trends in the management of multimorbidities in Europe. Astellas event: "Individual, sustainable, holistic: improving the support for people living with multimorbidities". 30th March 2022. Online meeting

Adapting care for older cancer patients during the COVID-19 pandemic: Recommendations from the International Society of Geriatric Oncology COVID-19 Working Group. Podcast for the Journal of Geriatric Oncology. 28th March 2022. (Available here: https://www.geriatriconcology.net/content/podcast)

Geriatric oncology: moving the needle towards evidence-based precision oncology for older adults with cancer.
British Geriatrics Society OncoGeriatrics Meeting 2022. 22nd March 2022. Online meeting.

Breast cancer in older adults. Biomedical Research Centre at The Royal Marsden and The ICR public event: "What does the future hold for breast cancer?". 10th March 2022. Online meeting. (Recording available here:

https://www.cancerbrc.org/what-does-the-future-hold-for-breast-cancer-event)

Panel discussion on cancer and ageing: how to improve quality of life among the older population. Union for International Cancer Control World Cancer Day. 4th February 2022. Online meeting. (Recording available here: https://www.worldcancerday.org/live)

Addressing treatment challenges for ER+ HER2- metastatic breast cancer specific patient populations. The UK Interdisciplinary Breast Cancer Symposium. 25th January 2022. Online meeting

Cancer care gaps for older patients with cancer: implications for research and innovation. "The role of research & innovation in the enhancement of older cancer patients care & treatment options, accessibility and quality of life during survivorship" - LifeChamps European Parliament event. 9th December 2021. Online meeting

Geriatric oncology: evidence-based precision oncology for older adults with cancer. Anticancer Fund meeting. 6th December 2021. Online meeting

Medical oncology updates. Italian Group of Geriatric Oncology (GIOGER) 2021 online conference. 3rd-4th December 2021. Online meeting

Oncogeriatrics: moving the needle towards evidence-based precision oncology for older adults with cancer. Association of Cancer Physicians trainees weekend. 16th-17th October 2021. Bristol, UK

Cancer in older adults: moving the needle towards evidence-based personalised oncology. RM Partners future focus webinar programme. 13th October 2021. Online meeting

Moving the needle towards precision oncology for older adults with breast cancer: when we should treat them differently and when we should not. Breast

Cancer Expert Series: Breast Cancer Management in Elderly Patients. 13th October 2021. Online meeting

Moving the needle towards precision oncology for older adults with cancer at global level. International Cancer Control Partnership meeting. 12th October 2021. Online meeting

Geriatric assessment for breast cancer management. The 14th Annual Royal Marsden Breast Cancer Virtual Meeting. 8th October 2021. Online meeting

Frailty and Treatment Outcome in Advanced Gastro-Oesophageal Cancer: An Exploratory Analysis of the GO2 Trial. Cancer and Aging Research Group meeting. 5th October 2021. Online meeting

Side effects in older patients with breast cancer: differences in incidence and management. European School of Oncology course “Breast Cancer in the Elderly”. 1st-2nd October 2021. Online meeting

Systemic anticancer therapy: assessing older patients. Royal Marsden course on “Principles of systemic anticancer therapy”. October 2021. Online meeting

Ageing and inequalities in cancer care: opportunities to foster precision oncology for older adults with cancer. American Society of Clinical Oncology/European Cancer Organisation joint virtual meeting on inequalities in cancer care. 13th October 2021. Online meeting

Adapting the care for older patients with cancer during COVID-19. SIOG/Turkish Geriatric Hematology Association joint workshop. 24th September 2021. Online meeting

Cancer in older adults: paving the way for personalised oncology through multidisciplinarity. “Oncology-focused Living Labs: a new challenge to be addressed” meeting. 8th September 2021. Online meeting

Cancer in older adults: moving the needle toward evidence-based personalised oncology. Royal Marsden Drink and Think SACT meeting. 12th August 2021. Online meeting

Geriatric oncology: a field coming of age. UICC Roundtable on cancer in the decade of healthy ageing. 9th June 2021. Online meeting

Geriatric oncology: personalising cancer care for older adults. NHS Professionals - Doctors Direct Webinar. 26th March 2021. Online meeting

Global geriatric oncology: the European perspective. Cancer and Aging Research Group meeting. 9th March 2021. Online meeting

Geriatric oncology: an overview. LifeChamps 2nd Plenary Project Meeting. 3rd March 2021. Online meeting

Challenges and opportunities to improve the care of older patients with cancer in Europe. Special Committee on Beating Cancer (BECA) public hearing on "Beating cancer - empowering patients and their caregivers". 11th January 2021. Online meeting (recording and slides available here: https://www.europarl.europa.eu/committees/en/public-hearing-beating-cancer-empowering/product-details/20210115CAN59346)

2020 Geriatric Oncology updates. OncoAlert Colloquium. December 2020. Online meeting

Breast cancer in older adults. Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán Geriatric Oncology module. 23rd November 2020. Online meeting

Learnings from a solid tumour expert and the involvement of the multidisciplinary team in oncogeriatrics. The Royal College of Pathologists. Empowering change in haematological oncology. Optimising outcome through best practice sharing. 4th November 2020. Online meeting

Adapting care for older cancer patients during COVID-19. Union for International Cancer Control Special Focus Dialogue - Caring for older cancer patients during COVID-19. 29th June 2020. Online meeting (recording available here: https://www.uicc.org/events/special-focus-dialogue-caring-older-cancer-patients-during-covid-19)

Optimization of chemotherapy for older breast cancer patients. International Society of Geriatric Oncology 2019 Annual Conference. 14th-16th November 2019. Geneva, Switzerland

Young SIOG Geriatric Assessment workshop: chemotherapy toxicity calculators.
International Society of Geriatric Oncology 2019 Annual Conference. 14th-16th November 2019. Geneva, Switzerland

Indication, timing, and type of chemotherapy in older adults with triple-negative breast cancer. International Society of Geriatric Oncology 2019 Annual Conference. 14th-16th November 2019. Geneva, Switzerland

Impact of the external validity of the National Comprehensive Cancer Network and European Society for Medical Oncology guidelines for NSCLC on treatment outcomes in a population of patients aged 80 years and older. International Society of Geriatric Oncology 2019 Annual Conference. 14th-16th November 2019. Geneva, Switzerland

Is age a barrier to systemic anti-cancer therapy? A national registry study on behalf of the ABC steering group. National Cancer Research Institute 2019 Conference. 3rd-5th November 2019. Glasgow, Scotland, UK

Good clinical practice in geriatric oncology. Innovators in breast cancer: the value of academic research. 8th-9th November 2019. Turin, Italy

APPENDIX

SUPPLEMENTARY TABLES

Chapter 2

Supplementary table 2.1 – List of participant sites.

Site number	Site name
1	Sheffield
2	Barnsley
3	Doncaster
4	Milton Keynes
5	Scunthorpe and Grimsby
6	Leicester
7	Derby
8	East Lancashire
9	Harrogate
10	St Helens and Knowsley
11	York
12	Liverpool
13	Airedale
14	Leeds
15	Bradford
16	Cardiff
17	Aneurin Bevan Health Board
18	Royal Lancaster
19	Coventry
20	Grantham
21	Lincoln
22	Pilgrim
23	Hull
24	Nottingham
25	Southport
26	Leighton
27	Royal Marsden
28	Cheltenham General
29	Guys and St Thomas
30	Dorset County
31	Mid Essex
32	Mid Yorkshire
33	Bristol

Site number	Site name
34	Chesterfield
35	Rotherham
36	Darent Valley
37	Kingston
38	Colchester
39	Yeovil
40	Croydon
41	North Tees
42	South Tees
43	Luton and Dunstable
44	Weston General
45	Tameside
46	Macclesfield
47	Wrightington, Wigan and Leigh
48	Birmingham
49	Kings Mill
50	Wythenshawe
51	Aintree
52	Brighton
53	St Margaret's
54	St Marys
55	Oxford
56	Frimley and Wexham

Supplementary table 2.2 – Summary of the quality of life instruments used in the study and their meaning.

Instrument	Question number	Domain number	Domains	No. items	Score positive or negative
Generic cancer EORTC QLQ C30	30	2 visual analogue scales,	Health status	1	High score means higher level of function
			Quality of life	1	
		5 multi-item functional scales	Physical	5	
			Role	2	
			Emotional	4	
			Cognitive	2	
			Social	2	
		9 symptom scales	Fatigue	3	Higher score means higher symptom severity
			Nausea and vomiting	2	
			Pain	2	
			Dyspnoea	1	
			Insomnia	1	
			Appetite loss	1	
			Constipation	1	
			Diarrhoea	1	
			Financial difficulties	1	
Breast cancer-specific EORTC QLQ BR23	23	5 multi-item scales	Body image	4	High score means higher level of function
			Sexual function	2	
			Sexual enjoyment	1	
			Future perspectives	1	
		4 single item symptom scales	Systemic therapy side effects	7	Higher score means higher symptom severity
			Breast symptoms	4	

			Arm symptoms	3	
			Upset by hair loss	1	
Older person-specific EORTC ELD15	14	2 functional scales	Family support	2	High score means higher level of function
			Maintaining autonomy and purpose	2	
		3 symptom scales	Mobility	3	Higher score means higher symptom severity
			Future worries	5	
			Burden of illness	2	
Generic EQ5D-5L	5 plus a visual analogue scale	3 functional scales	Mobility	5	All scored from 1-5 with score of 1 being the best outcome, 5 the worst
			Self-care	5	
			Usual activities	5	
		2 symptom scales	Pain/discomfort	5	
			Anxiety/depression	5	
		1 visual analogue scale	How good/bad is health today	1	Scored 1-100 with 100 meaning best health possible

Abbreviations: EORTC: European Organisation for Research and Treatment of Cancer; QLQ: quality of life questionnaire.

Supplementary table 2.3 – Baseline tumour, patient and treatment characteristics by age.

Variables	Categories	Age group (years)				
		70-74	75-79	80-84	>=85	All
		N = 1,173	N = 899	N = 506	N = 233	N = 2,811
Participation level	Full	926 (78.9%)	674 (75.0%)	368 (72.7%)	143 (61.4%)	2,111 (75.1%)
	Partial	225 (19.2%)	209 (23.2%)	123 (24.3%)	64 (27.5%)	621 (22.1%)
	Consultee	22 (1.9%)	16 (1.8%)	15 (3.0%)	26 (11.2%)	79 (2.8%)
Main side	Right	535 (45.6%)	418 (46.5%)	247 (48.8%)	105 (45.1%)	1,305 (46.4%)
	Left	638 (54.4%)	481 (53.5%)	259 (51.2%)	128 (54.9%)	1,506 (53.6%)
Tumour size (mm)	≤ 20	649 (55.3%)	371 (41.3%)	184 (36.4%)	75 (32.2%)	1,279 (45.5%)
	21-50	439 (37.4%)	439 (48.8%)	271 (53.6%)	136 (58.4%)	1,285 (45.7%)
	> 50	66 (5.6%)	66 (7.3%)	40 (7.9%)	16 (6.9%)	188 (6.7%)
	Unknown	19 (1.6%)	23 (2.6%)	11 (2.2%)	6 (2.6%)	59 (2.1%)
Tumour size (mm)	n	1,154	876	495	227	2,752
	Mean (SD)	23.1 (17.7)	26.5 (16.2)	27.6 (15.4)	28.8 (15.7)	25.4 (16.8)
	Median (IQR)	19.0 (12.0, 28.0)	22.0 (16.0, 32.0)	25.0 (17.0, 35.0)	25.0 (19.0, 35.0)	21.0 (15.0, 31.0)
	Min, Max	0, 210	0, 155	0, 120	7, 120	0, 210
Nodal status	pN0-1mi	867 (73.9%)	573 (63.7%)	326 (64.4%)	147 (63.1%)	1,913 (68.1%)
	pN1	212 (18.1%)	223 (24.8%)	117 (23.1%)	60 (25.8%)	612 (21.8%)
	pN2	46 (3.9%)	54 (6.0%)	36 (7.1%)	11 (4.7%)	147 (5.2%)
	pN3	29 (2.5%)	25 (2.8%)	16 (3.2%)	8 (3.4%)	78 (2.8%)
	pNx	19 (1.6%)	24 (2.7%)	11 (2.2%)	7 (3.0%)	61 (2.2%)
Grade	Grade 1	199 (17.0%)	110 (12.2%)	47 (9.3%)	25 (10.7%)	381 (13.6%)
	Grade 2	635 (54.1%)	482 (53.6%)	255 (50.4%)	113 (48.5%)	1,485 (52.8%)
	Grade 3	311 (26.5%)	278 (30.9%)	190 (37.5%)	86 (36.9%)	865 (30.8%)
	Unknown	28 (2.4%)	29 (3.2%)	14 (2.8%)	9 (3.9%)	80 (2.8%)

Variables	Categories	Age group (years)				
		70-74	75-79	80-84	>=85	All
		N = 1,173	N = 899	N = 506	N = 233	N = 2,811
Histology	Ductal carcinoma	761 (64.9%)	567 (63.1%)	341 (67.4%)	146 (62.7%)	1,815 (64.6%)
	Lobular carcinoma	164 (14.0%)	128 (14.2%)	58 (11.5%)	25 (10.7%)	375 (13.3%)
	Tubular carcinoma	21 (1.8%)	5 (0.6%)	3 (0.6%)	0 (0.0%)	29 (1.0%)
	Mucinous carcinoma	18 (1.5%)	28 (3.1%)	12 (2.4%)	13 (5.6%)	71 (2.5%)
	Other	110 (9.4%)	83 (9.2%)	53 (10.5%)	20 (8.6%)	266 (9.5%)
	Unknown	99 (8.4%)	88 (9.8%)	39 (7.7%)	29 (12.4%)	255 (9.1%)
ER status	Negative	141 (12.0%)	117 (13.0%)	74 (14.6%)	40 (17.2%)	372 (13.2%)
	Positive	1,002 (85.4%)	753 (83.8%)	414 (81.8%)	185 (79.4%)	2,354 (83.7%)
	Unknown	30 (2.6%)	29 (3.2%)	18 (3.6%)	8 (3.4%)	85 (3.0%)
HER2 status	Negative	981 (83.6%)	724 (80.5%)	375 (74.1%)	192 (82.4%)	2,272 (80.8%)
	Inconclusive	9 (0.8%)	7 (0.8%)	4 (0.8%)	2 (0.9%)	22 (0.8%)
	Positive	136 (11.6%)	115 (12.8%)	63 (12.5%)	18 (7.7%)	332 (11.8%)
	Unknown	47 (4.0%)	53 (5.9%)	64 (12.6%)	21 (9.0%)	185 (6.6%)
Oncotype DX test performed	No	212 (18.1%)	138 (15.4%)	76 (15.0%)	38 (16.3%)	464 (16.5%)
	Yes	26 (2.2%)	13 (1.4%)	2 (0.4%)	0 (0.0%)	41 (1.5%)
	Not applicable	306 (26.1%)	265 (29.5%)	186 (36.8%)	75 (32.2%)	832 (29.6%)
	Unknown	629 (53.6%)	483 (53.7%)	242 (47.8%)	120 (51.5%)	1,474 (52.4%)
Charlson comorbidity index (no age)	n	1,133	869	481	224	2,707
	Mean (SD)	0.90 (1.21)	1.10 (1.36)	1.19 (1.37)	1.09 (1.30)	1.03 (1.30)
	Median (IQR)	0.00 (0.00, 2.00)	1.00 (0.00, 2.00)	1.00 (0.00, 2.00)	1.00 (0.00, 2.00)	1.00 (0.00, 2.00)
	Min, Max	0, 6	0, 9	0, 9	0, 6	0, 9
	n	1,133	869	481	224	2707
	Mean (SD)	0.55 (0.28)	0.51 (0.29)	0.28 (0.24)	0.26 (0.23)	0.47 (0.29)

Variables	Categories	Age group (years)				
		70-74	75-79	80-84	>=85	All
		N = 1,173	N = 899	N = 506	N = 233	N = 2,811
Charlson calculated 10-year survival probability*	Median (IQR)	0.77 (0.21, 0.77)	0.53 (0.21, 0.77)	0.21 (0.02, 0.53)	0.21 (0.02, 0.53)	0.53 (0.21, 0.77)
	Min, Max	0, 0.77	0, 0.77	0, 0.77	0, 0.53	0, 0.77
Number of concurrent medications	n	973	801	462	210	2,446
	Mean (SD)	3.85 (2.66)	4.16 (2.63)	4.26 (2.63)	4.21 (2.53)	4.06 (2.64)
	Median (IQR)	3.00 (2.00, 5.00)	4.00 (2.00, 6.00)	4.00 (2.00, 6.00)	4.00 (2.00, 6.00)	4.00 (2.00, 5.75)
	Min, Max	0, 14	0, 18	0, 14	0, 14	0, 18
ADL category	No dependency	924 (78.8%)	623 (69.3%)	331 (65.4%)	126 (54.1%)	2,004 (71.3%)
	Mild dependency	89 (7.6%)	109 (12.1%)	67 (13.2%)	43 (18.5%)	308 (11.0%)
	Moderate/severe dependency	70 (6.0%)	101 (11.2%)	60 (11.9%)	47 (20.2%)	278 (9.9%)
	Unknown	90 (7.7%)	66 (7.3%)	48 (9.5%)	17 (7.3%)	221 (7.9%)
IADL category	No dependency	955 (81.4%)	679 (75.5%)	332 (65.6%)	103 (44.2%)	2,069 (73.6%)
	Mild dependency	54 (4.6%)	78 (8.7%)	70 (13.8%)	47 (20.2%)	249 (8.9%)
	Moderate/severe dependency	67 (5.7%)	70 (7.8%)	55 (10.9%)	66 (28.3%)	258 (9.2%)
	Unknown	97 (8.3%)	72 (8.0%)	49 (9.7%)	17 (7.3%)	235 (8.4%)
MMSE category	Normal function	1,059 (90.3%)	805 (89.5%)	444 (87.7%)	186 (79.8%)	2,494 (88.7%)
	Mild impairment	91 (7.8%)	74 (8.2%)	50 (9.9%)	33 (14.2%)	248 (8.8%)
	Moderate impairment	11 (0.9%)	12 (1.3%)	5 (1.0%)	8 (3.4%)	36 (1.3%)
	Severe	12 (1.0%)	8 (0.9%)	7 (1.4%)	6 (2.6%)	33 (1.2%)
aPG-SGA category	Low	929 (79.2%)	709 (78.9%)	370 (73.1%)	172 (73.8%)	2,180 (77.6%)
	Moderate	111 (9.5%)	88 (9.8%)	62 (12.3%)	27 (11.6%)	288 (10.2%)
	High	15 (1.3%)	13 (1.4%)	10 (2.0%)	2 (0.9%)	40 (1.4%)
	Unknown	118 (10.1%)	89 (9.9%)	64 (12.6%)	32 (13.7%)	303 (10.8%)
ECOG PS	0	930 (79.3%)	619 (68.9%)	305 (60.3%)	90 (38.6%)	1,944 (69.2%)

Variables	Categories	Age group (years)				
		70-74	75-79	80-84	>=85	All
		N = 1,173	N = 899	N = 506	N = 233	N = 2,811
	1	151 (12.9%)	205 (22.8%)	142 (28.1%)	109 (46.8%)	607 (21.6%)
	2	21 (1.8%)	24 (2.7%)	23 (4.5%)	12 (5.2%)	80 (2.8%)
	3	10 (0.9%)	9 (1.0%)	8 (1.6%)	9 (3.9%)	36 (1.3%)
	4	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
	Unknown	60 (5.1%)	42 (4.7%)	28 (5.5%)	13 (5.6%)	143 (5.1%)
Breast surgery	Wide local excision	769 (65.5%)	504 (56.1%)	236 (46.7%)	89 (38.2%)	1,598 (56.8%)
	Therapeutic mammoplasty / breast reshaping after wide local excision	35 (3.0%)	12 (1.3%)	2 (0.4%)	2 (0.9%)	51 (1.8%)
	Mastectomy	316 (26.9%)	346 (38.5%)	251 (49.6%)	136 (58.4%)	1,049 (37.3%)
	Mastectomy and reconstruction	25 (2.1%)	10 (1.1%)	2 (0.4%)	0 (0.0%)	37 (1.3%)
	Other	10 (0.9%)	5 (0.6%)	5 (1.0%)	0 (0.0%)	20 (0.7%)
	Unknown	18 (1.5%)	22 (2.4%)	10 (2.0%)	6 (2.6%)	56 (2.0%)
Axillary surgery	Axillary sample	38 (3.2%)	30 (3.3%)	11 (2.2%)	9 (3.9%)	88 (3.1%)
	Axillary clearance	134 (11.4%)	134 (14.9%)	99 (19.6%)	47 (20.2%)	414 (14.7%)
	Sentinel lymph node biopsy	881 (75.1%)	633 (70.4%)	336 (66.4%)	130 (55.8%)	1,980 (70.4%)
	Internal mammary node biopsy	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
	No axillary surgery	23 (2.0%)	16 (1.8%)	22 (4.3%)	19 (8.2%)	80 (2.8%)
	Unknown	97 (8.3%)	85 (9.5%)	38 (7.5%)	28 (12.0%)	248 (8.8%)

Abbreviations: ER: oestrogen receptor; HER2: human epidermal growth factor receptor; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ADL: activities of daily living; IADL: instrumental activities of daily living; aPG-SGA: abridged patient-generated subjective global assessment; MMSE: Mini Mental State Examination.

Supplementary table 2.4 – Baseline patient characteristics by receipt of chemotherapy.

Variables	Categories	No chemotherapy	Chemotherapy
		N = 2,414	N = 397
Participation level	Full	1,789 (74.1%)	322 (81.1%)
	Partial	550 (22.8%)	71 (17.9%)
	Consultee	75 (3.1%)	4 (1.0%)
Age	n	2414	397
	Mean (SD)	76.98 (5.25)	73.62 (3.30)
	Median (IQR)	76.00 (73.00, 80.00)	73.00 (71.00, 76.00)
	Min, Max	69, 95	69, 87
Charlson comorbidity index (no age)	n	2,322	385
	Mean (SD)	1.07 (1.33)	0.81 (1.10)
	Median (IQR)	1.00 (0.00, 2.00)	0.00 (0.00, 2.00)
	Min, Max	0, 9	0, 6
Charlson calculated probability	n	2,322	385
	Mean (SD)	0.45 (0.30)	0.56 (0.27)
	Median (IQR)	0.53 (0.21, 0.77)	0.77 (0.21, 0.77)
	Min, Max	0, 0.77	0, 0.77
Number of concurrent medications	n	2,116	330
	Mean (SD)	4.13 (2.66)	3.63 (2.49)
	Median (IQR)	4.00 (2.00, 6.00)	3.00 (2.00, 5.00)
	Min, Max	0, 18	0, 14
ADL category	No dependency	1,683 (69.7%)	321 (80.9%)
	Mild dependency	274 (11.4%)	34 (8.6%)
	Moderate/severe dependency	262 (10.9%)	16 (4.0%)
	Unknown	195 (8.1%)	26 (6.5%)
IADL category	No dependency	1737 (72.0%)	332 (83.6%)

Variables	Categories	No chemotherapy	Chemotherapy
		N = 2,414	N = 397
	Mild dependency	221 (9.2%)	28 (7.1%)
	Moderate/severe dependency	248 (10.3%)	10 (2.5%)
	Unknown	208 (8.6%)	27 (6.8%)
MMSE category	Normal function	2,133 (88.4%)	361 (90.9%)
	Mild impairment	220 (9.1%)	28 (7.1%)
	Moderate impairment	30 (1.2%)	6 (1.5%)
	Severe	31 (1.3%)	2 (0.5%)
aPG-SGA category	Low	1,864 (77.2%)	316 (79.6%)
	Moderate	249 (10.3%)	39 (9.8%)
	High	36 (1.5%)	4 (1.0%)
	Unknown	265 (11.0%)	38 (9.6%)
ECOG PS	0	1,632 (67.6%)	312 (78.6%)
	1	544 (22.5%)	63 (15.9%)
	2	77 (3.2%)	3 (0.8%)
	3	34 (1.4%)	2 (0.5%)
	4	1 (0.0%)	0 (0.0%)
	Unknown	126 (5.2%)	17 (4.3%)

Abbreviations: ECOG PS: Eastern Cooperative Oncology Group Performance Status; ADL: activities of daily living; IADL: instrumental activities of daily living; aPG-SGA: abridged patient-generated subjective global assessment; MMSE: Mini Mental State Examination.

Supplementary table 2.5 – Postoperative tumour characteristics by receipt of chemotherapy.

Variables	Categories	No chemotherapy	Chemotherapy
		N = 2,414	N = 397
Main side	Right	1,128 (46.7%)	177 (44.6%)
	Left	1,286 (53.3%)	220 (55.4%)
Tumour size (mm)	n	2,365	387
	Mean (SD)	24.2 (15.8)	32.8 (20.5)
	Median (IQR)	20.0 (14.0, 30.0)	29.0 (21.0, 40.0)
	Min, Max	0, 155	0, 210
Tumour size (mm)	≤ 20	1,183 (49.0%)	96 (24.2%)
	21-50	1,043 (43.2%)	242 (61.0%)
	> 50	139 (5.8%)	49 (12.3%)
	Unknown	49 (2.0%)	10 (2.5%)
Nodal status	pN0-1mi	1,726 (71.5%)	187 (47.1%)
	pN1	495 (20.5%)	117 (29.5%)
	pN2	95 (3.9%)	52 (13.1%)
	pN3	46 (1.9%)	32 (8.1%)
	pNx	52 (2.2%)	9 (2.3%)
Grade	Grade 1	377 (15.6%)	4 (1.0%)
	Grade 2	1,355 (56.1%)	130 (32.7%)
	Grade 3	618 (25.6%)	247 (62.2%)
	Unknown	64 (2.7%)	16 (4.0%)
Histology	Ductal carcinoma	1,534 (63.5%)	281 (70.8%)
	Lobular carcinoma	321 (13.3%)	54 (13.6%)
	Tubular carcinoma	29 (1.2%)	0 (0.0%)
	Mucinous carcinoma	70 (2.9%)	1 (0.3%)
	Other	235 (9.7%)	31 (7.8%)
	Unknown	225 (9.3%)	30 (7.6%)

Variables	Categories	No chemotherapy	Chemotherapy
		N = 2,414	N = 397
ER positive	Negative	240 (9.9%)	132 (33.2%)
	Positive	2,101 (87.0%)	253 (63.7%)
	Unknown	73 (3.0%)	12 (3.0%)
HER2 status	Negative	2,050 (84.9%)	222 (55.9%)
	Inconclusive	19 (0.8%)	3 (0.8%)
	Positive	173 (7.2%)	159 (40.1%)
	Unknown	172 (7.1%)	13 (3.3%)
Oncotype DX test performed	No	428 (17.7%)	36 (9.1%)
	Yes	35 (1.4%)	6 (1.5%)
	Not Applicable	571 (23.7%)	261 (65.7%)
	Unknown	1,380 (57.2%)	94 (23.7%)
Breast surgery	Wide local excision	1,433 (59.4%)	165 (41.5%)
	Therapeutic mammoplasty / breast reshaping after WLE	33 (1.4%)	18 (4.5%)
	Mastectomy	860 (35.6%)	189 (47.6%)
	Mastectomy and reconstruction	25 (1.0%)	12 (3.0%)
	Other	16 (0.7%)	4 (1.0%)
	Unknown	47 (1.9%)	9 (2.3%)
Axillary surgery	Axillary sample	76 (3.1%)	12 (3.0%)
	Axillary clearance	274 (11.4%)	140 (35.3%)
	Sentinel lymph node biopsy	1,770 (73.3%)	210 (52.9%)
	Internal mammary node biopsy	1 (0.0%)	0 (0.0%)
	No axillary surgery	73 (3.0%)	7 (1.8%)
	Unknown	220 (9.1%)	28 (7.1%)

Abbreviations: ER: oestrogen receptor; HER2: human epidermal growth factor receptor.

Supplementary table 2.6 – Covariate balance in the final matched dataset: chemotherapy versus no chemotherapy.

Variables	Categories	Chemotherapy	No chemotherapy
		N = 200	N = 350
Age	n	200	350
	Mean (SD)	73.48 (2.91)	74.36 (3.06)
	Median (IQR)	73.00 (71.00, 76.00)	74.00 (72.00, 77.00)
	Min, Max	70, 80	69, 80
aPG-SGA category	Low	173 (86.5%)	302 (86.3%)
	Moderate	24 (12.0%)	45 (12.9%)
	High	3 (1.5%)	3 (0.9%)
ADL category	No dependency	162 (81.0%)	273 (78.0%)
	Mild dependency	26 (13.0%)	46 (13.1%)
	Moderate/severe dependency	12 (6.0%)	31 (8.9%)
IADL category	No dependency	174 (87.0%)	299 (85.4%)
	Mild dependency	19 (9.5%)	31 (8.9%)
	Moderate/severe dependency	7 (3.5%)	20 (5.7%)
MMSE category	Normal function	182 (91.0%)	317 (90.6%)
	Mild impairment	15 (7.5%)	28 (8.0%)
	Moderate impairment	3 (1.5%)	5 (1.4%)
Charlson comorbidity index category	0-1	176 (88.0%)	301 (86.0%)
	> 2	24 (12.0%)	49 (14.0%)
Medications	3 or fewer	109 (54.5%)	172 (49.1%)
	4 or more	91 (45.5%)	178 (50.9%)
ECOG PS category	0-1	195 (97.5%)	339 (96.9%)
	2	3 (1.5%)	6 (1.7%)
	3-4	2 (1.0%)	5 (1.4%)
Nottingham Prognostic Index category	Moderate	137 (68.5%)	245 (70.0%)

Variables	Categories	Chemotherapy	No chemotherapy
		N = 200	N = 350
	Good	10 (5.0%)	17 (4.9%)
	Poor	53 (26.5%)	88 (25.1%)
HER2 status	Negative	139 (69.5%)	269 (76.9%)
	Positive	61 (30.5%)	81 (23.1%)

Abbreviations: ER: oestrogen receptor; HER2: human epidermal growth factor receptor; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ADL: activities of daily living; IADL: instrumental activities of daily living; aPG-SGA: abridged patient-generated subjective global assessment; MMSE: Mini Mental State Examination.

Chapter 3

Supplementary table 3.1 – Baseline postoperative tumour and patient characteristics by chemotherapy receipt.

Variables	Categories	Chemotherapy	No chemotherapy	Total
		N = 376	N = 1,144	N = 1,520
Participation level	Full	304 (80.9%)	816 (71.3%)	1,120 (73.7%)
	Partial	68 (18.1%)	284 (24.8%)	352 (23.2%)
	Consultee	4 (1.1%)	44 (3.8%)	48 (3.2%)
Main side	Right	169 (44.9%)	545 (47.6%)	714 (47.0%)
	Left	207 (55.1%)	599 (52.4%)	806 (53.0%)
Tumour size (mm)	n	375	1,143	1,518
	Mean (SD)	32.9 (20.7)	29.0 (17.5)	29.9 (18.4)
	Median (IQR)	29.0 (21.0, 40.0)	25.0 (18.0, 35.0)	25.0 (18.2, 36.0)
	Min, Max	0, 210	0, 155	0, 210
Tumour size (mm)	<= 20	93 (24.7%)	399 (34.9%)	492 (32.4%)
	21-50	233 (62.0%)	644 (56.3%)	877 (57.7%)
	> 50	49 (13.0%)	100 (8.7%)	149 (9.8%)
	Unknown	1 (0.3%)	1 (0.1%)	2 (0.1%)
Grade	Grade 1	2 (0.5%)	77 (6.7%)	79 (5.2%)
	Grade 2	122 (32.4%)	447 (39.1%)	569 (37.4%)
	Grade 3	247 (65.7%)	617 (53.9%)	864 (56.8%)
	Unknown	5 (1.3%)	3 (0.3%)	8 (0.5%)
Histology	Ductal NST	270 (71.8%)	813 (71.1%)	1,083 (71.2%)
	Lobular carcinoma	52 (13.8%)	110 (9.6%)	162 (10.7%)
	Tubular carcinoma	0 (0.0%)	5 (0.4%)	5 (0.3%)
	Mucinous carcinoma	1 (0.3%)	13 (1.1%)	14 (0.9%)
	Other	29 (7.7%)	97 (8.5%)	126 (8.3%)

Variables	Categories	Chemotherapy	No chemotherapy	Total
		N = 376	N = 1,144	N = 1,520
	Unknown	24 (6.4%)	106 (9.3%)	130 (8.6%)
ER status	Negative	132 (35.1%)	240 (21.0%)	372 (24.5%)
	Positive	241 (64.1%)	893 (78.1%)	1,134 (74.6%)
	Unknown	3 (0.8%)	11 (1.0%)	14 (0.9%)
HER2 status	Negative	210 (55.9%)	908 (79.4%)	1,118 (73.6%)
	Inconclusive	3 (0.8%)	7 (0.6%)	10 (0.7%)
	Positive	159 (42.3%)	173 (15.1%)	332 (21.8%)
	Unknown	4 (1.1%)	56 (4.9%)	60 (3.9%)
Oncotype DX test performed	No	35 (9.3%)	150 (13.1%)	185 (12.2%)
	Yes	5 (1.3%)	16 (1.4%)	21 (1.4%)
	Not applicable	252 (67.0%)	434 (37.9%)	686 (45.1%)
	Unknown	84 (22.3%)	544 (47.6%)	628 (41.3%)
Breast surgery	Wide local excision (non wire localised)	113 (30.1%)	412 (36.0%)	525 (34.5%)
	Wire localised wide local excision	43 (11.4%)	150 (13.1%)	193 (12.7%)
	Therapeutic mammoplasty / breast reshaping after wide local excision	18 (4.8%)	14 (1.2%)	32 (2.1%)
	Mastectomy	186 (49.5%)	549 (48.0%)	735 (48.4%)
	Mastectomy and reconstruction	12 (3.2%)	11 (1.0%)	23 (1.5%)
	Other	4 (1.1%)	8 (0.7%)	12 (0.8%)
Axillary surgery	Axillary sample	11 (2.9%)	38 (3.3%)	49 (3.2%)
	Axillary clearance	136 (36.2%)	247 (21.6%)	383 (25.2%)
	Sentinel lymph node biopsy	200 (53.2%)	725 (63.4%)	925 (60.9%)
	Internal mammary node biopsy	0 (0.0%)	1 (0.1%)	1 (0.1%)
	No axillary surgery	7 (1.9%)	27 (2.4%)	34 (2.2%)
	Unknown	22 (5.9%)	106 (9.3%)	128 (8.4%)

Variables	Categories	Chemotherapy	No chemotherapy	Total
		N = 376	N = 1,144	N = 1,520
Nodal status	pN0-1mi	175 (46.5%)	508 (44.4%)	683 (44.9%)
	pN1	117 (31.1%)	494 (43.2%)	611 (40.2%)
	pN2	52 (13.8%)	95 (8.3%)	147 (9.7%)
	pN3	32 (8.5%)	46 (4.0%)	78 (5.1%)
	pNx	0 (0.0%)	1 (0.1%)	1 (0.1%)
Nottingham Prognostic Index	n	371	1139	1510
	Mean (SD)	5.1 (1.0)	4.7 (0.9)	4.8 (1.0)
	Median (IQR)	4.9 (4.4, 5.7)	4.5 (4.3, 5.3)	4.6 (4.3, 5.4)
	Min, Max	2.4, 10.2	2.1, 8.1	2.1, 10.2
Age	n	376	1144	1520
	Mean (SD)	73.65 (3.33)	77.97 (5.19)	76.90 (5.14)
	Median (IQR)	73.00 (71.00, 76.00)	78.00 (74.00, 81.00)	76.00 (72.00, 80.00)
	Min, Max	69, 87	69, 95	69, 95
Charlson comorbidity index (no age)	n	365	1,103	1,468
	Mean (SD)	0.79 (1.08)	1.11 (1.38)	1.03 (1.32)
	Median (IQR)	0.00 (0.00, 2.00)	1.00 (0.00, 2.00)	1.00 (0.00, 2.00)
	Min, Max	0, 6	0, 9	0, 9
Charlson calculated probability	n	365	1,103	1,468
	Mean (SD)	0.56 (0.26)	0.43 (0.29)	0.46 (0.29)
	Median (IQR)	0.77 (0.21, 0.77)	0.53 (0.21, 0.77)	0.53 (0.21, 0.77)
	Min, Max	0, 0.77	0, 0.77	0, 0.77
Number of concurrent medications	n	314	1,021	1,335
	Mean (SD)	3.66 (2.51)	4.30 (2.69)	4.15 (2.66)
	Median (IQR)	3.00 (2.00, 5.00)	4.00 (2.00, 6.00)	4.00 (2.00, 6.00)

Variables	Categories	Chemotherapy	No chemotherapy	Total
		N = 376	N = 1,144	N = 1,520
	Min, Max	0, 14	0, 18	0, 18
ADL category	No dependency	303 (80.6%)	760 (66.4%)	1,063 (69.9%)
	Mild dependency	33 (8.8%)	146 (12.8%)	179 (11.8%)
	Moderate/severe dependency	16 (4.3%)	136 (11.9%)	152 (10.0%)
	Unknown	24 (6.4%)	102 (8.9%)	126 (8.3%)
IADL category	No dependency	315 (83.8%)	776 (67.8%)	1,091 (71.8%)
	Mild dependency	26 (6.9%)	124 (10.8%)	150 (9.9%)
	Moderate/severe dependency	10 (2.7%)	136 (11.9%)	146 (9.6%)
	Unknown	25 (6.6%)	108 (9.4%)	133 (8.7%)
MMSE category	Normal function	342 (91.0%)	1,004 (87.8%)	1,346 (88.6%)
	Mild impairment	28 (7.4%)	111 (9.7%)	139 (9.1%)
	Moderate impairment	4 (1.1%)	14 (1.2%)	18 (1.2%)
	Severe	2 (0.5%)	15 (1.3%)	17 (1.1%)
aPG-SGA category	Low	299 (79.5%)	869 (76.0%)	1,168 (76.8%)
	Moderate	38 (10.1%)	125 (10.9%)	163 (10.7%)
	High	4 (1.1%)	19 (1.7%)	23 (1.5%)
	Unknown	35 (9.3%)	131 (11.5%)	166 (10.9%)
ECOG PS	0	296 (78.7%)	740 (64.7%)	1,036 (68.2%)
	1	59 (15.7%)	284 (24.8%)	343 (22.6%)
	2	3 (0.8%)	43 (3.8%)	46 (3.0%)
	3	2 (0.5%)	18 (1.6%)	20 (1.3%)
	Unknown	16 (4.3%)	59 (5.2%)	75 (4.9%)

Abbreviations: ER: oestrogen receptor; HER2: human epidermal growth factor receptor; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ADL: activities of daily living; IADL: instrumental activities of daily living; aPG-SGA: abridged patient-generated subjective global assessment; MMSE: Mini Mental State Examination.

Supplementary table 3.2 – Completion of the EORTC-QLQ-C30 at each time point.

Time points	Completion	Chemotherapy	No Chemotherapy	Total
		N = 304	N = 816	N = 1,120
Baseline	All	276 (90.8%)	736 (90.2%)	1,012 (90.4%)
	Some	9 (3.0%)	36 (4.4%)	45 (4.0%)
	None	19 (6.2%)	44 (5.4%)	63 (5.6%)
6 weeks	All	254 (83.6%)	663 (81.2%)	917 (81.9%)
	Some	12 (3.9%)	35 (4.3%)	47 (4.2%)
	None	38 (12.5%)	118 (14.5%)	156 (13.9%)
6 months	All	236 (77.6%)	627 (76.8%)	863 (77.1%)
	Some	12 (3.9%)	29 (3.6%)	41 (3.7%)
	None	56 (18.4%)	160 (19.6%)	216 (19.3%)
12 months	All	217 (71.4%)	511 (62.6%)	728 (65.0%)
	Some	10 (3.3%)	42 (5.1%)	52 (4.6%)
	None	77 (25.3%)	263 (32.2%)	340 (30.4%)
18 months	All	184 (60.5%)	431 (52.8%)	615 (54.9%)
	Some	8 (2.6%)	36 (4.4%)	44 (3.9%)
	None	112 (36.8%)	349 (42.8%)	461 (41.2%)
24 months	All	150 (49.3%)	379 (46.4%)	529 (47.2%)
	Some	8 (2.6%)	23 (2.8%)	31 (2.8%)
	None	146 (48.0%)	414 (50.7%)	560 (50.0%)

Supplementary table 3.3 – Completion of the EORTC-QLQ-BR23 at each time point.

Time points	Completion	Chemotherapy	No Chemotherapy	Total
		N = 304	N = 816	N = 1,120
Baseline	All	2 (0.7%)	4 (0.5%)	6 (0.5%)
	Some	282 (92.8%)	766 (93.9%)	1,048 (93.6%)
	None	20 (6.6%)	46 (5.6%)	66 (5.9%)
6 weeks	All	2 (0.7%)	4 (0.5%)	6 (0.5%)
	Some	264 (86.8%)	694 (85.0%)	958 (85.5%)
	None	38 (12.5%)	118 (14.5%)	156 (13.9%)
6 months	All	11 (3.6%)	16 (2.0%)	27 (2.4%)
	Some	236 (77.6%)	633 (77.6%)	869 (77.6%)
	None	57 (18.8%)	167 (20.5%)	224 (20.0%)
12 months	All	2 (0.7%)	15 (1.8%)	17 (1.5%)
	Some	225 (74.0%)	539 (66.1%)	764 (68.2%)
	None	77 (25.3%)	262 (32.1%)	339 (30.3%)
18 months	All	9 (3.0%)	10 (1.2%)	19 (1.7%)
	Some	183 (60.2%)	457 (56.0%)	640 (57.1%)
	None	112 (36.8%)	349 (42.8%)	461 (41.2%)
24 months	All	6 (2.0%)	17 (2.1%)	23 (2.1%)
	Some	151 (49.7%)	386 (47.3%)	537 (47.9%)
	None	147 (48.4%)	413 (50.6%)	560 (50.0%)

Supplementary table 3.4 – Completion of the EORTC-QLQ-ELD15 at each time point.

Time points	Completion	Chemotherapy	No Chemotherapy	Total
		N = 304	N = 816	N = 1,120
Baseline	All	274 (90.1%)	732 (89.7%)	1,006 (89.8%)
	Some	9 (3.0%)	33 (4.0%)	42 (3.8%)
	None	21 (6.9%)	51 (6.2%)	72 (6.4%)
6 weeks	All	260 (85.5%)	675 (82.7%)	935 (83.5%)
	Some	4 (1.3%)	14 (1.7%)	18 (1.6%)
	None	40 (13.2%)	127 (15.6%)	167 (14.9%)
6 months	All	232 (76.3%)	625 (76.6%)	857 (76.5%)
	Some	10 (3.3%)	17 (2.1%)	27 (2.4%)
	None	62 (20.4%)	174 (21.3%)	236 (21.1%)
12 months	All	221 (72.7%)	521 (63.8%)	742 (66.2%)
	Some	5 (1.6%)	28 (3.4%)	33 (2.9%)
	None	78 (25.7%)	267 (32.7%)	345 (30.8%)
18 months	All	185 (60.9%)	439 (53.8%)	624 (55.7%)
	Some	5 (1.6%)	18 (2.2%)	23 (2.1%)
	None	114 (37.5%)	359 (44.0%)	473 (42.2%)
24 months	All	147 (48.4%)	379 (46.4%)	526 (47.0%)
	Some	6 (2.0%)	20 (2.5%)	26 (2.3%)
	None	151 (49.7%)	417 (51.1%)	568 (50.7%)

Supplementary table 3.5 – Mean (SD) scores for the EORTC QLQ-C30 scale at each time point in the chemotherapy versus no chemotherapy cohorts with adjusted mean difference (95% CI) and p-value.

Domain	Time point		Chemotherapy	No chemotherapy	Adjusted mean difference (95% CI)	P-value
Global health status / QoL	Baseline	n	282	767	-	-
		Mean (SD)	77.9 (17.7)	75.4 (18.4)		
	6 weeks	n	263	692	-2.81 (-5.17, -0.44)	0.02
		Mean (SD)	68.4 (20.1)	69.3 (18.6)		
	6 months	n	243	651	-9.20 (-11.95, -6.44)	<0.001
		Mean (SD)	61.7 (22.3)	69.5 (19.2)		
	12 months	n	225	548	1.25 (-1.19, 3.69)	0.315
		Mean (SD)	73.9 (17.2)	70.9 (18.6)		
	18 months	n	190	456	-0.42 (-3.42, 2.59)	0.784
		Mean (SD)	69.8 (21.2)	69.9 (19.1)		
	24 months	n	157	400	0.53 (-2.70, 3.75)	0.749
		Mean (SD)	69.5 (19.2)	68.3 (19.3)		
Physical functioning	Baseline	n	285	769	-	-
		Mean (SD)	87.1 (16.0)	82.1 (19.9)		
	6 weeks	n	264	697	-1.25 (-3.08, 0.58)	0.18
		Mean (SD)	79.3 (18.8)	76.2 (19.9)		
	6 months	n	246	655	-8.05 (-10.21, -5.89)	<0.001
		Mean (SD)	71.8 (20.5)	75.7 (20.5)		
	12 months	n	227	551	-2.76 (-4.95, -0.57)	0.014
		Mean (SD)	76.9 (19.5)	74.9 (21.6)		
	18 months	n	191	466	-0.35 (-2.74, 2.04)	0.773
		Mean (SD)	75.6 (20.9)	74.1 (21.0)		
	24 months	n	158	400	0.22 (-2.61, 3.06)	0.877
		Mean (SD)	75.8 (19.5)	73.4 (22.0)		

Domain	Time point		Chemotherapy	No chemotherapy	Adjusted mean difference (95% CI)	P-value
Role functioning	Baseline	n	280	757	-	-
		Mean (SD)	89.9 (20.8)	87.1 (23.1)		
	6 weeks	n	263	689	-3.25 (-6.90, 0.40)	0.081
		Mean (SD)	70.2 (28.5)	71.1 (27.0)		
	6 months	n	248	646	-17.59 (-21.24, -13.95)	<0.001
		Mean (SD)	62.7 (29.3)	77.3 (25.6)		
	12 months	n	226	537	-4.41 (-8.17, -0.64)	0.022
		Mean (SD)	74.7 (26.3)	76.3 (26.1)		
	18 months	n	190	455	-3.23 (-7.55, 1.09)	0.143
		Mean (SD)	74.3 (26.5)	75.6 (27.8)		
	24 months	n	156	398	-4.46 (-9.40, 0.48)	0.077
		Mean (SD)	71.2 (29.0)	73.8 (28.7)		
Emotional functioning	Baseline	n	283	769	-	-
		Mean (SD)	77.0 (19.7)	78.3 (19.2)		
	6 weeks	n	264	689	0.10 (-2.26, 2.45)	0.936
		Mean (SD)	78.9 (18.0)	79.5 (19.6)		
	6 months	n	244	651	-0.57 (-3.15, 2.00)	0.662
		Mean (SD)	79.1 (20.0)	80.7 (19.5)		
	12 months	n	226	549	0.55 (-2.23, 3.33)	0.699
		Mean (SD)	80.5 (19.4)	80.0 (20.0)		
	18 months	n	191	460	-0.76 (-3.85, 2.33)	0.629
		Mean (SD)	79.6 (20.8)	80.6 (19.7)		
	24 months	n	155	399	-1.90 (-5.08, 1.28)	0.24
		Mean (SD)	78.4 (20.3)	80.4 (18.8)		
Cognitive functioning	Baseline	n	285	772	-	-
		Mean (SD)	89.6 (15.7)	88.3 (16.0)		

Domain	Time point		Chemotherapy	No chemotherapy	Adjusted mean difference (95% CI)	P-value
	6 weeks	n	265	697	-1.07 (-3.25, 1.11)	0.335
		Mean (SD)	85.8 (16.6)	85.6 (19.0)		
	6 months	n	248	655	-5.55 (-7.97, -3.13)	<0.001
		Mean (SD)	80.0 (20.8)	84.3 (18.4)		
	12 months	n	226	553	0.49 (-2.02, 2.99)	0.704
		Mean (SD)	84.0 (16.7)	83.0 (18.8)		
	18 months	n	191	466	-1.66 (-4.37, 1.05)	0.23
		Mean (SD)	82.7 (19.2)	84.1 (19.8)		
	24 months	n	158	401	-0.90 (-3.70, 1.90)	0.527
		Mean (SD)	83.4 (18.1)	83.7 (18.0)		
Social functioning	Baseline	n	282	766	-	-
		Mean (SD)	89.4 (19.9)	90.6 (18.6)		
	6 weeks	n	263	692	-3.57 (-6.71, -0.43)	0.026
		Mean (SD)	76.1 (25.3)	79.7 (23.7)		
	6 months	n	244	651	-18.72 (-22.17, -15.27)	<0.001
		Mean (SD)	65.2 (29.1)	84.2 (22.9)		
	12 months	n	226	551	-3.78 (-7.00, -0.56)	0.022
		Mean (SD)	81.4 (22.6)	85.2 (22.2)		
	18 months	n	190	460	-3.21 (-6.87, 0.45)	0.085
		Mean (SD)	82.2 (23.9)	86.0 (23.6)		
	24 months	n	156	399	-2.37 (-6.68, 1.94)	0.28
		Mean (SD)	80.8 (24.8)	84.4 (24.1)		
Fatigue	Baseline	n	281	761	-	-
		Mean (SD)	18.2 (19.5)	20.2 (20.0)		
	6 weeks	n	263	690	2.39 (-0.26, 5.04)	0.077
		Mean (SD)	33.5 (24.1)	32.8 (21.1)		

Domain	Time point		Chemotherapy	No chemotherapy	Adjusted mean difference (95% CI)	P-value
	6 months	n	248	648	13.09 (9.92, 16.26)	<0.001
		Mean (SD)	44.3 (26.2)	33.3 (22.7)		
	12 months	n	225	540	3.38 (0.30, 6.46)	0.032
		Mean (SD)	33.7 (22.9)	32.2 (21.9)		
	18 months	n	191	458	1.64 (-1.78, 5.05)	0.347
		Mean (SD)	32.9 (23.1)	31.7 (22.5)		
	24 months	n	156	397	0.86 (-2.62, 4.34)	0.627
		Mean (SD)	31.9 (21.4)	32.5 (22.1)		
Nausea / vomiting	Baseline	n	281	761	-	-
		Mean (SD)	2.1 (6.5)	2.3 (7.3)		
	6 weeks	n	263	691	1.27 (-0.33, 2.87)	0.119
		Mean (SD)	5.4 (13.0)	4.4 (10.6)		
	6 months	n	247	650	5.23 (3.28, 7.17)	<0.001
		Mean (SD)	9.8 (16.8)	4.6 (11.4)		
	12 months	n	226	539	0.78 (-0.86, 2.42)	0.351
		Mean (SD)	4.4 (12.2)	4.1 (9.8)		
	18 months	n	191	459	-0.20 (-1.88, 1.48)	0.816
		Mean (SD)	3.6 (9.1)	4.1 (10.3)		
	24 months	n	156	398	-0.54 (-2.43, 1.35)	0.577
		Mean (SD)	3.7 (10.6)	4.4 (10.4)		
Pain	Baseline	n	280	759	-	-
		Mean (SD)	14.5 (20.2)	15.4 (23.1)		
	6 weeks	n	263	692	-0.32 (-3.19, 2.55)	0.829
		Mean (SD)	21.1 (21.2)	22.8 (23.6)		
	6 months	n	247	650	1.83 (-1.32, 4.98)	0.255
		Mean (SD)	21.0 (25.5)	20.7 (23.4)		

Domain	Time point		Chemotherapy	No chemotherapy	Adjusted mean difference (95% CI)	P-value
	12 months	n	226	540	1.92 (-1.64, 5.48)	0.29
		Mean (SD)	23.4 (24.7)	23.6 (25.9)		
	18 months	n	191	458	3.71 (-0.60, 8.03)	0.092
		Mean (SD)	26.7 (29.3)	23.4 (26.4)		
	24 months	n	155	398	0.29 (-4.45, 5.04)	0.903
		Mean (SD)	24.3 (28.7)	26.0 (28.1)		
Dyspnoea	Baseline	n	281	758	-	-
		Mean (SD)	9.7 (18.7)	13.7 (22.0)		
	6 weeks	n	263	686	-2.14 (-4.49, 0.20)	0.073
		Mean (SD)	9.9 (17.8)	15.0 (21.9)		
	6 months	n	247	645	3.86 (0.54, 7.18)	0.023
		Mean (SD)	21.3 (25.6)	21.2 (26.3)		
	12 months	n	222	536	-0.08 (-3.73, 3.58)	0.967
		Mean (SD)	17.6 (24.1)	21.4 (26.9)		
	18 months	n	191	456	0.15 (-3.84, 4.15)	0.941
		Mean (SD)	18.3 (24.6)	20.9 (27.8)		
	24 months	n	155	397	0.94 (-3.36, 5.23)	0.669
		Mean (SD)	20.0 (25.4)	22.1 (26.8)		
Insomnia	Baseline	n	281	762	-	-
		Mean (SD)	27.9 (29.0)	26.7 (28.6)		
	6 weeks	n	261	688	3.09 (-0.66, 6.85)	0.106
		Mean (SD)	33.1 (29.8)	29.9 (29.5)		
	6 months	n	246	648	-0.36 (-4.16, 3.45)	0.854
		Mean (SD)	28.9 (29.9)	29.3 (28.9)		
	12 months	n	226	537	-1.87 (-5.88, 2.15)	0.361
		Mean (SD)	29.4 (27.7)	31.7 (29.2)		

Domain	Time point		Chemotherapy	No chemotherapy	Adjusted mean difference (95% CI)	P-value
	18 months	n	189	458	2.19 (-2.44, 6.81)	0.353
		Mean (SD)	33.3 (30.9)	30.4 (30.2)		
	24 months	n	153	398	0.42 (-4.48, 5.31)	0.868
		Mean (SD)	30.7 (28.5)	30.4 (28.9)		
Appetite loss	Baseline	n	280	759	-	-
		Mean (SD)	10.0 (17.9)	9.0 (18.5)		
	6 weeks	n	262	690	1.29 (-1.70, 4.28)	0.396
		Mean (SD)	15.9 (23.6)	13.9 (22.2)		
	6 months	n	247	647	13.50 (9.81, 17.19)	<0.001
		Mean (SD)	26.2 (32.6)	12.7 (22.7)		
	12 months	n	225	536	-0.59 (-4.02, 2.85)	0.738
		Mean (SD)	12.3 (22.5)	13.4 (22.7)		
	18 months	n	191	460	-1.63 (-5.20, 1.95)	0.372
		Mean (SD)	10.3 (21.2)	11.7 (22.5)		
	24 months	n	156	394	-1.86 (-5.89, 2.16)	0.363
		Mean (SD)	11.3 (21.3)	13.1 (22.2)		
Constipation	Baseline	n	281	758	-	-
		Mean (SD)	7.8 (17.0)	9.5 (19.2)		
	6 weeks	n	263	690	3.43 (0.23, 6.62)	0.035
		Mean (SD)	17.0 (26.7)	15.3 (23.7)		
	6 months	n	245	647	3.84 (0.50, 7.18)	0.024
		Mean (SD)	17.1 (26.2)	15.1 (24.1)		
	12 months	n	226	538	-0.33 (-3.76, 3.10)	0.85
		Mean (SD)	12.4 (23.0)	14.8 (23.8)		
	18 months	n	190	455	1.24 (-2.68, 5.16)	0.534
		Mean (SD)	15.3 (25.3)	15.2 (24.3)		

Domain	Time point		Chemotherapy	No chemotherapy	Adjusted mean difference (95% CI)	P-value
	24 months	n	156	398	-1.67 (-5.75, 2.40)	0.42
		Mean (SD)	12.0 (21.7)	15.1 (24.2)		
Diarrhoea	Baseline	n	281	757	-	-
		Mean (SD)	3.8 (12.0)	4.4 (13.5)		
	6 weeks	n	263	687	1.25 (-0.98, 3.48)	0.272
		Mean (SD)	6.2 (17.5)	5.5 (15.3)		
	6 months	n	247	644	7.68 (5.01, 10.35)	<0.001
		Mean (SD)	13.0 (24.1)	5.7 (15.2)		
	12 months	n	226	534	4.15 (1.62, 6.68)	0.001
		Mean (SD)	9.0 (19.4)	5.3 (14.5)		
	18 months	n	190	454	1.88 (-0.73, 4.49)	0.159
		Mean (SD)	6.8 (16.3)	5.4 (15.0)		
	24 months	n	156	395	-2.42 (-5.57, 0.74)	0.133
		Mean (SD)	4.3 (13.5)	6.8 (18.0)		
Financial problems	Baseline	n	282	765	-	-
		Mean (SD)	2.5 (9.6)	2.9 (10.7)		
	6 weeks	n	263	689	1.04 (-0.74, 2.82)	0.253
		Mean (SD)	4.8 (14.3)	4.5 (13.6)		
	6 months	n	243	650	3.28 (1.16, 5.39)	0.002
		Mean (SD)	6.9 (18.1)	4.2 (13.3)		
	12 months	n	225	549	2.50 (0.27, 4.73)	0.028
		Mean (SD)	6.1 (17.5)	4.3 (13.3)		
	18 months	n	190	458	1.36 (-0.72, 3.44)	0.199
		Mean (SD)	4.2 (15.1)	2.8 (12.2)		
	24 months	n	156	400	2.60 (-0.09, 5.29)	0.058
		Mean (SD)	5.8 (17.8)	4.0 (14.2)		

Abbreviations: SD: standard deviation; CI: confidence interval.

Supplementary table 3.6 - Fixed coefficients from the longitudinal model of global health status included in the EORTC QLQ-C30 scale on the matched chemotherapy versus no chemotherapy cohorts.

Term	Level	Effect (95% CI)	P-value
Treatment	Chemotherapy	-1.914 (-5.396, 1.568)	0.282
Time	6 weeks	-	-
	6 months	-1.970 (-4.502, 0.561)	0.127
	12 months	0.492 (-2.171, 3.156)	0.717
	18 months	-2.354 (-5.154, 0.446)	0.1
	24 months	-2.234 (-5.207, 0.738)	0.141
Treatment : Time	Chemotherapy : 6 weeks	-	-
	Chemotherapy : 6 months	-7.153 (-11.317, -2.989)	0.001
	Chemotherapy : 12 months	3.698 (-0.621, 8.017)	0.094
	Chemotherapy : 18 months	1.419 (-3.129, 5.966)	0.541
	Chemotherapy : 24 months	-0.242 (-5.164, 4.681)	0.923
Baseline		0.500 (0.430, 0.569)	<0.001

Abbreviations: CI: confidence interval.

Supplementary table 3.7 – Mean (SD) scores for the EORTC QLQ-BR23 scale at each time point in chemotherapy versus no chemotherapy cohorts with adjusted mean difference (95% CI) and p-value.

Domain	Time point		Chemotherapy	No chemotherapy	Adjusted mean difference (95% CI)	P-value
Body image	Baseline	n	280	746	-	-
		Mean (SD)	92.7 (13.8)	92.5 (14.8)		
	6 weeks	n	260	685	-0.81 (-3.58, 1.96)	0.565
		Mean (SD)	86.5 (20.8)	86.6 (20.1)		
	6 months	n	244	640	-11.18 (-14.43, -7.94)	<0.001
		Mean (SD)	73.3 (26.0)	84.5 (23.0)		
	12 months	n	224	547	-3.73 (-6.93, -0.52)	0.023
		Mean (SD)	81.8 (22.4)	85.3 (21.3)		
	18 months	n	190	460	-1.59 (-5.19, 2.01)	0.386
		Mean (SD)	84.0 (23.0)	86.1 (21.3)		
	24 months	n	155	397	-1.35 (-5.33, 2.63)	0.506
		Mean (SD)	83.0 (22.7)	84.8 (22.1)		
Sexual functioning	Baseline	n	248	644	-	-
		Mean (SD)	9.2 (18.1)	7.9 (17.6)		
	6 weeks	n	234	569	0.95 (-0.84, 2.74)	0.296
		Mean (SD)	6.1 (13.7)	5.3 (13.3)		
	6 months	n	212	543	-2.57 (-4.60, -0.54)	0.013
		Mean (SD)	4.4 (12.5)	7.2 (16.0)		
	12 months	n	198	465	0.85 (-1.32, 3.03)	0.442
		Mean (SD)	8.0 (16.1)	7.2 (15.8)		
	18 months	n	164	392	2.11 (-0.50, 4.72)	0.113
		Mean (SD)	8.4 (16.4)	7.5 (16.2)		
	24 months	n	129	338	-0.14 (-2.94, 2.67)	0.924
		Mean (SD)	7.4 (15.4)	8.4 (16.8)		

Domain	Time point		Chemotherapy	No chemotherapy	Adjusted mean difference (95% CI)	P-value
Sexual enjoyment	Baseline	n	42	76	-	-
		Mean (SD)	61.1 (28.4)	61.4 (30.8)		
	6 weeks	n	30	55	1.41 (-11.23, 14.05)	0.823
		Mean (SD)	50.0 (30.0)	59.4 (29.9)		
	6 months	n	17	59	-5.19 (-22.01, 11.64)	0.538
		Mean (SD)	49.0 (31.4)	60.5 (26.6)		
	12 months	n	31	61	-8.82 (-22.57, 4.93)	0.203
		Mean (SD)	50.5 (27.0)	59.6 (30.5)		
	18 months	n	30	48	-8.67 (-26.09, 8.74)	0.32
		Mean (SD)	42.2 (26.2)	59.0 (25.9)		
	24 months	n	17	54	1.48 (-14.42, 17.38)	0.852
		Mean (SD)	58.8 (32.3)	61.1 (26.5)		
Future perspective	Baseline	n	280	747	-	-
		Mean (SD)	66.4 (26.9)	66.0 (27.8)		
	6 weeks	n	260	685	-7.20 (-10.72, -3.68)	<0.001
		Mean (SD)	59.1 (27.6)	66.4 (27.2)		
	6 months	n	243	641	-7.54 (-11.28, -3.80)	<0.001
		Mean (SD)	58.6 (27.5)	66.7 (27.3)		
	12 months	n	222	547	-4.96 (-8.89, -1.03)	0.013
		Mean (SD)	63.1 (28.1)	67.8 (26.6)		
	18 months	n	190	459	-4.97 (-9.37, -0.57)	0.027
		Mean (SD)	63.2 (27.0)	68.4 (27.6)		
	24 months	n	154	397	-3.13 (-7.98, 1.72)	0.205
		Mean (SD)	63.9 (28.3)	66.8 (27.1)		
Systemic therapy side effects	Baseline	n	284	765	-	-
		Mean (SD)	9.1 (10.0)	9.5 (10.6)		

Domain	Time point		Chemotherapy	No chemotherapy	Adjusted mean difference (95% CI)	P-value
	6 weeks	n	260	690	3.04 (1.47, 4.61)	<0.001
		Mean (SD)	14.8 (15.0)	12.4 (12.2)		
	6 months	n	246	648	16.97 (15.00, 18.94)	<0.001
		Mean (SD)	31.9 (18.5)	15.7 (13.2)		
	12 months	n	225	549	3.32 (1.41, 5.22)	0.001
		Mean (SD)	18.0 (15.5)	15.7 (13.8)		
	18 months	n	191	463	0.53 (-1.43, 2.49)	0.593
		Mean (SD)	15.9 (14.6)	15.3 (13.6)		
	24 months	n	155	398	-0.98 (-3.11, 1.15)	0.368
		Mean (SD)	14.5 (12.9)	16.0 (14.8)		
Breast symptoms	Baseline	n	276	747	-	-
		Mean (SD)	12.4 (13.9)	11.3 (13.6)		
	6 weeks	n	258	689	-0.80 (-3.46, 1.85)	0.553
		Mean (SD)	22.2 (19.0)	22.7 (18.7)		
	6 months	n	241	638	0.07 (-2.23, 2.37)	0.951
		Mean (SD)	15.5 (16.3)	15.2 (15.2)		
	12 months	n	224	537	1.47 (-0.72, 3.66)	0.188
		Mean (SD)	14.2 (13.8)	13.0 (14.2)		
	18 months	n	190	453	1.07 (-1.49, 3.64)	0.412
		Mean (SD)	13.3 (15.3)	11.8 (14.9)		
	24 months	n	154	397	1.03 (-1.51, 3.56)	0.426
		Mean (SD)	12.4 (14.1)	10.8 (13.4)		
Arm symptoms	Baseline	n	276	748	-	-
		Mean (SD)	8.3 (14.1)	9.3 (15.1)		
	6 weeks	n	259	685	-0.32 (-3.03, 2.39)	0.819
		Mean (SD)	17.4 (19.0)	18.8 (19.9)		

Domain	Time point		Chemotherapy	No chemotherapy	Adjusted mean difference (95% CI)	P-value
	6 months	n	240	638	-1.95 (-4.55, 0.64)	0.14
		Mean (SD)	12.8 (16.6)	15.7 (18.3)		
	12 months	n	225	537	4.94 (2.18, 7.69)	<0.001
		Mean (SD)	18.5 (19.8)	14.6 (17.5)		
	18 months	n	190	453	3.27 (0.01, 6.54)	0.049
		Mean (SD)	19.5 (23.0)	16.0 (19.1)		
	24 months	n	153	399	4.02 (0.13, 7.90)	0.043
		Mean (SD)	19.3 (22.5)	16.2 (21.3)		
Upset by hair loss	Baseline	n	19	60	-	-
		Mean (SD)	33.3 (29.4)	31.7 (30.3)		
	6 weeks	n	43	64	9.92 (-22.58, 42.42)	0.538
		Mean (SD)	45.0 (33.2)	29.7 (27.3)		
	6 months	n	180	150	-7.58 (-30.35, 15.19)	0.505
		Mean (SD)	45.9 (35.1)	32.2 (32.4)		
	12 months	n	38	141	-10.35 (-55.00, 34.31)	0.639
		Mean (SD)	50.9 (37.0)	32.4 (31.1)		
	18 months	n	36	108	-29.87 (-65.77, 6.03)	0.098
		Mean (SD)	35.2 (34.7)	35.2 (31.5)		
	24 months	n	35	96	-5.05 (-35.78, 25.69)	0.73
		Mean (SD)	38.1 (36.3)	34.4 (30.8)		

Abbreviations: SD: standard deviation; CI: confidence interval.

Supplementary table 3.8 – Mean (SD) scores for the EORTC QLQ-ELD15 scale at each timepoint in chemotherapy versus no chemotherapy cohorts with adjusted mean differences and p-values.

Domain	Time point		Chemotherapy	No chemotherapy	Adjusted mean difference (95% CI)	P-value
Mobility	Baseline	n	283	765	-	-
		Mean (SD)	12.0 (19.6)	17.0 (23.1)		
	6 weeks	n	263	689	-0.99 (-3.26, 1.27)	0.389
		Mean (SD)	19.1 (21.2)	24.6 (24.1)		
	6 months	n	241	640	9.82 (6.87, 12.78)	<0.001
		Mean (SD)	30.5 (26.5)	25.3 (25.4)		
	12 months	n	226	547	2.20 (-0.88, 5.27)	0.161
		Mean (SD)	25.0 (24.6)	27.6 (27.2)		
	18 months	n	190	455	-0.21 (-3.62, 3.20)	0.905
		Mean (SD)	25.6 (25.3)	27.7 (26.8)		
	24 months	n	153	399	-0.57 (-4.59, 3.45)	0.782
		Mean (SD)	27.2 (26.0)	30.2 (28.0)		
Worries about others	Baseline	n	280	755	-	-
		Mean (SD)	45.4 (31.0)	41.9 (30.7)		
	6 weeks	n	263	685	5.31 (1.55, 9.07)	0.006
		Mean (SD)	46.8 (29.4)	39.1 (30.7)		
	6 months	n	240	635	6.19 (2.44, 9.95)	0.001
		Mean (SD)	41.1 (29.1)	34.4 (29.3)		
	12 months	n	226	540	4.47 (0.42, 8.52)	0.031
		Mean (SD)	38.1 (28.4)	33.3 (28.8)		
	18 months	n	190	452	3.17 (-1.30, 7.64)	0.164
		Mean (SD)	35.2 (29.7)	31.7 (28.6)		
	24 months	n	152	392	4.41 (-0.24, 9.05)	0.063
		Mean (SD)	36.1 (28.3)	31.7 (26.4)		

Domain	Time point		Chemotherapy	No chemotherapy	Adjusted mean difference (95% CI)	P-value
Worries	Baseline	n	283	757	-	-
		Mean (SD)	37.1 (27.7)	36.5 (26.9)		
	6 weeks	n	264	686	4.09 (0.92, 7.27)	0.011
		Mean (SD)	40.7 (27.4)	35.4 (27.0)		
	6 months	n	241	639	4.18 (0.89, 7.46)	0.013
		Mean (SD)	39.1 (26.6)	34.0 (27.0)		
	12 months	n	226	545	0.01 (-3.57, 3.60)	0.995
		Mean (SD)	34.8 (26.1)	34.6 (26.8)		
	18 months	n	190	454	0.86 (-3.09, 4.80)	0.67
		Mean (SD)	34.5 (24.5)	32.8 (27.2)		
	24 months	n	153	395	0.78 (-3.62, 5.17)	0.729
		Mean (SD)	34.9 (25.5)	34.2 (26.4)		
Maintaining purpose	Baseline	n	283	758	-	-
		Mean (SD)	68.5 (35.0)	64.4 (33.6)		
	6 weeks	n	264	687	0.37 (-4.03, 4.77)	0.87
		Mean (SD)	63.6 (30.2)	62.7 (31.9)		
	6 months	n	241	640	0.71 (-4.09, 5.51)	0.773
		Mean (SD)	64.2 (29.1)	61.8 (33.4)		
	12 months	n	224	544	-0.16 (-5.14, 4.82)	0.95
		Mean (SD)	64.4 (33.4)	63.9 (31.5)		
	18 months	n	190	454	2.90 (-2.66, 8.46)	0.306
		Mean (SD)	65.3 (32.9)	62.0 (32.0)		
	24 months	n	153	398	1.29 (-4.49, 7.08)	0.661
		Mean (SD)	64.6 (29.3)	62.3 (31.8)		
Burden of illness	Baseline	n	281	753	-	-
		Mean (SD)	20.2 (23.1)	20.4 (23.4)		

Domain	Time point		Chemotherapy	No chemotherapy	Adjusted mean difference (95% CI)	P-value
	6 weeks	n	263	688	4.68 (1.25, 8.11)	0.007
		Mean (SD)	35.8 (26.1)	31.8 (24.9)		
	6 months	n	242	641	21.60 (17.82, 25.39)	<0.001
		Mean (SD)	48.9 (28.5)	28.2 (25.3)		
	12 months	n	225	541	15.21 (11.30, 19.12)	<0.001
		Mean (SD)	38.6 (27.0)	24.5 (24.6)		
	18 months	n	190	455	12.99 (8.81, 17.17)	<0.001
		Mean (SD)	34.3 (26.0)	22.0 (24.5)		
	24 months	n	153	397	8.80 (3.93, 13.66)	<0.001
		Mean (SD)	33.3 (25.6)	24.6 (26.9)		
Joint stiffness	Baseline	n	282	759	-	-
		Mean (SD)	25.4 (27.9)	27.1 (28.1)		
	6 weeks	n	262	686	-2.80 (-5.92, 0.33)	0.079
		Mean (SD)	22.4 (26.9)	27.0 (27.7)		
	6 months	n	237	639	-0.91 (-4.89, 3.06)	0.652
		Mean (SD)	36.1 (30.9)	38.6 (29.7)		
	12 months	n	225	543	1.46 (-2.57, 5.50)	0.476
		Mean (SD)	42.2 (29.0)	42.4 (29.4)		
	18 months	n	189	453	4.05 (-0.28, 8.38)	0.067
		Mean (SD)	46.4 (28.0)	41.6 (28.9)		
	24 months	n	151	396	0.17 (-4.81, 5.16)	0.946
		Mean (SD)	43.9 (29.7)	44.0 (30.5)		
Family support	Baseline	n	278	751	-	-
		Mean (SD)	77.9 (31.8)	74.6 (32.0)		
	6 weeks	n	263	681	6.21 (2.26, 10.17)	0.002
		Mean (SD)	81.2 (25.9)	73.2 (30.5)		

Domain	Time point		Chemotherapy	No chemotherapy	Adjusted mean difference (95% CI)	P-value
	6 months	n	237	634	4.91 (0.26, 9.56)	0.038
		Mean (SD)	76.7 (29.3)	69.6 (32.6)		
	12 months	n	224	531	5.43 (0.39, 10.46)	0.035
		Mean (SD)	71.4 (30.7)	64.3 (34.4)		
	18 months	n	186	444	1.48 (-4.32, 7.29)	0.616
		Mean (SD)	66.0 (34.7)	63.2 (33.6)		
	24 months	n	149	385	-0.73 (-7.13, 5.67)	0.822
		Mean (SD)	62.4 (33.4)	60.5 (34.2)		

Abbreviations: SD: standard deviation; CI: confidence interval.

Supplementary table 3.9 – Mean scores and 95% confidence intervals (CIs) adjusted for baseline score for the EQ-5D-5L scale at each timepoint in chemotherapy versus no chemotherapy cohorts.

Domain	Time point		Chemotherapy	No chemotherapy	Adjusted mean difference (95% CI)	P-value
Score	Baseline	n	335	980	-	-
		Mean (SD)	0.8769 (0.1327)	0.8693 (0.1489)		
	6 weeks	n	299	807	0.0130 (-0.0030, 0.0289)	0.112
		Mean (SD)	0.8409 (0.1414)	0.8242 (0.1572)	-0.0028 (-0.0231, 0.0175)	
	6 months	n	279	760	-0.0013 (-0.0228, 0.0201)	0.789
		Mean (SD)	0.8247 (0.1767)	0.8241 (0.1721)	0.0114 (-0.0143, 0.0372)	
	12 months	n	261	659	0.0001 (-0.0286, 0.0288)	0.903
		Mean (SD)	0.8274 (0.1639)	0.8185 (0.1753)	0.0130 (-0.0030, 0.0289)	
	18 months	n	224	556	-0.0028 (-0.0231, 0.0175)	0.384
		Mean (SD)	0.8186 (0.1937)	0.8088 (0.1910)	-0.0013 (-0.0228, 0.0201)	
	24 months	n	185	474	0.0114 (-0.0143, 0.0372)	0.994
		Mean (SD)	0.8013 (0.1787)	0.8020 (0.1968)		
VAS	Baseline	n	324	951	-	-
		Mean (SD)	78.9 (16.3)	76.9 (16.6)		
	6 weeks	n	296	793	-1.44 (-3.52, 0.64)	0.176
		Mean (SD)	74.5 (17.4)	74.9 (17.0)		
	6 months	n	280	757	-6.57 (-8.74, -4.40)	<0.001
		Mean (SD)	70.1 (18.0)	75.3 (16.7)		
	12 months	n	256	656	0.72 (-1.60, 3.05)	0.541
		Mean (SD)	76.7 (15.8)	74.8 (17.6)		
	18 months	n	230	549	0.92 (-1.78, 3.63)	0.503

Domain	Time point		Chemotherapy	No chemotherapy	Adjusted mean difference (95% CI)	P-value
		Mean (SD)	74.9 (17.6)	73.6 (18.3)		
	24 months	n	185	479	1.48 (-1.41, 4.36)	0.315
		Mean (SD)	74.7 (16.3)	72.7 (18.2)		

Abbreviations: SD: standard deviation; CI: confidence interval.

Chapter 4

Supplementary table 4.1 - Postoperative tumour, patient and treatment characteristics by surgery type.

Variables	Categories	BCS	Mastectomy	Unknown	Total
		N = 1,669	N = 1,087	N = 55	N = 2,811
Age (years)	70-74	813 (48.7%)	342 (31.5%)	18 (32.7%)	1,173 (41.7%)
	75-79	521 (31.2%)	356 (32.7%)	22 (40.0%)	899 (32.0%)
	80-84	243 (14.5%)	253 (23.3%)	10 (18.2%)	506 (18.0%)
	≥85	92 (5.6%)	136 (12.5%)	5 (9.1%)	233 (8.3%)
Participation level	Full	1,277 (76.5%)	792 (72.9%)	42 (76.4%)	2,111 (75.1%)
	Partial	356 (21.3%)	253 (23.3%)	12 (21.8%)	621 (22.1%)
	Consultee	36 (2.2%)	42 (3.9%)	1 (1.8%)	79 (2.8%)
Laterality	Right	776 (46.5%)	501 (46.1%)	28 (50.9%)	1,305 (46.4%)
	Left	893 (53.5%)	586 (53.9%)	27 (49.1%)	1,506 (53.6%)
Tumour size (mm)	≤ 20	1,001 (60.0%)	278 (25.6%)	0 (0.0%)	1,279 (45.5%)
	21-50	641 (38.4%)	644 (59.2%)	0 (0.0%)	1,285 (45.7%)
	> 50	24 (1.4%)	163 (15.0%)	1 (1.8%)	188 (6.7%)
	Unknown	3 (0.2%)	2 (0.2%)	54 (98.2%)	59 (2.1%)
Nodal status	pN0	1,302 (78.0%)	610 (56.1%)	1 (1.8%)	1,913 (68.1%)
	pN1	302 (18.1%)	310 (28.5%)	0 (0.0%)	612 (21.8%)
	pN2	48 (2.9%)	99 (9.1%)	0 (0.0%)	147 (5.2%)
	pN3	13 (0.8%)	64 (5.9%)	0 (0.0%)	77 (2.7%)
	Unknown	4 (0.2%)	4 (0.4%)	54 (98.2%)	62 (2.2%)
Grade	1	306 (18.3%)	75 (6.9%)	0 (0.0%)	381 (13.6%)
	2	920 (55.1%)	565 (52.0%)	0 (0.0%)	1,485 (52.8%)

Variables	Categories	BCS	Mastectomy	Unknown	Total
		N = 1,669	N = 1,087	N = 55	N = 2,811
	3	427 (25.6%)	437 (40.2%)	1 (1.8%)	865 (30.8%)
	Unknown	16 (1.0%)	10 (0.9%)	54 (98.2%)	80 (2.8%)
Histology	Ductal carcinoma	1,133 (67.9%)	658 (60.5%)	24 (43.6%)	1,815 (64.6%)
	Lobular carcinoma	163 (9.8%)	202 (18.6%)	10 (18.2%)	375 (13.3%)
	Tubular carcinoma	27 (1.6%)	2 (0.2%)	0 (0.0%)	29 (1.0%)
	Mucinous carcinoma	47 (2.8%)	23 (2.1%)	1 (1.8%)	71 (2.5%)
	Other	162 (9.7%)	103 (9.5%)	1 (1.8%)	266 (9.5%)
	Unknown	137 (8.2%)	99 (9.1%)	19 (34.5%)	255 (9.1%)
ER status	Negative	167 (10.0%)	205 (18.9%)	0 (0.0%)	372 (13.2%)
	Positive	1,487 (89.1%)	866 (79.7%)	1 (1.8%)	2,354 (83.7%)
	Unknown	15 (0.9%)	16 (1.5%)	54 (98.2%)	85 (3.0%)
HER2 status	Negative	1,424 (85.3%)	847 (77.9%)	1 (1.8%)	2,272 (80.8%)
	Positive	146 (8.7%)	186 (17.1%)	0 (0.0%)	332 (11.8%)
	Inconclusive	16 (1.0%)	6 (0.6%)	0 (0.0%)	22 (0.8%)
	Unknown	83 (5.0%)	48 (4.4%)	54 (98.2%)	185 (6.6%)
ADL category	No dependency	1,203 (72.1%)	759 (69.8%)	42 (76.4%)	2,004 (71.3%)
	Mild dependency	184 (11.0%)	122 (11.2%)	2 (3.6%)	308 (11.0%)
	Moderate/severe dependency	152 (9.1%)	123 (11.3%)	3 (5.5%)	278 (9.9%)
	Unknown	130 (7.8%)	83 (7.6%)	8 (14.5%)	221 (7.9%)
IADL category	No dependency	1,269 (76.0%)	767 (70.6%)	33 (60.0%)	2,069 (73.6%)
	Mild dependency	134 (8.0%)	108 (9.9%)	7 (12.7%)	249 (8.9%)
	Moderate/severe dependency	128 (7.7%)	122 (11.2%)	8 (14.5%)	258 (9.2%)
	Unknown	138 (8.3%)	90 (8.3%)	7 (12.7%)	235 (8.4%)

Variables	Categories	BCS	Mastectomy	Unknown	Total
		N = 1,669	N = 1,087	N = 55	N = 2,811
MMSE category	Normal function	1,498 (89.8%)	945 (86.9%)	51 (92.7%)	2,494 (88.7%)
	Mild impairment	135 (8.1%)	111 (10.2%)	2 (3.6%)	248 (8.8%)
	Moderate impairment	19 (1.1%)	16 (1.5%)	1 (1.8%)	36 (1.3%)
	Severe impairment	17 (1.0%)	15 (1.4%)	1 (1.8%)	33 (1.2%)
aPG-SGA category	Low	1,310 (78.5%)	834 (76.7%)	36 (65.5%)	2,180 (77.6%)
	Moderate	159 (9.5%)	122 (11.2%)	7 (12.7%)	288 (10.2%)
	High	27 (1.6%)	13 (1.2%)	0 (0.0%)	40 (1.4%)
	Unknown	173 (10.4%)	118 (10.9%)	12 (21.8%)	303 (10.8%)
ECOG PS	0	1,197 (71.7%)	717 (66.0%)	30 (54.5%)	1,944 (69.2%)
	1	332 (19.9%)	259 (23.8%)	16 (29.1%)	607 (21.6%)
	2	39 (2.3%)	38 (3.5%)	3 (5.5%)	80 (2.8%)
	3	15 (0.9%)	21 (1.9%)	0 (0.0%)	36 (1.3%)
	4	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)
	Unknown	86 (5.2%)	51 (4.7%)	6 (10.9%)	143 (5.1%)
Charlson comorbidity index (no age)	n	1,607	1,052	48	2,707
	Mean (SD)	1.00 (1.26)	1.05 (1.36)	1.58 (1.32)	1.03 (1.30)
	Median (IQR)	1.00 (0.00, 2.00)	0.00 (0.00, 2.00)	2.00 (1.00, 2.00)	1.00 (0.00, 2.00)
	Min, Max	0, 9	0, 9	0, 6	0, 9
Number of concurrent medications	n	1,447	961	38	2,446
	Mean (SD)	4.02 (2.63)	4.11 (2.66)	4.37 (2.55)	4.06 (2.64)
	Median (IQR)	4.00 (2.00, 6.00)	4.00 (2.00, 5.00)	4.00 (3.00, 5.75)	4.00 (2.00, 5.75)
	Min, Max	0, 15	0, 18	1, 13	0, 18
Axillary surgery	Axillary sampling	49 (2.9%)	37 (3.4%)	2 (3.6%)	88 (3.1%)

Variables	Categories	BCS	Mastectomy	Unknown	Total
		N = 1,669	N = 1,087	N = 55	N = 2,811
	Axillary clearance	113 (6.8%)	292 (26.9%)	9 (16.4%)	414 (14.7%)
	Sentinel lymph node biopsy	1329 (79.6%)	628 (57.8%)	23 (41.8%)	1,980 (70.4%)
	Internal mammary node biopsy	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)
	No axillary surgery	44 (2.6%)	34 (3.1%)	2 (3.6%)	80 (2.8%)
	Unknown	134 (8.0%)	95 (8.7%)	19 (34.5%)	248 (8.8%)
Chemotherapy use	Yes	186 (11.1%)	202 (18.6%)	9 (16.4%)	397 (14.1%)
	No	1,483 (88.9%)	885 (81.4%)	46 (83.6%)	2,414 (85.9%)
Radiotherapy use	Yes	1,385 (83.0%)	341 (31.4%)	27 (49.1%)	1,753 (62.4%)
	No	284 (17.0%)	746 (68.6%)	28 (50.9%)	1,058 (37.6%)

Abbreviations: ER: oestrogen receptor; HER2: human epidermal growth factor receptor; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ADL: activities of daily living; IADL: instrumental activities of daily living; aPG-SGA: abridged patient-generated subjective global assessment; MMSE: Mini Mental State Examination.

Supplementary table 4.2 – Postoperative tumour, patient and treatment characteristics by receipt of radiotherapy.

Variables	Categories	No radiotherapy	Radiotherapy	Total
		N = 1,058	N = 1,753	N = 2,811
Age (years)	70-74	374 (35.3%)	799 (45.6%)	1,173 (41.7%)
	75-79	318 (30.1%)	581 (33.1%)	899 (32.0%)
	80-84	225 (21.3%)	281 (16.1%)	506 (18.0%)
	≥85	141 (13.3%)	92 (5.2%)	233 (8.3%)
Participation level	Full	784 (74.1%)	1,327 (75.7%)	2,111 (75.1%)
	Partial	232 (21.9%)	389 (22.2%)	621 (22.1%)
	Consultee	42 (4.0%)	37 (2.1%)	79 (2.8%)
Main side	Right	487 (46.0%)	818 (46.7%)	1,305 (46.4%)
	Left	571 (54.0%)	935 (53.3%)	1,506 (53.6%)
Tumour size (mm)	≤ 20	432 (40.8%)	847 (48.3%)	1,279 (45.5%)
	21-50	530 (50.1%)	755 (43.1%)	1,285 (45.7%)
	> 50	66 (6.2%)	122 (7.0%)	188 (6.7%)
	Unknown	30 (2.8%)	29 (1.7%)	59 (2.1%)
Nodal status	pN0	764 (72.2%)	1,149 (65.5%)	1,913 (68.1%)
	pN1	204 (19.3%)	408 (23.3%)	612 (21.8%)
	pN2	36 (3.4%)	111 (6.3%)	147 (5.2%)
	pN3	21 (2.0%)	56 (3.2%)	77 (2.7%)
	Unknown	33 (3.1%)	29 (1.7%)	62 (2.2%)
Grade	Grade 1	147 (13.9%)	234 (13.3%)	381 (13.6%)
	Grade 2	540 (51.0%)	945 (53.9%)	1,485 (52.8%)
	Grade 3	331 (31.3%)	534 (30.5%)	865 (30.8%)

Variables	Categories	No radiotherapy	Radiotherapy	Total
		N = 1,058	N = 1,753	N = 2,811
	Unknown	40 (3.8%)	40 (2.3%)	80 (2.8%)
Histology	Ductal carcinoma	685 (64.7%)	1,130 (64.5%)	1,815 (64.6%)
	Lobular carcinoma	143 (13.5%)	232 (13.2%)	375 (13.3%)
	Tubular carcinoma	5 (0.5%)	24 (1.4%)	29 (1.0%)
	Mucinous carcinoma	34 (3.2%)	37 (2.1%)	71 (2.5%)
	Other	107 (10.1%)	159 (9.1%)	266 (9.5%)
	Unknown	84 (7.9%)	171 (9.8%)	255 (9.1%)
ER status	Negative	166 (15.7%)	206 (11.8%)	372 (13.2%)
	Positive	844 (79.8%)	1510 (86.1%)	2,354 (83.7%)
	Unknown	48 (4.5%)	37 (2.1%)	85 (3.0%)
HER2 status	Negative	816 (77.1%)	1,456 (83.1%)	2,272 (80.8%)
	Inconclusive	9 (0.9%)	13 (0.7%)	22 (0.8%)
	Positive	153 (14.5%)	179 (10.2%)	332 (11.8%)
	Unknown	80 (7.6%)	105 (6.0%)	185 (6.6%)
ADL category	No dependency	729 (68.9%)	1,275 (72.7%)	2,004 (71.3%)
	Mild dependency	125 (11.8%)	183 (10.4%)	308 (11.0%)
	Moderate/severe dependency	120 (11.3%)	158 (9.0%)	278 (9.9%)
	Unknown	84 (7.9%)	137 (7.8%)	221 (7.9%)
IADL category	No dependency	739 (69.8%)	1,330 (75.9%)	2,069 (73.6%)
	Mild dependency	104 (9.8%)	145 (8.3%)	249 (8.9%)
	Moderate/severe dependency	126 (11.9%)	132 (7.5%)	258 (9.2%)
	Unknown	89 (8.4%)	146 (8.3%)	235 (8.4%)
MMSE category	Normal function	907 (85.7%)	1,587 (90.5%)	2,494 (88.7%)

Variables	Categories	No radiotherapy	Radiotherapy	Total
		N = 1,058	N = 1,753	N = 2,811
	Mild impairment	112 (10.6%)	136 (7.8%)	248 (8.8%)
	Moderate impairment	15 (1.4%)	21 (1.2%)	36 (1.3%)
	Severe impairment	24 (2.3%)	9 (0.5%)	33 (1.2%)
aPG-SGA category	Low	805 (76.1%)	1,375 (78.4%)	2,180 (77.6%)
	Moderate	122 (11.5%)	166 (9.5%)	288 (10.2%)
	High	12 (1.1%)	28 (1.6%)	40 (1.4%)
	Unknown	119 (11.2%)	184 (10.5%)	303 (10.8%)
ECOG PS	0	675 (63.8%)	1,269 (72.4%)	1,944 (69.2%)
	1	270 (25.5%)	337 (19.2%)	607 (21.6%)
	2	42 (4.0%)	38 (2.2%)	80 (2.8%)
	3	18 (1.7%)	18 (1.0%)	36 (1.3%)
	4	1 (0.1%)	0 (0.0%)	1 (0.0%)
	Unknown	52 (4.9%)	91 (5.2%)	143 (5.1%)
Charlson comorbidity index (no age)	n	1,021	1,686	2,707
	Mean (SD)	1.06 (1.29)	1.02 (1.31)	1.03 (1.30)
	Median (IQR)	1.00 (0.00, 2.00)	0.00 (0.00, 2.00)	1.00 (0.00, 2.00)
	Min, Max	0, 9	0, 9	0, 9
Number of concurrent medications	n	926	1,520	2,446
	Mean (SD)	4.12 (2.70)	4.03 (2.60)	4.06 (2.64)
	Median (IQR)	4.00 (2.00, 6.00)	4.00 (2.00, 5.00)	4.00 (2.00, 5.75)
	Min, Max	0, 18	0, 15	0, 18
Breast surgery	Breast-conserving surgery	284 (26.8%)	1,385 (79.1%)	1,669 (59.4%)
	Mastectomy	746 (70.5%)	341 (19.4%)	1,087 (38.7%)

Variables	Categories	No radiotherapy	Radiotherapy	Total
		N = 1,058	N = 1,753	N = 2,811
	Unknown	28 (2.7%)	27 (1.5%)	55 (1.9%)
Axillary surgery	Axillary sample	32 (3.0%)	56 (3.2%)	88 (3.1%)
	Axillary clearance	166 (15.7%)	248 (14.1%)	414 (14.7%)
	Sentinel lymph node biopsy	724 (68.4%)	1,256 (71.6%)	1,980 (70.4%)
	Internal mammary node biopsy	0 (0.0%)	1 (0.1%)	1 (0.0%)
	No axillary surgery	55 (5.2%)	25 (1.4%)	80 (2.8%)
	Unknown	81 (7.7%)	167 (9.5%)	248 (8.8%)
Chemotherapy	Chemotherapy	146 (13.8%)	251 (14.3%)	397 (14.1%)
	No chemotherapy	912 (86.2%)	1,502 (85.7%)	2,414 (85.9%)

Abbreviations: ER: oestrogen receptor; HER2: human epidermal growth factor receptor; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ADL: activities of daily living; IADL: instrumental activities of daily living; aPG-SGA: abridged patient-generated subjective global assessment; MMSE: Mini Mental State Examination.

Table 4.3 - Postoperative tumour, patient and treatment characteristics by age.

Variables	Categories	70-74	75-79	80-84	>=85	Total
		N = 1,173	N = 899	N = 506	N = 233	N = 2,811
Participation level	Full	926 (78.9%)	674 (75.0%)	368 (72.7%)	143 (61.4%)	2,111 (75.1%)
	Partial	225 (19.2%)	209 (23.2%)	123 (24.3%)	64 (27.5%)	621 (22.1%)
	Consultee	22 (1.9%)	16 (1.8%)	15 (3.0%)	26 (11.2%)	79 (2.8%)
Main side	Right	535 (45.6%)	418 (46.5%)	247 (48.8%)	105 (45.1%)	1,305 (46.4%)
	Left	638 (54.4%)	481 (53.5%)	259 (51.2%)	128 (54.9%)	1,506 (53.6%)
Tumour size (mm)	≤ 20	649 (55.3%)	371 (41.3%)	184 (36.4%)	75 (32.2%)	1,279 (45.5%)
	21-50	439 (37.4%)	439 (48.8%)	271 (53.6%)	136 (58.4%)	1,285 (45.7%)
	> 50	66 (5.6%)	66 (7.3%)	40 (7.9%)	16 (6.9%)	188 (6.7%)
	Unknown	19 (1.6%)	23 (2.6%)	11 (2.2%)	6 (2.6%)	59 (2.1%)
Tumour size (mm)	N	1154	876	495	227	2,752
	Mean (SD)	23.07 (17.68)	26.53 (16.19)	27.55 (15.40)	28.75 (15.74)	25.45 (16.79)
	Median (IQR)	19.00 (12.00, 28.00)	22.00 (16.00, 32.00)	25.00 (17.00, 35.00)	25.00 (19.00, 35.00)	21.00 (15.00, 31.00)
	Min, Max	0, 210	0, 155	0, 120	7, 120	0, 210
Nodal involvement	pN0	867 (73.9%)	573 (63.7%)	326 (64.4%)	147 (63.1%)	1,913 (68.1%)
	pN1	212 (18.1%)	223 (24.8%)	117 (23.1%)	60 (25.8%)	612 (21.8%)
	pN2	46 (3.9%)	54 (6.0%)	36 (7.1%)	11 (4.7%)	147 (5.2%)
	pN3	29 (2.5%)	24 (2.7%)	16 (3.2%)	8 (3.4%)	77 (2.7%)
	Unknown	19 (1.6%)	25 (2.8%)	11 (2.2%)	7 (3.0%)	62 (2.2%)
Grade	1	199 (17.0%)	110 (12.2%)	47 (9.3%)	25 (10.7%)	381 (13.6%)
	2	635 (54.1%)	482 (53.6%)	255 (50.4%)	113 (48.5%)	1,485 (52.8%)
	3	311 (26.5%)	278 (30.9%)	190 (37.5%)	86 (36.9%)	865 (30.8%)

Variables	Categories	70-74	75-79	80-84	>=85	Total
		N = 1,173	N = 899	N = 506	N = 233	N = 2,811
	Unknown	28 (2.4%)	29 (3.2%)	14 (2.8%)	9 (3.9%)	80 (2.8%)
Histology	Ductal carcinoma	761 (64.9%)	567 (63.1%)	341 (67.4%)	146 (62.7%)	1,815 (64.6%)
	Lobular carcinoma	164 (14.0%)	128 (14.2%)	58 (11.5%)	25 (10.7%)	375 (13.3%)
	Tubular carcinoma	21 (1.8%)	5 (0.6%)	3 (0.6%)	0 (0.0%)	29 (1.0%)
	Mucinous carcinoma	18 (1.5%)	28 (3.1%)	12 (2.4%)	13 (5.6%)	71 (2.5%)
	Other	110 (9.4%)	83 (9.2%)	53 (10.5%)	20 (8.6%)	266 (9.5%)
	Unknown	99 (8.4%)	88 (9.8%)	39 (7.7%)	29 (12.4%)	255 (9.1%)
ER status	Negative	141 (12.0%)	117 (13.0%)	74 (14.6%)	40 (17.2%)	372 (13.2%)
	Positive	1002 (85.4%)	753 (83.8%)	414 (81.8%)	185 (79.4%)	2,354 (83.7%)
	Unknown	30 (2.6%)	29 (3.2%)	18 (3.6%)	8 (3.4%)	85 (3.0%)
HER2 status	Negative	981 (83.6%)	724 (80.5%)	375 (74.1%)	192 (82.4%)	2,272 (80.8%)
	Positive	136 (11.6%)	115 (12.8%)	63 (12.5%)	18 (7.7%)	332 (11.8%)
	Inconclusive	9 (0.8%)	7 (0.8%)	4 (0.8%)	2 (0.9%)	22 (0.8%)
	Unknown	47 (4.0%)	53 (5.9%)	64 (12.6%)	21 (9.0%)	185 (6.6%)
ADL category	No dependency	924 (78.8%)	623 (69.3%)	331 (65.4%)	126 (54.1%)	2,004 (71.3%)
	Mild dependency	89 (7.6%)	109 (12.1%)	67 (13.2%)	43 (18.5%)	308 (11.0%)
	Moderate/severe dependency	70 (6.0%)	101 (11.2%)	60 (11.9%)	47 (20.2%)	278 (9.9%)
	Unknown	90 (7.7%)	66 (7.3%)	48 (9.5%)	17 (7.3%)	221 (7.9%)
IADL category	No dependency	955 (81.4%)	679 (75.5%)	332 (65.6%)	103 (44.2%)	2,069 (73.6%)
	Mild dependency	54 (4.6%)	78 (8.7%)	70 (13.8%)	47 (20.2%)	249 (8.9%)
	Moderate/severe dependency	67 (5.7%)	70 (7.8%)	55 (10.9%)	66 (28.3%)	258 (9.2%)
	Unknown	97 (8.3%)	72 (8.0%)	49 (9.7%)	17 (7.3%)	235 (8.4%)

Variables	Categories	70-74	75-79	80-84	>=85	Total
		N = 1,173	N = 899	N = 506	N = 233	N = 2,811
MMSE category	Normal function	1,059 (90.3%)	805 (89.5%)	444 (87.7%)	186 (79.8%)	2,494 (88.7%)
	Mild impairment	91 (7.8%)	74 (8.2%)	50 (9.9%)	33 (14.2%)	248 (8.8%)
	Moderate impairment	11 (0.9%)	12 (1.3%)	5 (1.0%)	8 (3.4%)	36 (1.3%)
	Severe	12 (1.0%)	8 (0.9%)	7 (1.4%)	6 (2.6%)	33 (1.2%)
aPG-SGA category	Low	929 (79.2%)	709 (78.9%)	370 (73.1%)	172 (73.8%)	2,180 (77.6%)
	Moderate	111 (9.5%)	88 (9.8%)	62 (12.3%)	27 (11.6%)	288 (10.2%)
	High	15 (1.3%)	13 (1.4%)	10 (2.0%)	2 (0.9%)	40 (1.4%)
	Unknown	118 (10.1%)	89 (9.9%)	64 (12.6%)	32 (13.7%)	303 (10.8%)
ECOG PS	0	930 (79.3%)	619 (68.9%)	305 (60.3%)	90 (38.6%)	1,944 (69.2%)
	1	151 (12.9%)	205 (22.8%)	142 (28.1%)	109 (46.8%)	607 (21.6%)
	2	21 (1.8%)	24 (2.7%)	23 (4.5%)	12 (5.2%)	80 (2.8%)
	3	10 (0.9%)	9 (1.0%)	8 (1.6%)	9 (3.9%)	36 (1.3%)
	4	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
	Unknown	60 (5.1%)	42 (4.7%)	28 (5.5%)	13 (5.6%)	143 (5.1%)
Charlson comorbidity index (no age)	N	1133	869	481	224	2,707
	Mean (SD)	0.90 (1.21)	1.10 (1.36)	1.19 (1.37)	1.09 (1.30)	1.03 (1.30)
	Median (IQR)	0.00 (0.00, 2.00)	1.00 (0.00, 2.00)	1.00 (0.00, 2.00)	1.00 (0.00, 2.00)	1.00 (0.00, 2.00)
	Min, Max	0, 6	0, 9	0, 9	0, 6	0, 9
Number of concurrent medications	N	973	801	462	210	2,446
	Mean (SD)	3.85 (2.66)	4.16 (2.63)	4.26 (2.63)	4.21 (2.53)	4.06 (2.64)
	Median (IQR)	3.00 (2.00, 5.00)	4.00 (2.00, 6.00)	4.00 (2.00, 6.00)	4.00 (2.00, 6.00)	4.00 (2.00, 5.75)
	Min, Max	0, 14	0, 18	0, 14	0, 14	0, 18

Variables	Categories	70-74	75-79	80-84	>=85	Total
		N = 1,173	N = 899	N = 506	N = 233	N = 2,811
Surgery type	Mastectomy	342 (29.2%)	356 (39.6%)	253 (50.0%)	136 (58.4%)	1,087 (38.7%)
	Breast conservation	813 (69.3%)	521 (58.0%)	243 (48.0%)	92 (39.5%)	1,669 (59.4%)
	Unknown	18 (1.5%)	22 (2.4%)	10 (2.0%)	5 (2.1%)	55 (2.0%)
Axillary surgery	Axillary sampling	38 (3.2%)	30 (3.3%)	11 (2.2%)	9 (3.9%)	88 (3.1%)
	Axillary clearance	134 (11.4%)	134 (14.9%)	99 (19.6%)	47 (20.2%)	414 (14.7%)
	Sentinel lymph node biopsy	881 (75.1%)	633 (70.4%)	336 (66.4%)	130 (55.8%)	1,980 (70.4%)
	Internal mammary node biopsy	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
	No axillary surgery	23 (2.0%)	16 (1.8%)	22 (4.3%)	19 (8.2%)	80 (2.8%)
	Unknown	97 (8.3%)	85 (9.5%)	38 (7.5%)	28 (12.0%)	248 (8.8%)
Chemotherapy use	Yes	256 (21.8%)	120 (13.3%)	20 (4.0%)	1 (0.4%)	397 (14.1%)
	No	917 (78.2%)	779 (86.7%)	486 (96.0%)	232 (99.6%)	2,414 (85.9%)
Radiotherapy use	Yes	799 (68.1%)	581 (64.6%)	281 (55.5%)	92 (39.5%)	1,753 (62.4%)
	No	374 (31.9%)	318 (35.4%)	225 (44.5%)	141 (60.5%)	1,058 (37.6%)

Abbreviations: ER: oestrogen receptor; HER2: human epidermal growth factor receptor; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ADL: activities of daily living; IADL: instrumental activities of daily living; aPG-SGA: abridged patient-generated subjective global assessment; MMSE: Mini Mental State Examination.

Supplementary table 4.4 – Radiotherapy details by treatment side for all women whose primary treatment was breast-conserving surgery.

BREAST-CONSERVING SURGERY COHORT			
Site		Left	Right
		N = 741	N = 666
Breast		733 (98.9%)	663 (99.5%)
Breast fractions	n	728	658
	Mean (SD)	14.99 (2.39)	14.99 (2.74)
	Median (IQR)	15.00 (15.00, 15.00)	15.00 (15.00, 15.00)
	Min, Max	1, 40	1, 40
Axilla		38 (5.1%)	24 (3.6%)
Axilla fractions	n	37	24
	Mean (SD)	14.54 (2.73)	14.08 (3.16)
	Median (IQR)	15.00 (15.00, 15.00)	15.00 (15.00, 15.00)
	Min, Max	5, 20	2, 15
Supraclavicular fossa		54 (7.3%)	38 (5.7%)
Supraclavicular fossa fractions	n	53	37
	Mean (SD)	14.81 (2.54)	14.35 (2.57)
	Median (IQR)	15.00 (15.00, 15.00)	15.00 (15.00, 15.00)
	Min, Max	5, 25	2, 15
Chest wall		6 (0.8%)	5 (0.8%)
Chest wall fractions	n	5	5
	Mean (SD)	11.00 (5.48)	11.00 (5.48)
	Median (IQR)	15.00 (5.00, 15.00)	15.00 (5.00, 15.00)
	Min, Max	5, 15	5, 15

Other		18 (2.4%)	15 (2.3%)
Other fractions	n	18	15
	Mean (SD)	6.78 (3.66)	7.20 (3.55)
	Median (IQR)	5.00 (5.00, 7.25)	5.00 (5.00, 8.00)
	Min, Max	3, 16	3, 15
MASTECTOMY COHORT			
Site		Left	Right
		N = 192	N = 148
Breast		48 (25.0%)	43 (29.1%)
Breast fractions[1]	n	48	43
	Mean (SD)	15.33 (1.23)	15.58 (2.49)
	Median (IQR)	15.00 (15.00, 15.00)	15.00 (15.00, 15.00)
	Min, Max	15, 20	15, 30
Axilla		41 (21.4%)	27 (18.2%)
Axilla fractions	n	41	27
	Mean (SD)	15.51 (1.87)	15.52 (2.14)
	Median (IQR)	15.00 (15.00, 15.00)	15.00 (15.00, 15.00)
	Min, Max	15, 25	14, 25
Supraclavicular fossa		83 (43.2%)	70 (47.3%)
Supraclavicular fossa fractions	n	83	67
	Mean (SD)	15.31 (2.57)	15.51 (1.78)
	Median (IQR)	15.00 (15.00, 15.00)	15.00 (15.00, 15.00)
	Min, Max	4, 25	14, 25

[1] This category in the mastectomy cohort includes radiotherapy given to contralateral breast for patients with bilateral breast cancer.

Chest wall		145 (75.5%)	102 (68.9%)
Chest wall fractions	n	145	100
	Mean (SD)	15.14 (2.60)	15.35 (2.24)
	Median (IQR)	15.00 (15.00, 15.00)	15.00 (15.00, 15.00)
	Min, Max	2, 30	5, 25
Other		6 (3.1%)	6 (4.1%)
Other fractions	n	6	6
	Mean (SD)	15.67 (6.98)	15.00 (6.32)
	Median (IQR)	15.00 (15.00, 18.75)	15.00 (15.00, 15.00)
	Min, Max	4, 25	5, 25

Abbreviations: SD: standard deviation; IQR: interquartile range.

Supplementary table 4.5 – Radiotherapy use by site.

Site ID	Availability of radiotherapy on site	n/N (%)
1	No	10/11 (90.9%)
2	Yes	37/41 (90.2%)
3	Yes	66/78 (84.6%)
4	No	21/25 (84.0%)
5	Yes	28/34 (82.4%)
6	No	13/16 (81.2%)
7	Yes	92/117 (78.6%)
8	Yes	29/37 (78.4%)
9	No	42/54 (77.8%)
10	No	37/49 (75.5%)
11	Yes	66/88 (75.0%)
12	No	38/51 (74.5%)
13	Yes	62/85 (72.9%)
14	Yes	72/101 (71.3%)
15	Yes	27/38 (71.1%)
16	No	12/17 (70.6%)
17	No	7/10 (70.0%)
18	No	18/26 (69.2%)
19	No	33/48 (68.8%)
20	No	16/24 (66.7%)
21	No	26/39 (66.7%)
22	No	34/52 (65.4%)
23	No	43/66 (65.2%)

Site ID	Availability of radiotherapy on site	n/N (%)
24	No	48/74 (64.9%)
25	No	14/22 (63.6%)
26	No	44/71 (62.0%)
27	Yes	13/21 (61.9%)
28	No	35/57 (61.4%)
29	Yes	92/153 (60.1%)
30	No	15/25 (60.0%)
31	Yes	3/5 (60.0%)
32	No	77/132 (58.3%)
33	No	90/155 (58.1%)
34	No	8/14 (57.1%)
35	No	25/44 (56.8%)
36	Yes	108/192 (56.2%)
37	Yes	46/82 (56.1%)
38	No	54/98 (55.1%)
39	No	18/33 (54.5%)
40	Yes	6/11 (54.5%)
41	Yes	13/24 (54.2%)
42	Yes	13/24 (54.2%)
43	Yes	23/44 (52.3%)
44	No	29/57 (50.9%)
45	No	3/6 (50.0%)
46	Yes	3/6 (50.0%)
47	No	14/28 (50.0%)

Site ID	Availability of radiotherapy on site	n/N (%)
48	No	38/78 (48.7%)
49	No	25/57 (43.9%)
50	No	9/21 (42.9%)
51	No	7/17 (41.2%)
52	No	15/37 (40.5%)
53	No	3/8 (37.5%)
54	No	19/54 (35.2%)
55	Yes	11/37 (29.7%)
56	No	3/17 (17.6%)

Supplementary table 4.6 – Completion of the quality of life questionnaires at each time point for patients undergoing breast-conserving surgery or mastectomy.

BREAST-CONSERVING SURGERY COHORT				
Questionnaires		No radiotherapy	Radiotherapy	Total
		N = 210	N = 915	N = 1,125
EORTC-QLQ-C30				
Baseline	All	181 (86.2%)	823 (89.9%)	1,004 (89.2%)
	Some	8 (3.8%)	40 (4.4%)	48 (4.3%)
	None	21 (10.0%)	52 (5.7%)	73 (6.5%)
6 weeks	All	157 (74.8%)	758 (82.8%)	915 (81.3%)
	Some	7 (3.3%)	44 (4.8%)	51 (4.5%)
	None	46 (21.9%)	113 (12.3%)	159 (14.1%)
6 months	All	134 (63.8%)	728 (79.6%)	862 (76.6%)
	Some	8 (3.8%)	33 (3.6%)	41 (3.6%)
	None	68 (32.4%)	154 (16.8%)	222 (19.7%)
12 months	All	114 (54.3%)	646 (70.6%)	760 (67.6%)
	Some	11 (5.2%)	33 (3.6%)	44 (3.9%)
	None	85 (40.5%)	236 (25.8%)	321 (28.5%)
18 months	All	101 (48.1%)	531 (58.0%)	632 (56.2%)
	Some	7 (3.3%)	35 (3.8%)	42 (3.7%)
	None	102 (48.6%)	349 (38.1%)	451 (40.1%)
24 months	All	83 (39.5%)	472 (51.6%)	555 (49.3%)
	Some	6 (2.9%)	24 (2.6%)	30 (2.7%)
	None	121 (57.6%)	419 (45.8%)	540 (48.0%)

EORTC-QLQ-BR23				
Baseline	All	0 (0.0%)	8 (0.9%)	8 (0.7%)
	Some	188 (89.5%)	854 (93.3%)	1,042 (92.6%)
	None	22 (10.5%)	53 (5.8%)	75 (6.7%)
6 weeks	All	0 (0.0%)	8 (0.9%)	8 (0.7%)
	Some	164 (78.1%)	789 (86.2%)	953 (84.7%)
	None	46 (21.9%)	118 (12.9%)	164 (14.6%)
6 months	All	7 (3.3%)	22 (2.4%)	29 (2.6%)
	Some	133 (63.3%)	733 (80.1%)	866 (77.0%)
	None	70 (33.3%)	160 (17.5%)	230 (20.4%)
12 months	All	7 (3.3%)	27 (3.0%)	34 (3.0%)
	Some	118 (56.2%)	650 (71.0%)	768 (68.3%)
	None	85 (40.5%)	238 (26.0%)	323 (28.7%)
18 months	All	5 (2.4%)	16 (1.7%)	21 (1.9%)
	Some	102 (48.6%)	548 (59.9%)	650 (57.8%)
	None	103 (49.0%)	351 (38.4%)	454 (40.4%)
24 months	All	2 (1.0%)	26 (2.8%)	28 (2.5%)
	Some	87 (41.4%)	472 (51.6%)	559 (49.7%)
	None	121 (57.6%)	417 (45.6%)	538 (47.8%)
EORTC-QLQ-ELD15				
Baseline	All	182 (86.7%)	820 (89.6%)	1,002 (89.1%)
	Some	6 (2.9%)	36 (3.9%)	42 (3.7%)
	None	22 (10.5%)	59 (6.4%)	81 (7.2%)
6 weeks	All	161 (76.7%)	777 (84.9%)	938 (83.4%)
	Some	1 (0.5%)	16 (1.7%)	17 (1.5%)

	None	48 (22.9%)	122 (13.3%)	170 (15.1%)
6 months	All	134 (63.8%)	715 (78.1%)	849 (75.5%)
	Some	7 (3.3%)	29 (3.2%)	36 (3.2%)
	None	69 (32.9%)	171 (18.7%)	240 (21.3%)
12 months	All	119 (56.7%)	646 (70.6%)	765 (68.0%)
	Some	5 (2.4%)	27 (3.0%)	32 (2.8%)
	None	86 (41.0%)	242 (26.4%)	328 (29.2%)
18 months	All	101 (48.1%)	531 (58.0%)	632 (56.2%)
	Some	5 (2.4%)	23 (2.5%)	28 (2.5%)
	None	104 (49.5%)	361 (39.5%)	465 (41.3%)
24 months	All	88 (41.9%)	473 (51.7%)	561 (49.9%)
	Some	0 (0.0%)	18 (2.0%)	18 (1.6%)
	None	122 (58.1%)	424 (46.3%)	546 (48.5%)
MASTECTOMY COHORT				
Questionnaires		No radiotherapy	Radiotherapy	Total
		N = 459	N = 169	N = 628
EORTC-QLQ-C30				
Baseline	All	416 (90.6%)	151 (89.3%)	567 (90.3%)
	Some	19 (4.1%)	7 (4.1%)	26 (4.1%)
	None	24 (5.2%)	11 (6.5%)	35 (5.6%)
6 weeks	All	384 (83.7%)	130 (76.9%)	514 (81.8%)
	Some	18 (3.9%)	5 (3.0%)	23 (3.7%)
	None	57 (12.4%)	34 (20.1%)	91 (14.5%)
6 months	All	354 (77.1%)	129 (76.3%)	483 (76.9%)
	Some	19 (4.1%)	7 (4.1%)	26 (4.1%)

	None	86 (18.7%)	33 (19.5%)	119 (18.9%)
12 months	All	285 (62.1%)	98 (58.0%)	383 (61.0%)
	Some	22 (4.8%)	9 (5.3%)	31 (4.9%)
	None	152 (33.1%)	62 (36.7%)	214 (34.1%)
18 months	All	237 (51.6%)	78 (46.2%)	315 (50.2%)
	Some	13 (2.8%)	11 (6.5%)	24 (3.8%)
	None	209 (45.5%)	80 (47.3%)	289 (46.0%)
24 months	All	204 (44.4%)	80 (47.3%)	284 (45.2%)
	Some	10 (2.2%)	6 (3.6%)	16 (2.5%)
	None	245 (53.4%)	83 (49.1%)	328 (52.2%)
EORTC-QLQ-BR23				
Baseline	All	2 (0.4%)	1 (0.6%)	3 (0.5%)
	Some	430 (93.7%)	158 (93.5%)	588 (93.6%)
	None	27 (5.9%)	10 (5.9%)	37 (5.9%)
6 weeks	All	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Some	403 (87.8%)	134 (79.3%)	537 (85.5%)
	None	56 (12.2%)	35 (20.7%)	91 (14.5%)
6 months	All	3 (0.7%)	3 (1.8%)	6 (1.0%)
	Some	368 (80.2%)	132 (78.1%)	500 (79.6%)
	None	88 (19.2%)	34 (20.1%)	122 (19.4%)
12 months	All	10 (2.2%)	1 (0.6%)	11 (1.8%)
	Some	296 (64.5%)	106 (62.7%)	402 (64.0%)
	None	153 (33.3%)	62 (36.7%)	215 (34.2%)
18 months	All	6 (1.3%)	1 (0.6%)	7 (1.1%)
	Some	245 (53.4%)	88 (52.1%)	333 (53.0%)

	None	208 (45.3%)	80 (47.3%)	288 (45.9%)
24 months	All	7 (1.5%)	2 (1.2%)	9 (1.4%)
	Some	207 (45.1%)	84 (49.7%)	291 (46.3%)
	None	245 (53.4%)	83 (49.1%)	328 (52.2%)
EORTC-QLQ-ELD15				
Baseline	All	408 (88.9%)	151 (89.3%)	559 (89.0%)
	Some	16 (3.5%)	7 (4.1%)	23 (3.7%)
	None	35 (7.6%)	11 (6.5%)	46 (7.3%)
6 weeks	All	391 (85.2%)	130 (76.9%)	521 (83.0%)
	Some	11 (2.4%)	3 (1.8%)	14 (2.2%)
	None	57 (12.4%)	36 (21.3%)	93 (14.8%)
6 months	All	356 (77.6%)	131 (77.5%)	487 (77.5%)
	Some	14 (3.1%)	3 (1.8%)	17 (2.7%)
	None	89 (19.4%)	35 (20.7%)	124 (19.7%)
12 months	All	291 (63.4%)	99 (58.6%)	390 (62.1%)
	Some	12 (2.6%)	8 (4.7%)	20 (3.2%)
	None	156 (34.0%)	62 (36.7%)	218 (34.7%)
18 months	All	234 (51.0%)	84 (49.7%)	318 (50.6%)
	Some	12 (2.6%)	4 (2.4%)	16 (2.5%)
	None	213 (46.4%)	81 (47.9%)	294 (46.8%)
24 months	All	200 (43.6%)	80 (47.3%)	280 (44.6%)
	Some	13 (2.8%)	6 (3.6%)	19 (3.0%)
	None	246 (53.6%)	83 (49.1%)	329 (52.4%)

Supplementary table 4.7 – Mean (standard deviation) scores for the EORTC QLQ-BR23 scale at each time point in the radiotherapy versus no radiotherapy cohorts with adjusted mean difference (95% confidence interval) and p-value.

BREAST-CONSERVING SURGERY COHORT (N=1,042)[1]					
Time point	Domain	No radiotherapy	Radiotherapy	Treatment effect	P-value
6 weeks	Body image	92.81 (90.84, 94.78)	92.08 (91.24, 92.92)	-0.73 (-2.88, 1.41)	0.502
	Sexual functioning	7.79 (5.22, 10.35)	8.08 (7.01, 9.14)	0.29 (-2.49, 3.07)	0.837
	Sexual enjoyment	60.30 (46.13, 74.46)	60.35 (54.38, 66.32)	0.06 (-15.33, 15.44)	0.994
	Future perspective	70.17 (66.42, 73.92)	67.01 (65.42, 68.61)	-3.16 (-7.24, 0.92)	0.128
	Systemic therapy side effects	11.14 (9.54, 12.73)	12.61 (11.93, 13.28)	1.47 (-0.26, 3.20)	0.095
	Breast symptoms	21.12 (18.15, 24.10)	22.26 (20.97, 23.54)	1.13 (-2.11, 4.38)	0.493
	Arm symptoms	13.03 (10.47, 15.60)	14.75 (13.64, 15.85)	1.71 (-1.08, 4.51)	0.229
	Upset by hair loss	49.27 (28.22, 70.32)	29.56 (20.71, 38.40)	-19.71 (-42.52, 3.10)	0.088
6 months	Body image	90.93 (88.36, 93.50)	91.29 (90.25, 92.32)	0.36 (-2.41, 3.14)	0.798
	Sexual functioning	11.30 (8.40, 14.20)	9.09 (7.95, 10.23)	-2.21 (-5.33, 0.90)	0.163
	Sexual enjoyment	59.01 (46.32, 71.71)	53.04 (47.74, 58.34)	-5.97 (-19.68, 7.74)	0.389
	Future perspective	69.73 (65.45, 74.01)	69.77 (68.05, 71.50)	0.04 (-4.57, 4.66)	0.985
	Systemic therapy side effects	16.88 (14.82, 18.95)	15.87 (15.03, 16.71)	-1.01 (-3.24, 1.21)	0.373
	Breast symptoms	11.00 (8.30, 13.71)	17.27 (16.16, 18.38)	6.27 (3.34, 9.19)	<0.001
	Arm symptoms	11.73 (8.83, 14.62)	13.71 (12.53, 14.89)	1.98 (-1.14, 5.11)	0.213
	Upset by hair loss	43.90 (16.78, 71.03)	36.32 (26.65, 45.99)	-7.58 (-36.43, 21.26)	0.598
12 months	Body image	90.06 (87.31, 92.80)	91.38 (90.27, 92.48)	1.32 (-1.64, 4.28)	0.382
	Sexual functioning	9.54 (6.60, 12.49)	9.53 (8.35, 10.71)	-0.02 (-3.20, 3.16)	0.992

[1] Patients with questionnaires available at baseline.

	Sexual enjoyment	53.44 (35.79, 71.10)	59.54 (53.53, 65.56)	6.10 (-12.30, 24.49)	0.51
	Future perspective	66.61 (62.18, 71.04)	69.27 (67.48, 71.05)	2.65 (-2.12, 7.43)	0.276
	Systemic therapy side effects	16.06 (13.94, 18.18)	15.75 (14.90, 16.61)	-0.31 (-2.60, 1.98)	0.793
	Breast symptoms	9.90 (7.35, 12.45)	13.79 (12.74, 14.83)	3.89 (1.13, 6.64)	0.006
	Arm symptoms	14.05 (10.92, 17.19)	13.29 (12.00, 14.57)	-0.77 (-4.16, 2.62)	0.657
	Upset by hair loss	54.96 (32.04, 77.87)	41.52 (31.63, 51.41)	-13.44 (-38.42, 11.55)	0.283
18 months	Body image	89.80 (86.73, 92.88)	90.84 (89.55, 92.13)	1.04 (-2.30, 4.37)	0.542
	Sexual functioning	9.85 (6.36, 13.34)	8.81 (7.39, 10.24)	-1.03 (-4.81, 2.74)	0.591
	Sexual enjoyment	52.47 (31.38, 73.55)	56.69 (49.52, 63.86)	4.22 (-17.76, 26.21)	0.701
	Future perspective	72.24 (67.25, 77.23)	69.73 (67.63, 71.83)	-2.51 (-7.92, 2.90)	0.363
	Systemic therapy side effects	16.28 (13.94, 18.61)	15.89 (14.91, 16.87)	-0.39 (-2.92, 2.14)	0.764
	Breast symptoms	9.96 (7.24, 12.67)	12.18 (11.02, 13.34)	2.22 (-0.73, 5.18)	0.14
	Arm symptoms	13.92 (10.67, 17.18)	13.08 (11.69, 14.46)	-0.85 (-4.38, 2.69)	0.638
	Upset by hair loss	43.14 (14.33, 71.96)	40.63 (27.30, 53.96)	-2.52 (-34.27, 29.24)	0.872
24 months	Body image	88.24 (84.98, 91.51)	91.15 (89.83, 92.47)	2.91 (-0.61, 6.43)	0.105
	Sexual functioning	9.43 (5.78, 13.07)	9.48 (8.00, 10.96)	0.05 (-3.88, 3.99)	0.979
	Sexual enjoyment	60.67 (41.22, 80.11)	52.27 (45.36, 59.18)	-8.40 (-28.85, 12.05)	0.414
	Future perspective	69.22 (63.96, 74.49)	70.25 (68.10, 72.40)	1.02 (-4.66, 6.71)	0.724
	Systemic therapy side effects	17.06 (14.59, 19.52)	15.80 (14.80, 16.79)	-1.26 (-3.92, 1.39)	0.351
	Breast symptoms	8.63 (6.08, 11.17)	10.01 (8.95, 11.06)	1.38 (-1.38, 4.14)	0.325
	Arm symptoms	15.01 (11.18, 18.84)	12.84 (11.25, 14.43)	-2.17 (-6.32, 1.97)	0.304
	Upset by hair loss	73.42 (40.92, 105.93)	38.16 (26.93, 49.38)	-35.27 (-69.79, -0.75)	0.046
MASTECTOMY COHORT (N=588)[2]					

[2] Patients with questionnaires available at baseline.

Time point	Domain	No radiotherapy	Radiotherapy	Treatment Effect	P value
6 weeks	Body image	81.92 (79.78, 84.05)	81.76 (78.19, 85.32)	-0.16 (-4.31, 4.00)	0.94
	Sexual functioning	4.04 (2.96, 5.11)	4.39 (2.53, 6.26)	0.36 (-1.79, 2.51)	0.745
	Sexual enjoyment	46.17 (31.77, 60.57)	61.86 (35.67, 88.05)	15.69 (-13.94, 45.31)	0.282
	Future perspective	69.71 (67.19, 72.23)	67.91 (63.70, 72.12)	-1.81 (-6.72, 3.10)	0.47
	Systemic therapy side effects	12.45 (11.44, 13.45)	12.05 (10.35, 13.74)	-0.40 (-2.37, 1.57)	0.689
	Breast symptoms	23.49 (21.65, 25.32)	23.84 (20.75, 26.94)	0.36 (-3.24, 3.96)	0.845
	Arm symptoms	19.46 (17.57, 21.36)	20.15 (16.95, 23.34)	0.68 (-3.03, 4.39)	0.718
	Upset by hair loss	37.37 (22.14, 52.61)	64.87 (36.01, 93.73)	27.50 (-4.90, 59.90)	0.091
6 months	Body image	80.37 (78.01, 82.74)	79.99 (76.21, 83.77)	-0.38 (-4.84, 4.08)	0.866
	Sexual functioning	5.38 (4.06, 6.70)	6.01 (3.96, 8.06)	0.63 (-1.81, 3.07)	0.611
	Sexual enjoyment	67.61 (57.31, 77.90)	55.31 (39.45, 71.17)	-12.30 (-30.57, 5.98)	0.176
	Future perspective	70.59 (68.04, 73.13)	67.71 (63.62, 71.80)	-2.87 (-7.70, 1.95)	0.242
	Systemic therapy side effects	15.51 (14.43, 16.60)	14.46 (12.72, 16.21)	-1.05 (-3.10, 1.00)	0.316
	Breast symptoms	12.19 (10.66, 13.71)	17.71 (15.30, 20.12)	5.52 (2.67, 8.37)	<0.001
	Arm symptoms	14.80 (13.05, 16.56)	16.87 (14.10, 19.64)	2.07 (-1.21, 5.35)	0.215
	Upset by hair loss	37.36 (22.01, 52.71)	51.20 (28.92, 73.48)	13.84 (-13.42, 41.10)	0.3
12 months	Body image	81.27 (78.79, 83.75)	81.28 (77.24, 85.32)	0.01 (-4.73, 4.75)	0.997
	Sexual functioning	5.85 (4.37, 7.33)	5.27 (2.86, 7.69)	-0.57 (-3.41, 2.26)	0.69
	Sexual enjoyment	53.70 (41.21, 66.19)	45.79 (24.53, 67.05)	-7.91 (-33.12, 17.30)	0.521
	Future perspective	69.82 (66.89, 72.75)	67.04 (62.23, 71.86)	-2.78 (-8.42, 2.86)	0.333
	Systemic therapy side effects	15.94 (14.61, 17.27)	17.05 (14.84, 19.25)	1.11 (-1.46, 3.69)	0.396
	Breast symptoms	10.04 (8.43, 11.65)	17.16 (14.57, 19.75)	7.12 (4.07, 10.17)	<0.001
	Arm symptoms	12.00 (10.24, 13.77)	18.35 (15.49, 21.20)	6.34 (2.99, 9.70)	<0.001
	Upset by hair loss	40.20 (23.58, 56.83)	51.73 (28.06, 75.40)	11.53 (-17.27, 40.33)	0.415

18 months	Body image	82.33 (79.68, 84.97)	81.68 (77.43, 85.93)	-0.65 (-5.65, 4.36)	0.8
	Sexual functioning	6.07 (4.28, 7.86)	5.74 (2.82, 8.65)	-0.33 (-3.75, 3.08)	0.848
	Sexual enjoyment	54.24 (37.66, 70.81)	41.98 (19.11, 64.86)	-12.26 (-40.34, 15.83)	0.372
	Future perspective	71.04 (67.85, 74.23)	65.22 (60.07, 70.38)	-5.82 (-11.88, 0.25)	0.06
	Systemic therapy side effects	15.69 (14.19, 17.18)	17.85 (15.43, 20.28)	2.16 (-0.68, 5.01)	0.135
	Breast symptoms	9.81 (8.08, 11.55)	11.29 (8.45, 14.13)	1.48 (-1.85, 4.80)	0.383
	Arm symptoms	13.98 (11.84, 16.13)	17.02 (13.47, 20.58)	3.04 (-1.11, 7.18)	0.15
	Upset by hair loss	48.18 (29.58, 66.77)	72.33 (49.30, 95.35)	24.15 (-5.31, 53.61)	0.099
24 months	Body image	81.84 (78.85, 84.83)	78.66 (74.08, 83.23)	-3.19 (-8.66, 2.28)	0.253
	Sexual functioning	6.15 (4.14, 8.16)	5.40 (2.51, 8.29)	-0.75 (-4.27, 2.77)	0.674
	Sexual enjoyment	59.71 (46.62, 72.80)	46.58 (28.38, 64.78)	-13.13 (-36.10, 9.83)	0.245
	Future perspective	69.58 (66.03, 73.13)	64.91 (59.49, 70.34)	-4.66 (-11.15, 1.82)	0.158
	Systemic therapy side effects	16.40 (14.78, 18.02)	17.67 (15.18, 20.16)	1.27 (-1.71, 4.24)	0.402
	Breast symptoms	10.17 (8.24, 12.10)	12.87 (9.95, 15.79)	2.70 (-0.79, 6.20)	0.129
	Arm symptoms	15.31 (12.58, 18.05)	21.50 (17.35, 25.66)	6.19 (1.21, 11.17)	0.015
	Upset by hair loss	33.81 (11.03, 56.59)	88.36 (56.49, 120.22)	54.55 (14.54, 94.55)	0.016

Supplementary table 4.8 – Mean (standard deviation) scores for the EORTC QLQ-C30 scale at each time point in the radiotherapy versus no radiotherapy cohorts with adjusted mean difference (95% confidence interval) and p-value.

BREAST-CONSERVING SURGERY COHORT					
Time point	Domain	No radiotherapy	Radiotherapy	Treatment effect	P-value
6 weeks	Global health status / quality of life	71.50 (68.98, 74.01)	71.58 (70.49, 72.67)	0.09 (-2.66, 2.83)	0.951
	Physical functioning	79.75 (78.01, 81.49)	79.01 (78.26, 79.76)	-0.74 (-2.64, 1.16)	0.445
	Role functioning	76.53 (72.79, 80.27)	74.47 (72.85, 76.09)	-2.06 (-6.14, 2.02)	0.322
	Emotional functioning	79.89 (77.28, 82.51)	79.39 (78.24, 80.54)	-0.50 (-3.36, 2.35)	0.729
	Cognitive functioning	86.97 (84.58, 89.36)	87.35 (86.31, 88.38)	0.38 (-2.22, 2.98)	0.775
	Social functioning	85.98 (82.79, 89.17)	82.46 (81.08, 83.85)	-3.51 (-7.00, -0.03)	0.048
	Fatigue	28.84 (26.02, 31.66)	30.85 (29.63, 32.07)	2.01 (-1.06, 5.08)	0.199
	Nausea / Vomiting	4.51 (2.90, 6.11)	4.27 (3.58, 4.96)	-0.24 (-1.98, 1.51)	0.791
	Pain	20.14 (16.98, 23.30)	21.99 (20.62, 23.37)	1.85 (-1.60, 5.29)	0.293
	Dyspnoea	14.09 (11.13, 17.04)	14.66 (13.38, 15.95)	0.58 (-2.64, 3.80)	0.725
	Insomnia	29.22 (25.21, 33.23)	30.26 (28.53, 31.99)	1.04 (-3.33, 5.40)	0.641
	Appetite loss	11.76 (8.84, 14.68)	11.29 (10.03, 12.56)	-0.47 (-3.65, 2.72)	0.773
	Constipation	14.11 (10.99, 17.23)	13.53 (12.18, 14.89)	-0.58 (-3.97, 2.82)	0.739
	Diarrhoea	3.34 (1.16, 5.52)	5.14 (4.20, 6.08)	1.80 (-0.58, 4.18)	0.138
	Financial problems	4.49 (2.68, 6.31)	4.06 (3.26, 4.85)	-0.44 (-2.42, 1.55)	0.665
6 months	Global health status / quality of life	71.64 (68.92, 74.36)	72.06 (70.93, 73.18)	0.41 (-2.53, 3.36)	0.783
	Physical functioning	78.52 (76.39, 80.65)	78.55 (77.67, 79.43)	0.03 (-2.28, 2.34)	0.978
	Role functioning	77.19 (73.38, 80.99)	79.46 (77.90, 81.01)	2.27 (-1.84, 6.38)	0.279
	Emotional functioning	79.80 (76.82, 82.77)	79.99 (78.75, 81.23)	0.19 (-3.03, 3.42)	0.906
	Cognitive functioning	83.92 (81.23, 86.62)	85.25 (84.14, 86.36)	1.33 (-1.59, 4.25)	0.373

	Social functioning	86.43 (83.07, 89.79)	86.23 (84.86, 87.60)	-0.20 (-3.83, 3.43)	0.913
	Fatigue	30.43 (27.02, 33.84)	31.28 (29.88, 32.67)	0.85 (-2.84, 4.54)	0.652
	Nausea / Vomiting	5.79 (3.91, 7.67)	3.76 (3.00, 4.53)	-2.03 (-4.06, 0.00)	0.05
	Pain	22.20 (18.57, 25.84)	22.73 (21.24, 24.22)	0.52 (-3.40, 4.45)	0.794
	Dyspnoea	22.60 (18.89, 26.31)	18.98 (17.47, 20.50)	-3.62 (-7.63, 0.39)	0.077
	Insomnia	28.06 (23.47, 32.64)	30.24 (28.36, 32.12)	2.18 (-2.77, 7.14)	0.388
	Appetite loss	14.63 (11.19, 18.07)	10.28 (8.87, 11.69)	-4.35 (-8.06, -0.63)	0.022
	Constipation	14.33 (10.41, 18.25)	14.76 (13.16, 16.36)	0.43 (-3.80, 4.66)	0.842
	Diarrhoea	6.80 (4.16, 9.43)	5.05 (3.98, 6.12)	-1.75 (-4.59, 1.10)	0.229
	Financial problems	4.12 (2.20, 6.05)	3.52 (2.72, 4.31)	-0.61 (-2.69, 1.47)	0.567
12 months	Global health status / quality of life	68.21 (65.33, 71.09)	71.40 (70.24, 72.55)	3.19 (0.08, 6.29)	0.044
	Physical functioning	77.82 (75.45, 80.19)	77.85 (76.89, 78.82)	0.03 (-2.53, 2.60)	0.98
	Role functioning	75.44 (71.10, 79.78)	78.62 (76.86, 80.38)	3.18 (-1.51, 7.87)	0.183
	Emotional functioning	76.91 (73.60, 80.23)	80.00 (78.65, 81.36)	3.09 (-0.49, 6.67)	0.09
	Cognitive functioning	83.85 (80.93, 86.77)	84.45 (83.26, 85.64)	0.60 (-2.55, 3.76)	0.707
	Social functioning	84.54 (80.87, 88.21)	86.95 (85.46, 88.43)	2.41 (-1.56, 6.37)	0.233
	Fatigue	32.29 (28.83, 35.74)	29.33 (27.93, 30.73)	-2.96 (-6.69, 0.77)	0.12
	Nausea / Vomiting	2.70 (1.11, 4.28)	3.60 (2.96, 4.24)	0.91 (-0.80, 2.61)	0.298
	Pain	24.68 (20.35, 29.01)	23.85 (22.10, 25.61)	-0.83 (-5.50, 3.84)	0.728
	Dyspnoea	22.28 (18.09, 26.46)	19.86 (18.16, 21.56)	-2.42 (-6.94, 2.11)	0.295
	Insomnia	29.58 (24.72, 34.45)	32.52 (30.55, 34.49)	2.94 (-2.31, 8.19)	0.272
	Appetite loss	11.71 (7.81, 15.61)	11.05 (9.47, 12.64)	-0.66 (-4.88, 3.56)	0.759
	Constipation	15.12 (10.99, 19.25)	14.52 (12.84, 16.19)	-0.61 (-5.07, 3.85)	0.789
	Diarrhoea	5.52 (2.81, 8.23)	4.98 (3.89, 6.06)	-0.55 (-3.47, 2.37)	0.713
	Financial problems	5.43 (3.31, 7.55)	3.05 (2.19, 3.91)	-2.38 (-4.67, -0.09)	0.041

18 months	Global health status / quality of life	69.00 (65.77, 72.24)	71.01 (69.63, 72.40)	2.01 (-1.52, 5.54)	0.264
	Physical functioning	76.87 (74.28, 79.45)	76.20 (75.09, 77.30)	-0.67 (-3.50, 2.16)	0.642
	Role functioning	72.91 (68.03, 77.80)	78.22 (76.14, 80.29)	5.30 (-0.02, 10.63)	0.051
	Emotional functioning	79.09 (75.71, 82.47)	80.81 (79.36, 82.27)	1.73 (-1.96, 5.41)	0.358
	Cognitive functioning	82.36 (79.08, 85.63)	84.68 (83.29, 86.07)	2.33 (-1.23, 5.89)	0.199
	Social functioning	84.40 (80.39, 88.41)	88.01 (86.30, 89.72)	3.61 (-0.75, 7.98)	0.105
	Fatigue	31.27 (27.45, 35.09)	29.70 (28.07, 31.33)	-1.57 (-5.73, 2.60)	0.46
	Nausea / Vomiting	6.86 (4.66, 9.07)	3.33 (2.40, 4.27)	-3.53 (-5.93, -1.14)	0.004
	Pain	28.18 (23.55, 32.80)	24.06 (22.09, 26.03)	-4.11 (-9.14, 0.91)	0.109
	Dyspnoea	21.09 (16.65, 25.54)	19.36 (17.47, 21.24)	-1.74 (-6.57, 3.10)	0.481
	Insomnia	31.91 (26.63, 37.20)	30.65 (28.43, 32.87)	-1.26 (-6.99, 4.47)	0.666
	Appetite loss	13.60 (9.70, 17.49)	9.86 (8.22, 11.51)	-3.73 (-7.97, 0.50)	0.084
	Constipation	16.70 (12.11, 21.28)	14.18 (12.26, 16.11)	-2.51 (-7.49, 2.46)	0.322
	Diarrhoea	4.69 (1.69, 7.69)	5.94 (4.69, 7.19)	1.25 (-2.00, 4.49)	0.451
	Financial problems	5.43 (3.24, 7.62)	2.41 (1.48, 3.35)	-3.02 (-5.40, -0.63)	0.013
24 months	Global health status / quality of life	69.80 (66.08, 73.52)	69.76 (68.24, 71.28)	-0.04 (-4.07, 3.98)	0.983
	Physical functioning	74.42 (71.33, 77.51)	75.69 (74.42, 76.97)	1.27 (-2.08, 4.63)	0.456
	Role functioning	72.87 (67.68, 78.07)	77.88 (75.74, 80.03)	5.01 (-0.62, 10.64)	0.081
	Emotional functioning	80.77 (77.20, 84.34)	79.95 (78.49, 81.41)	-0.82 (-4.68, 3.04)	0.676
	Cognitive functioning	80.64 (77.18, 84.10)	85.15 (83.74, 86.56)	4.51 (0.78, 8.25)	0.018
	Social functioning	84.45 (79.68, 89.23)	86.73 (84.81, 88.65)	2.28 (-2.87, 7.42)	0.385
	Fatigue	32.48 (28.40, 36.56)	29.32 (27.65, 30.99)	-3.16 (-7.58, 1.25)	0.16
	Nausea / Vomiting	5.84 (3.69, 7.99)	3.41 (2.52, 4.30)	-2.43 (-4.76, -0.10)	0.041
	Pain	25.25 (20.20, 30.30)	23.88 (21.79, 25.96)	-1.37 (-6.84, 4.09)	0.622
	Dyspnoea	24.79 (19.88, 29.70)	20.17 (18.16, 22.19)	-4.62 (-9.93, 0.69)	0.088

	Insomnia	33.09 (27.39, 38.79)	30.48 (28.14, 32.83)	-2.61 (-8.77, 3.55)	0.406
	Appetite loss	13.70 (9.44, 17.96)	10.27 (8.50, 12.04)	-3.43 (-8.05, 1.18)	0.145
	Constipation	17.54 (12.65, 22.43)	13.67 (11.64, 15.70)	-3.87 (-9.16, 1.42)	0.152
	Diarrhoea	7.27 (3.62, 10.92)	6.08 (4.58, 7.58)	-1.19 (-5.13, 2.75)	0.554
	Financial problems	4.31 (1.95, 6.67)	3.18 (2.23, 4.14)	-1.13 (-3.67, 1.42)	0.386
MASTECTOMY COHORT					
Time point	Domain	No radiotherapy	Radiotherapy	Treatment effect	P-value
6 weeks	Global health status / quality of life	69.78 (68.19, 71.37)	66.60 (63.90, 69.31)	-3.18 (-6.32, -0.04)	0.047
	Physical functioning	75.75 (74.47, 77.02)	71.82 (69.67, 73.98)	-3.93 (-6.43, -1.42)	0.002
	Role functioning	68.38 (65.80, 70.96)	67.58 (63.25, 71.91)	-0.80 (-5.84, 4.24)	0.756
	Emotional functioning	80.93 (79.28, 82.59)	79.85 (77.03, 82.66)	-1.09 (-4.35, 2.18)	0.514
	Cognitive functioning	85.98 (84.47, 87.48)	84.79 (82.23, 87.34)	-1.19 (-4.16, 1.77)	0.429
	Social functioning	80.38 (78.17, 82.59)	77.11 (73.35, 80.87)	-3.27 (-7.63, 1.09)	0.141
	Fatigue	33.22 (31.44, 34.99)	34.78 (31.78, 37.78)	1.56 (-1.92, 5.05)	0.379
	Nausea / Vomiting	3.80 (2.85, 4.76)	4.25 (2.64, 5.86)	0.45 (-1.42, 2.32)	0.637
	Pain	23.53 (21.40, 25.66)	22.13 (18.54, 25.71)	-1.40 (-5.57, 2.77)	0.51
	Dyspnoea	14.74 (13.15, 16.33)	14.14 (11.47, 16.81)	-0.59 (-3.70, 2.52)	0.709
	Insomnia	27.54 (24.95, 30.12)	27.45 (23.09, 31.82)	-0.08 (-5.16, 4.99)	0.974
	Appetite loss	13.99 (11.88, 16.11)	14.98 (11.42, 18.55)	0.99 (-3.15, 5.14)	0.638
	Constipation	14.05 (11.87, 16.24)	15.66 (12.00, 19.33)	1.61 (-2.66, 5.88)	0.459
	Diarrhoea	4.60 (3.22, 5.99)	4.39 (2.03, 6.74)	-0.21 (-2.94, 2.52)	0.878
	Financial problems	3.60 (2.44, 4.75)	4.54 (2.57, 6.51)	0.94 (-1.34, 3.22)	0.416
6 months	Global health status / quality of life	69.95 (68.14, 71.76)	69.31 (66.40, 72.21)	-0.64 (-4.06, 2.78)	0.714
	Physical functioning	75.42 (74.05, 76.78)	73.82 (71.60, 76.03)	-1.60 (-4.20, 1.00)	0.227
	Role functioning	77.98 (75.59, 80.37)	77.33 (73.45, 81.20)	-0.65 (-5.20, 3.90)	0.779

	Emotional functioning	82.45 (80.71, 84.20)	81.47 (78.65, 84.28)	-0.99 (-4.30, 2.33)	0.558
	Cognitive functioning	83.72 (82.09, 85.34)	84.23 (81.60, 86.87)	0.52 (-2.58, 3.61)	0.743
	Social functioning	86.23 (84.04, 88.42)	83.77 (80.23, 87.30)	-2.46 (-6.62, 1.70)	0.245
	Fatigue	30.40 (28.45, 32.35)	34.85 (31.72, 37.98)	4.45 (0.77, 8.14)	0.018
	Nausea / Vomiting	3.91 (2.91, 4.91)	4.36 (2.76, 5.97)	0.45 (-1.44, 2.34)	0.639
	Pain	20.22 (18.17, 22.27)	18.51 (15.22, 21.80)	-1.71 (-5.58, 2.16)	0.386
	Dyspnoea	19.57 (17.39, 21.76)	20.81 (17.28, 24.34)	1.23 (-2.92, 5.39)	0.559
	Insomnia	26.85 (24.28, 29.42)	26.74 (22.59, 30.88)	-0.12 (-5.00, 4.77)	0.963
	Appetite loss	10.56 (8.41, 12.71)	13.00 (9.56, 16.45)	2.44 (-1.62, 6.50)	0.238
	Constipation	12.12 (10.06, 14.18)	15.81 (12.51, 19.11)	3.69 (-0.20, 7.58)	0.063
	Diarrhoea	5.88 (4.50, 7.27)	2.88 (0.65, 5.12)	-3.00 (-5.63, -0.37)	0.026
	Financial problems	4.64 (3.27, 6.00)	2.99 (0.78, 5.20)	-1.65 (-4.24, 0.95)	0.213
12 months	Global health status / quality of life	71.13 (69.26, 73.00)	71.04 (67.92, 74.15)	-0.09 (-3.72, 3.53)	0.96
	Physical functioning	73.50 (71.97, 75.02)	71.89 (69.39, 74.40)	-1.60 (-4.54, 1.33)	0.284
	Role functioning	76.24 (73.50, 78.97)	74.72 (70.29, 79.16)	-1.52 (-6.73, 3.69)	0.567
	Emotional functioning	82.44 (80.40, 84.49)	76.75 (73.34, 80.15)	-5.70 (-9.67, -1.73)	0.005
	Cognitive functioning	82.50 (80.64, 84.35)	82.44 (79.36, 85.52)	-0.06 (-3.65, 3.54)	0.975
	Social functioning	86.22 (84.00, 88.43)	83.55 (79.89, 87.21)	-2.67 (-6.94, 1.60)	0.22
	Fatigue	29.95 (27.76, 32.15)	37.22 (33.63, 40.80)	7.26 (3.07, 11.46)	0.001
	Nausea / Vomiting	2.87 (1.80, 3.94)	4.57 (2.81, 6.33)	1.70 (-0.36, 3.76)	0.105
	Pain	21.42 (18.92, 23.93)	24.90 (20.80, 29.01)	3.48 (-1.32, 8.28)	0.154
	Dyspnoea	19.22 (16.60, 21.84)	27.35 (23.07, 31.63)	8.13 (3.11, 13.14)	0.002
	Insomnia	27.21 (24.40, 30.02)	29.26 (24.61, 33.90)	2.04 (-3.38, 7.47)	0.459
	Appetite loss	11.99 (9.54, 14.44)	17.00 (12.98, 21.03)	5.01 (0.31, 9.72)	0.037
	Constipation	12.18 (9.87, 14.49)	14.65 (10.87, 18.42)	2.47 (-1.96, 6.89)	0.273

	Diarrhoea	6.06 (4.22, 7.90)	5.56 (2.51, 8.62)	-0.49 (-4.06, 3.08)	0.786
	Financial problems	3.63 (2.16, 5.10)	6.72 (4.29, 9.15)	3.09 (0.26, 5.93)	0.033
18 months	Global health status / quality of life	70.24 (67.95, 72.54)	66.05 (62.23, 69.86)	-4.20 (-8.63, 0.24)	0.064
	Physical functioning	72.15 (70.44, 73.87)	69.62 (66.85, 72.39)	-2.54 (-5.80, 0.72)	0.127
	Role functioning	75.63 (72.48, 78.79)	70.46 (65.30, 75.62)	-5.17 (-11.23, 0.89)	0.094
	Emotional functioning	82.82 (80.73, 84.91)	78.79 (75.36, 82.22)	-4.03 (-8.04, -0.02)	0.049
	Cognitive functioning	84.09 (82.01, 86.16)	79.87 (76.48, 83.25)	-4.22 (-8.19, -0.26)	0.037
	Social functioning	86.97 (84.40, 89.54)	83.50 (79.31, 87.69)	-3.47 (-8.38, 1.44)	0.165
	Fatigue	31.71 (29.22, 34.21)	37.15 (33.05, 41.24)	5.44 (0.64, 10.23)	0.026
	Nausea / Vomiting	3.51 (2.20, 4.81)	5.25 (3.11, 7.38)	1.74 (-0.76, 4.24)	0.173
	Pain	21.95 (18.93, 24.98)	26.00 (21.08, 30.92)	4.05 (-1.72, 9.81)	0.168
	Dyspnoea	21.96 (19.26, 24.67)	22.45 (18.04, 26.85)	0.48 (-4.67, 5.64)	0.853
	Insomnia	27.20 (24.30, 30.10)	30.54 (25.78, 35.30)	3.35 (-2.20, 8.89)	0.236
	Appetite loss	10.86 (8.17, 13.55)	17.05 (12.65, 21.45)	6.19 (1.04, 11.34)	0.019
	Constipation	14.65 (11.93, 17.38)	14.99 (10.52, 19.45)	0.33 (-4.90, 5.56)	0.9
	Diarrhoea	4.71 (2.94, 6.48)	5.91 (3.03, 8.78)	1.19 (-2.18, 4.57)	0.487
	Financial problems	3.35 (1.97, 4.72)	3.81 (1.52, 6.10)	0.46 (-2.20, 3.13)	0.734
24 months	Global health status / quality of life	69.61 (67.13, 72.09)	65.45 (61.58, 69.31)	-4.17 (-8.75, 0.42)	0.075
	Physical functioning	70.82 (68.63, 73.02)	69.03 (65.67, 72.39)	-1.79 (-5.80, 2.22)	0.38
	Role functioning	71.81 (68.11, 75.51)	70.44 (64.73, 76.16)	-1.37 (-8.17, 5.44)	0.693
	Emotional functioning	82.60 (80.38, 84.81)	78.03 (74.59, 81.47)	-4.57 (-8.66, -0.47)	0.029
	Cognitive functioning	83.03 (80.90, 85.17)	80.46 (77.14, 83.79)	-2.57 (-6.52, 1.38)	0.201
	Social functioning	82.67 (79.60, 85.74)	82.35 (77.56, 87.14)	-0.32 (-6.00, 5.36)	0.912
	Fatigue	32.31 (29.71, 34.92)	38.88 (34.85, 42.91)	6.56 (1.76, 11.37)	0.008
	Nausea / Vomiting	4.11 (2.74, 5.48)	4.44 (2.31, 6.57)	0.33 (-2.20, 2.87)	0.796

	Pain	25.39 (22.14, 28.64)	28.59 (23.54, 33.64)	3.20 (-2.80, 9.20)	0.295
	Dyspnoea	21.52 (18.41, 24.63)	22.84 (17.99, 27.68)	1.31 (-4.45, 7.08)	0.654
	Insomnia	27.25 (23.82, 30.69)	32.29 (26.95, 37.63)	5.04 (-1.30, 11.37)	0.119
	Appetite loss	13.49 (10.54, 16.44)	13.78 (9.13, 18.43)	0.29 (-5.22, 5.80)	0.917
	Constipation	12.85 (10.00, 15.70)	17.33 (12.92, 21.75)	4.48 (-0.77, 9.73)	0.094
	Diarrhoea	5.52 (3.26, 7.78)	8.92 (5.45, 12.40)	3.40 (-0.73, 7.53)	0.106
	Financial problems	3.40 (1.72, 5.08)	4.86 (2.23, 7.49)	1.47 (-1.65, 4.59)	0.356

Supplementary table 4.9 – Fixed coefficients from the longitudinal model of global health status included in the EORTC QLQ-C30 scale.

BREAST-CONSERVING SURGERY COHORT			
Term	Level	Effect (95% CI)	P-value
Treatment	Radiotherapy	-0.819 (-3.856, 2.219)	0.597
Time	6 weeks	-	-
	6 months	-0.153 (-3.446, 3.141)	0.928
	12 months	-3.142 (-6.595, 0.311)	0.075
	18 months	-4.525 (-8.096, -0.954)	0.013
	24 months	-2.378 (-6.288, 1.531)	0.233
Treatment : Time	Radiotherapy: 6 weeks	-	-
	Radiotherapy: 6 months	0.720 (-2.851, 4.291)	0.693
	Radiotherapy: 12 months	2.729 (-1.006, 6.464)	0.152
	Radiotherapy: 18 months	3.816 (-0.066, 7.698)	0.054
	Radiotherapy: 24 months	0.021 (-4.198, 4.241)	0.992
Baseline		0.504 (0.456, 0.551)	<0.001
Age		-0.196 (-0.363, -0.030)	0.021
Charlson comorbidity index	1	-	-
	2	-0.876 (-3.531, 1.780)	0.518
MMSE category	Normal Function	-	-
	Mild impairment	-0.119 (-2.924, 2.687)	0.934
	Moderate impairment	-9.399 (-17.491, -1.307)	0.023
	Severe	3.895 (-17.826, 25.617)	0.725
ECOG PS category	Mild	-	-
	Moderate	-8.512 (-14.434, -2.590)	0.005

	High	-7.824 (-15.243, -0.405)	0.039
Medications		-0.446 (-0.789, -0.104)	0.011
MASTECTOMY COHORT			
Term	Level	Effect (95% CI)	P-value
Treatment	Radiotherapy	-3.129 (-6.587, 0.329)	0.076
Time	6 weeks	-	-
	6 months	-0.164 (-2.172, 1.843)	0.872
	12 months	1.180 (-0.963, 3.324)	0.281
	18 months	-0.359 (-2.649, 1.931)	0.759
	24 months	-1.785 (-4.239, 0.669)	0.154
Treatment : Time	Radiotherapy: 6 weeks	-	-
	Radiotherapy: 6 months	2.581 (-1.301, 6.462)	0.193
	Radiotherapy: 12 months	3.340 (-0.869, 7.549)	0.12
	Radiotherapy: 18 months	-0.129 (-4.649, 4.390)	0.955
	Radiotherapy: 24 months	4.214 (-0.427, 8.856)	0.075
Baseline		0.489 (0.420, 0.557)	<0.001
Age		-0.154 (-0.382, 0.075)	0.188
Charlson comorbidity index	1	-	-
	2	-1.161 (-4.327, 2.005)	0.473
MMSE category	Normal function	-	-
	Mild impairment	1.068 (-2.456, 4.591)	0.553
	Moderate impairment	-6.152 (-17.462, 5.159)	0.287
ECOG PS category	Mild	-	-
	Moderate	-7.067 (-13.113, -1.020)	0.022
	High	1.900 (-10.931, 14.731)	0.772

Medications		-0.844 (-1.296, -0.391)	<0.001

Abbreviations: CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; MMSE: Mini Mental State Examination.

Supplementary table 4.10 – Mean (standard deviation) scores for the EORTC QLQ-ELD15 scale at each time point in the radiotherapy versus no radiotherapy cohorts with adjusted mean difference (95% confidence interval) and p-value.

BREAST-CONSERVING SURGERY COHORT					
Time point	Domain	No radiotherapy	Radiotherapy	Treatment effect	P-value
6 weeks	Mobility	21.41 (18.86, 23.97)	20.76 (19.66, 21.86)	-0.65 (-3.44, 2.14)	0.648
	Worries about others	39.10 (35.12, 43.07)	38.14 (36.43, 39.86)	-0.96 (-5.29, 3.37)	0.664
	Worries	32.56 (29.10, 36.02)	34.17 (32.67, 35.67)	1.61 (-2.15, 5.38)	0.401
	Maintaining purpose	67.52 (62.58, 72.47)	64.70 (62.55, 66.85)	-2.82 (-8.21, 2.57)	0.305
	Burden of illness	29.48 (25.92, 33.04)	28.93 (27.39, 30.47)	-0.56 (-4.43, 3.32)	0.779
	Joint stiffness	29.29 (25.74, 32.83)	26.08 (24.53, 27.62)	-3.21 (-7.08, 0.66)	0.104
	Family support	74.72 (70.13, 79.30)	74.38 (72.39, 76.36)	-0.34 (-5.34, 4.66)	0.893
6 months	Mobility	23.97 (20.99, 26.94)	22.23 (21.00, 23.46)	-1.74 (-4.97, 1.49)	0.291
	Worries about others	33.97 (29.53, 38.41)	33.58 (31.75, 35.41)	-0.39 (-5.19, 4.41)	0.874
	Worries	32.53 (28.57, 36.48)	32.25 (30.63, 33.87)	-0.28 (-4.55, 4.00)	0.899
	Maintaining purpose	59.97 (54.26, 65.67)	63.22 (60.85, 65.59)	3.26 (-2.92, 9.43)	0.301
	Burden of illness	20.06 (16.22, 23.90)	25.55 (23.96, 27.13)	5.49 (1.33, 9.64)	0.01
	Joint stiffness	39.78 (35.29, 44.26)	38.71 (36.85, 40.57)	-1.06 (-5.92, 3.79)	0.667
	Family support	67.10 (61.91, 72.29)	69.99 (67.83, 72.14)	2.89 (-2.73, 8.51)	0.313
12 months	Mobility	25.13 (21.78, 28.47)	23.75 (22.39, 25.11)	-1.38 (-4.99, 2.24)	0.455
	Worries about others	33.51 (28.81, 38.22)	31.48 (29.58, 33.39)	-2.03 (-7.11, 3.05)	0.433
	Worries	34.62 (30.39, 38.85)	32.00 (30.27, 33.72)	-2.62 (-7.19, 1.95)	0.261
	Maintaining purpose	59.69 (53.74, 65.65)	63.28 (60.85, 65.71)	3.58 (-2.85, 10.02)	0.275
	Burden of illness	18.80 (14.73, 22.87)	21.67 (20.02, 23.32)	2.87 (-1.52, 7.26)	0.2
	Joint stiffness	42.31 (37.71, 46.92)	41.70 (39.81, 43.59)	-0.61 (-5.58, 4.37)	0.81

	Family support	61.37 (55.43, 67.31)	65.58 (63.17, 67.98)	4.20 (-2.21, 10.62)	0.199
18 months	Mobility	26.75 (23.06, 30.44)	25.38 (23.80, 26.96)	-1.37 (-5.41, 2.67)	0.506
	Worries about others	32.56 (27.73, 37.40)	29.94 (27.90, 31.99)	-2.62 (-7.87, 2.63)	0.327
	Worries	30.90 (26.19, 35.62)	31.68 (29.69, 33.68)	0.78 (-4.34, 5.91)	0.764
	Maintaining purpose	57.80 (51.56, 64.05)	63.81 (61.14, 66.48)	6.01 (-0.78, 12.80)	0.083
	Burden of illness	16.45 (12.23, 20.67)	18.20 (16.42, 19.97)	1.74 (-2.83, 6.32)	0.454
	Joint stiffness	44.80 (39.96, 49.63)	42.11 (40.05, 44.17)	-2.69 (-7.94, 2.57)	0.316
	Family support	58.77 (52.09, 65.44)	62.21 (59.39, 65.04)	3.45 (-3.80, 10.70)	0.351
24 months	Mobility	28.77 (24.55, 32.99)	26.50 (24.75, 28.25)	-2.27 (-6.85, 2.31)	0.331
	Worries about others	34.92 (29.84, 40.01)	28.72 (26.64, 30.79)	-6.21 (-11.70, -0.71)	0.027
	Worries	32.74 (27.70, 37.79)	32.66 (30.59, 34.73)	-0.09 (-5.54, 5.37)	0.975
	Maintaining purpose	62.09 (55.44, 68.75)	65.55 (62.80, 68.29)	3.45 (-3.75, 10.65)	0.347
	Burden of illness	20.73 (16.04, 25.41)	18.44 (16.51, 20.36)	-2.29 (-7.35, 2.77)	0.374
	Joint stiffness	45.46 (39.86, 51.05)	41.44 (39.11, 43.76)	-4.02 (-10.08, 2.03)	0.193
	Family support	65.26 (58.06, 72.46)	59.91 (56.92, 62.91)	-5.35 (-13.14, 2.45)	0.179
MASTECTOMY COHORT					
Time point	Domain	No radiotherapy	Radiotherapy	Treatment effect	P-value
6 weeks	Mobility	26.86 (25.25, 28.47)	27.80 (25.07, 30.53)	0.94 (-2.23, 4.11)	0.561
	Worries about others	36.60 (33.96, 39.24)	39.96 (35.46, 44.46)	3.36 (-1.86, 8.59)	0.207
	Worries	33.35 (31.04, 35.65)	36.38 (32.44, 40.31)	3.03 (-1.53, 7.59)	0.193
	Maintaining purpose	65.34 (62.28, 68.41)	62.62 (57.45, 67.80)	-2.72 (-8.74, 3.30)	0.375
	Burden of illness	30.00 (27.61, 32.40)	35.54 (31.50, 39.59)	5.54 (0.84, 10.24)	0.021
	Joint stiffness	28.45 (26.18, 30.72)	26.54 (22.73, 30.36)	-1.90 (-6.35, 2.54)	0.4
	Family support	76.33 (73.60, 79.05)	75.36 (70.72, 80.00)	-0.97 (-6.36, 4.42)	0.724
6 months	Mobility	27.43 (25.38, 29.48)	26.41 (23.14, 29.69)	-1.02 (-4.89, 2.85)	0.605

	Worries about others	31.96 (29.52, 34.40)	32.47 (28.54, 36.40)	0.51 (-4.13, 5.15)	0.829
	Worries	30.46 (28.26, 32.66)	33.31 (29.77, 36.86)	2.86 (-1.32, 7.03)	0.18
	Maintaining purpose	62.74 (59.11, 66.37)	65.91 (60.13, 71.68)	3.17 (-3.65, 9.99)	0.362
	Burden of illness	23.64 (21.00, 26.29)	33.31 (29.08, 37.54)	9.66 (4.67, 14.66)	<0.001
	Joint stiffness	38.93 (36.27, 41.60)	34.23 (29.96, 38.50)	-4.70 (-9.73, 0.33)	0.067
	Family support	67.57 (64.18, 70.96)	73.73 (68.29, 79.18)	6.16 (-0.26, 12.59)	0.06
12 months	Mobility	30.35 (28.10, 32.60)	31.69 (28.06, 35.31)	1.34 (-2.94, 5.62)	0.539
	Worries about others	33.71 (30.72, 36.69)	35.25 (30.32, 40.19)	1.55 (-4.23, 7.32)	0.599
	Worries	34.25 (31.62, 36.88)	35.01 (30.68, 39.34)	0.76 (-4.31, 5.83)	0.769
	Maintaining purpose	62.74 (59.07, 66.42)	66.24 (60.23, 72.24)	3.50 (-3.54, 10.53)	0.329
	Burden of illness	20.69 (17.89, 23.49)	26.39 (21.82, 30.96)	5.70 (0.34, 11.06)	0.037
	Joint stiffness	43.05 (40.13, 45.96)	43.49 (38.79, 48.19)	0.44 (-5.09, 5.97)	0.875
	Family support	62.88 (59.13, 66.64)	64.35 (58.07, 70.63)	1.47 (-5.86, 8.81)	0.693
18 months	Mobility	31.35 (28.89, 33.80)	33.12 (29.27, 36.98)	1.78 (-2.81, 6.36)	0.446
	Worries about others	30.12 (26.97, 33.27)	32.71 (27.61, 37.81)	2.59 (-3.42, 8.59)	0.397
	Worries	30.62 (27.70, 33.54)	34.66 (29.97, 39.35)	4.04 (-1.49, 9.56)	0.152
	Maintaining purpose	62.34 (58.06, 66.61)	63.63 (56.83, 70.43)	1.29 (-6.73, 9.31)	0.752
	Burden of illness	18.49 (15.53, 21.44)	26.68 (21.98, 31.37)	8.19 (2.64, 13.74)	0.004
	Joint stiffness	41.22 (37.83, 44.61)	43.32 (37.98, 48.66)	2.10 (-4.22, 8.42)	0.514
	Family support	64.45 (60.06, 68.84)	63.54 (56.47, 70.60)	-0.92 (-9.24, 7.41)	0.829
24 months	Mobility	33.91 (30.96, 36.86)	37.10 (32.70, 41.51)	3.19 (-2.11, 8.49)	0.237
	Worries about others	30.91 (27.45, 34.37)	32.49 (27.21, 37.77)	1.58 (-4.73, 7.89)	0.622
	Worries	33.03 (29.73, 36.33)	34.19 (29.14, 39.25)	1.16 (-4.87, 7.20)	0.704
	Maintaining purpose	61.34 (56.85, 65.82)	56.54 (49.78, 63.30)	-4.80 (-12.90, 3.30)	0.245
	Burden of illness	23.35 (19.43, 27.26)	31.68 (25.77, 37.59)	8.34 (1.25, 15.43)	0.021

	Joint stiffness	41.93 (38.22, 45.65)	47.60 (42.05, 53.16)	5.67 (-1.02, 12.35)	0.096
	Family support	61.53 (56.76, 66.30)	59.73 (52.47, 66.99)	-1.81 (-10.49, 6.88)	0.682

Supplementary table 4.11 – Mean scores and 95% confidence intervals adjusted for baseline score for the EQ-5D-5L scale at each timepoint in radiotherapy versus no radiotherapy cohorts.

BREAST-CONSERVING SURGERY COHORT					
Time point	Score	No radiotherapy	Radiotherapy	Treatment Effect	P value
6 weeks	Score	0.85 (0.83, 0.86)	0.84 (0.83, 0.85)	-0.0081 (-0.0264, 0.0102)	0.385
	VAS	76.22 (74.22, 78.23)	76.46 (75.59, 77.33)	0.23 (-1.96, 2.42)	0.835
6 months	Score	0.84 (0.81, 0.86)	0.83 (0.82, 0.84)	-0.0021 (-0.0271, 0.0229)	0.871
	VAS	76.64 (74.28, 79.00)	76.24 (75.27, 77.20)	-0.40 (-2.96, 2.15)	0.757
12 months	Score	0.81 (0.79, 0.84)	0.83 (0.82, 0.84)	0.0145 (-0.0130, 0.0420)	0.3
	VAS	73.62 (71.01, 76.23)	76.03 (75.00, 77.07)	2.41 (-0.40, 5.22)	0.093
18 months	Score	0.81 (0.78, 0.84)	0.82 (0.81, 0.83)	0.0107 (-0.0204, 0.0418)	0.501
	VAS	73.02 (69.87, 76.16)	75.01 (73.72, 76.30)	1.99 (-1.41, 5.40)	0.251
24 months	Score	0.83 (0.80, 0.86)	0.82 (0.80, 0.83)	-0.0148 (-0.0493, 0.0197)	0.399
	VAS	73.53 (70.21, 76.85)	74.56 (73.21, 75.90)	1.03 (-2.56, 4.61)	0.574
MASTECTOMY COHORT					
Time point	Score	No radiotherapy	Radiotherapy	Treatment Effect	P value
6 weeks	Score	0.83 (0.81, 0.84)	0.80 (0.79, 0.82)	-0.0202 (-0.0431, 0.0028)	0.085
	VAS	74.76 (73.30, 76.22)	74.03 (71.57, 76.49)	-0.73 (-3.59, 2.13)	0.615
6 months	Score	0.83 (0.82, 0.84)	0.82 (0.80, 0.84)	-0.0095 (-0.0329, 0.0140)	0.429
	VAS	75.77 (74.33, 77.20)	75.45 (73.14, 77.76)	-0.31 (-3.03, 2.40)	0.82
12 months	Score	0.82 (0.81, 0.84)	0.80 (0.78, 0.82)	-0.0254 (-0.0537, 0.0029)	0.079
	VAS	74.98 (73.31, 76.66)	74.70 (71.99, 77.40)	-0.29 (-3.47, 2.89)	0.859
18 months	Score	0.81 (0.79, 0.83)	0.77 (0.74, 0.80)	-0.0387 (-0.0735, -0.0040)	0.029
	VAS	74.29 (72.44, 76.15)	71.83 (68.89, 74.77)	-2.46 (-5.94, 1.01)	0.164

24 months	Score	0.81 (0.80, 0.83)	0.76 (0.73, 0.79)	-0.0511 (-0.0858, -0.0165)	0.004
	VAS	73.77 (71.70, 75.85)	72.29 (69.12, 75.45)	-1.49 (-5.27, 2.29)	0.439

Abbreviations: VAS: visual analogue scale.

Chapter 5

Supplementary table 5.1 – Description of databases included in analysis.

Database	Description
National Cancer Registration Dataset	Population-based cancer registry for England. It collects, quality assures and analyses data on all people living in England who are diagnosed with malignant and pre-malignant neoplasms. The dataset provides near real-time, cost-effective, comprehensive data collection and quality assurance over the entire cancer care pathway.
Systemic Anti-cancer therapy	Population-based resource of anti-cancer therapy activity reported routinely by National Health Service (NHS) trusts in England. Data are collected on the treatments of patients, delivered in secondary and tertiary settings, with the intention of increasing survival, delaying further cancer progression. Does not include supportive therapies or disease-modifying intent.
Radiotherapy Dataset	All National Health Service Acute Trust which provide radiotherapy services in England collect and submit standardised data monthly against a nationally defined data set. The purpose is to collect consistent and comparable data across all English providers of radiotherapy or private facilities where delivery is funded by the NHS, to produce a timely and definitive analytical resource of radiotherapy services across England.
Hospital Episode statistics Admitted Patient Care	Provides detailed clinical, demographic and organizational information for all patients admitted to hospital. The dataset contains data on International Classification of Diseases (ICD)-10 diagnoses, procedures, dates of admission, operations and discharge, admission method (e.g. emergency or planned), care provider and many geographical variables mapped from a patient's postcode. Data collection reimbursed by NHS which means the data are not collected for research purposes.
National Institute for Cardiovascular Outcomes Research databases	Manages data collection for 6 specific conditions/procedures. The audits included in this study are shown in italics below. Clinical information about cardiovascular patients is collected by hospitals across the UK. Audits

	and registries were set up with clinical input and backing from specialist cardiovascular societies to ensure that the audits and analyses are clinically relevant.
Myocardial Ischaemia National Audit Project	Collects information on patients admitted to hospital with suspected acute coronary syndromes. Data are collected in cardiology units with an emphasis on type 1 acute myocardial infarction and analysed to illustrate the 'patient journey' from a call to the emergency services or their self-presentation at an Emergency Department, through diagnosis and treatment at hospital, to the prescription of preventive medications on discharge.
National Adult Cardiac Surgery Audit	Collects data on all major heart operations carried out in National Health Service hospitals throughout the United Kingdom. Includes all procedures performed that involve the heart or structures attached to the heart. For the purposes of the Audit these operations involve surgically opening the chest wall and usually the pericardium (the sac around the heart). Procedures on the heart performed with catheters (tubes inserted via arteries or veins to access the heart) are not included.
National Adult Percutaneous Coronary Intervention	Collects data on patients who undergo a procedure to improve blood flow if symptoms due to obstructions in the heart arteries, that supply the heart muscle with blood, cannot be controlled by medical treatment. Focused on all percutaneous coronary intervention techniques (also referred to as 'angioplasty').
National Heart Failure Audit	Collects data on patients admitted to hospital with acute heart failure either due to congenital heart muscle abnormalities ('cardiomyopathies'), inflammation of the heart ('myocarditis') or damage associated with problems arising from coronary artery or valve disease.

Supplementary table 5.2 – Algorithm for the selection of synchronous tumours with worse prognosis diagnosed in the same site.

Breast cancer	Colon cancer	Rectal cancer	Prostate cancer	Non-small cell lung cancer	Diffuse large B-cell lymphoma	Hodgkin lymphoma
• Stage: III > II > I • HER2: positive > negative • ER: negative > positive • Grade: Undifferentiated / anaplastic > Poorly differentiated > Moderately differentiated > well differentiated • PR: negative > positive	• Stage: III > II > I • Grade: Undifferentiated / anaplastic > Poorly differentiated > Moderately differentiated > well differentiated	• Stage: III > II > I • Grade: Undifferentiated / anaplastic > Poorly differentiated > Moderately differentiated > well differentiated	• Stage: III > II > I • Gleason: group 5 > 4 > 3 > 1 > 1 • Grade: Undifferentiated / anaplastic > Poorly differentiated > Moderately differentiated > Well differentiated	• Stage: III > II > I • Grade: Undifferentiated / anaplastic > Poorly differentiated > Moderately differentiated > well differentiated	• Stage: III > II > I • Grade: Undifferentiated / anaplastic > Poorly differentiated > Moderately differentiated > well differentiated	• Stage: III > II > I • Grade: Undifferentiated / anaplastic > Poorly differentiated > Moderately differentiated > well differentiated

Abbreviations: HER2: human epidermal growth factor receptor 2; ER: oestrogen receptor; PR: progesterone receptor.

Supplementary table 5.3 – Calculation of the Charlson Comorbidity Index with and without inclusion of cardiovascular diseases.

Charlson group	Description	Charlson score	Notes
1	Acute myocardial infarction	1	Excluded from CVD-free comorbidity score
2	Congestive heart failure	1	
3	Peripheral vascular disease	1	
4	Cerebral vascular accident	1	
5	Dementia	1	-
6	Pulmonary disease	1	-
7	Connective tissue disorder	1	-
8	Peptic ulcer	1	-
9	Diabetes	1	Only highest score is counted
10	Diabetes complications	2	
11	Paraplegia	2	-
12	Renal disease	2	-
13	Cancer	2	Derived from cancer registry data rather than HES data
14	Metastatic cancer	N/A	
15	Liver disease	1	Only highest score is counted
16	Severe liver disease	3	
17	HIV	6	-

Abbreviations: HIV: Human Immunodeficiency Virus; N/A: not applicable; HES: Hospital Episode Statistics.

Supplementary table 5.4 – Definition of cardiovascular disease according to International Statistical Classification of Diseases and Related Health Problems (ICD)-10 codes.

ICD-10 code	Description
I05	Rheumatic mitral valve diseases
I05.0	Mitral stenosis
I05.1	Rheumatic mitral insufficiency
I05.2	Mitral stenosis with insufficiency
I05.8	Other mitral valve diseases
I05.9	Mitral valve disease, unspecified
I06	Rheumatic aortic valve diseases
I06.0	Rheumatic aortic stenosis
I06.1	Rheumatic aortic insufficiency
I06.2	Rheumatic aortic stenosis with insufficiency
I06.8	Other rheumatic aortic valve diseases
I06.9	Rheumatic aortic valve disease, unspecified
I08	Multiple valve diseases
I08.0	Disorders of both mitral and aortic valves
I08.1	Disorders of both mitral and tricuspid valves
I08.2	Disorders of both aortic and tricuspid valves
I08.3	Combined disorders of mitral, aortic and tricuspid valves
I08.8	Other multiple valve diseases
I08.9	Multiple valve disease, unspecified
I11	Hypertensive heart disease.

ICD-10 code	Description
I11.0	Hypertensive heart disease with (congestive) heart failure
I13	Hypertensive heart and chronic kidney disease.
I13.0	Hypertensive heart and renal disease with (congestive) heart failure
I13.2	Hypertensive heart and renal disease with both (congestive) heart failure and renal failure
I20	Angina pectoris
I20.0	Unstable angina
I20.8	Other forms of angina pectoris
I20.9	Angina pectoris, unspecified
I21	Acute myocardial infarction
I21.0	Acute transmural myocardial infarction of anterior wall
I21.1	Acute transmural myocardial infarction of inferior wall
I21.2	Acute transmural myocardial infarction of other sites
I21.3	Acute transmural myocardial infarction of unspecified site
I21.4	Acute subendocardial myocardial infarction
I21.9	Acute myocardial infarction, unspecified
I22	Subsequent myocardial infarction
I22.0	Subsequent myocardial infarction of anterior wall
I22.1	Subsequent myocardial infarction of inferior wall
I22.8	Other forms of acute ischaemic heart disease
I22.9	Acute ischaemic heart disease, unspecified
I23	Certain current complications following ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction (within the 28 day period)

ICD-10 code	Description
I23.0	Haemopericardium as current complication following acute myocardial infarction
I23.1	Atrial septal defect as current complication following acute myocardial infarction
I23.2	Ventricular septal defect as current complication following acute MI
I23.3	Rupture of cardiac wall without haemopericardium as current complication following acute myocardial infarction
I23.4	Rupture of chordae tendineae as current complication following acute myocardial infarction
I23.5	Rupture of papillary muscle as current complication following acute myocardial infarction
I23.6	Thrombosis of atrium, auricular appendage and ventricle as current complications following acute MI
I23.8	Other current complications following acute myocardial infarction
I24	Other acute ischaemic heart diseases
I24.8	Other forms of acute ischaemic heart disease
I24.9	Acute ischaemic heart disease, unspecified
I25	Chronic ischaemic heart disease
I25.0	Atherosclerotic cardiovascular disease, so described
I25.1	Atherosclerotic heart disease
I25.5	Ischaemic cardiomyopathy
I25.8	Other forms of chronic ischaemic heart disease
I25.9	Chronic ischaemic heart disease, unspecified
I27	Other pulmonary heart diseases
I27.9	Pulmonary heart disease, unspecified
I34	Nonrheumatic mitral valve disorders
I34.0	Mitral (valve) insufficiency
I34.1	Mitral (valve) prolapse

ICD-10 code	Description
I34.2	Nonrheumatic mitral (valve) stenosis
I34.8	Other nonrheumatic mitral valve disorders
I34.9	Nonrheumatic mitral valve disorder, unspecified
I35	Nonrheumatic aortic valve disorders
I35.0	Aortic (valve) stenosis
I35.1	Aortic (valve) insufficiency
I35.2	Aortic (valve) stenosis with insufficiency
I35.8	Other aortic valve disorders
I35.9	Aortic valve disorder, unspecified
I42	Cardiomyopathy
I42.0	Dilated cardiomyopathy
I42.5	Other restrictive cardiomyopathy
I42.6	Alcoholic cardiomyopathy
I42.7	Cardiomyopathy due to drugs and other external agents
I42.9	Cardiomyopathy, unspecified
I43	Cardiomyopathy in diseases classified elsewhere
I43.1	Cardiomyopathy in metabolic diseases
I43.8	Cardiomyopathy in other diseases classified elsewhere
I50	Heart failure
I50.0	Congestive heart failure
I50.1	Left ventricular failure
I50.9	Heart failure, unspecified

ICD-10 code	Description
I60	Subarachnoid haemorrhage
I60.0	Subarachnoid haemorrhage from carotid siphon and bifurcation
I60.1	Subarachnoid haemorrhage from middle cerebral artery
I60.2	Subarachnoid haemorrhage from anterior communicating artery
I60.3	Subarachnoid haemorrhage from posterior communicating artery
I60.4	Subarachnoid haemorrhage from basilar artery
I60.5	Subarachnoid haemorrhage from vertebral artery
I60.6	Subarachnoid haemorrhage from other intracranial arteries
I60.7	Subarachnoid haemorrhage from intracranial artery, unspecified
I60.8	Other subarachnoid haemorrhage
I61	Intracerebral haemorrhage
I61.0	Intracerebral haemorrhage in hemisphere, subcortical
I61.1	Intracerebral haemorrhage in hemisphere, cortical
I61.2	Intracerebral haemorrhage in hemisphere, unspecified
I61.4	Intracerebral haemorrhage in cerebellum
I61.6	Intracerebral haemorrhage, multiple localized
I61.9	Intracerebral haemorrhage, unspecified
I62	Other nontraumatic intracranial haemorrhage
I62.1	Nontraumatic extradural haemorrhage
I62.9	Intracranial haemorrhage (nontraumatic), unspecified
I63	Cerebral infarction
I63.0	Cerebral infarction due to thrombosis of precerebral arteries

ICD-10 code	Description
I63.1	Cerebral infarction due to embolism of precerebral arteries
I63.2	Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries
I63.3	Cerebral infarction due to thrombosis of cerebral arteries
I63.4	Cerebral infarction due to embolism of cerebral arteries
I63.5	Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries
I63.6	Cerebral infarction due to cerebral venous thrombosis, nonpyogenic
I63.8	Other cerebral infarction
I63.9	Cerebral infarction, unspecified
I64	Stroke, not specified as haemorrhage or infarction
I65	Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction.
I65.0	Occlusion and stenosis of vertebral artery
I65.1	Occlusion and stenosis of basilar artery
I65.2	Occlusion and stenosis of carotid artery
I65.3	Occlusion and stenosis of multiple and bilateral precerebral arteries
I65.8	Occlusion and stenosis of other precerebral artery
I65.9	Occlusion and stenosis of unspecified precerebral artery
I66	Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction.
I66.0	Occlusion and stenosis of middle cerebral artery
I66.1	Occlusion and stenosis of anterior cerebral artery
I66.2	Occlusion and stenosis of posterior cerebral artery
I66.3	Occlusion and stenosis of cerebellar arteries
I66.4	Occlusion and stenosis of multiple and bilateral cerebral arteries

ICD-10 code	Description
I66.8	Occlusion and stenosis of other cerebral artery
I66.9	Occlusion and stenosis of unspecified cerebral artery
I67	Other cerebrovascular diseases
I67.0	Dissection of cerebral arteries, nonruptured
I67.1	Cerebral aneurysm, nonruptured
I67.2	Cerebral atherosclerosis
I67.8	Other specified cerebrovascular diseases
I67.9	Cerebrovascular disease, unspecified
I69	Sequelae of cerebrovascular disease
I69.0	Sequelae of subarachnoid haemorrhage
I69.3	Sequelae of cerebral infarction
I69.4	Sequelae of stroke, not specified as haemorrhage or infarction
I69.8	Sequelae of other and unspecified cerebrovascular diseases
I70	Atherosclerosis
I70.0	Atherosclerosis of aorta
I70.1	Atherosclerosis of renal artery
I70.2	Atherosclerosis of arteries of the extremities
I70.8	Atherosclerosis of other arteries
I71	Aortic aneurysm and dissection
I71.0	Dissection of aorta [any part]
I71.1	Thoracic aortic aneurysm, ruptured
I71.2	Thoracic aortic aneurysm, without mention of rupture

ICD-10 code	Description
I71.3	Abdominal aortic aneurysm, ruptured
I71.4	Abdominal aortic aneurysm, without mention of rupture
I71.5	Thoracoabdominal aortic aneurysm, ruptured
I71.6	Thoracoabdominal aortic aneurysm, without mention of rupture
I71.8	Aortic aneurysm of unspecified site, ruptured
I71.9	Aortic aneurysm of unspecified site, without mention of rupture
I72	Other aneurysm
I72.0	Aneurysm of carotid artery
I72.1	Aneurysm of artery of upper extremity
I72.2	Aneurysm of renal artery
I72.3	Aneurysm of iliac artery
I72.5	Aneurysm of artery of other precerebral arteries
I72.6	Aneurysm and dissection of vertebral artery
I72.8	Aneurysm of other specified arteries
I72.9	Aneurysm of unspecified site
I73	Other peripheral vascular diseases
I73.8	Other specified peripheral vascular diseases
I73.9	Peripheral vascular disease, unspecified
I74	Arterial embolism and thrombosis
I74.0	Embolism and thrombosis of abdominal aorta
I74.1	Embolism and thrombosis of other and unspecified parts of aorta
I74.2	Embolism and thrombosis of arteries of the upper extremities

ICD-10 code	Description
I74.3	Embolism and thrombosis of arteries of the lower extremities
I74.4	Embolism and thrombosis of arteries of extremities, unspecified
I74.5	Embolism and thrombosis of iliac artery
I74.8	Embolism and thrombosis of other arteries
I74.9	Embolism and thrombosis of unspecified artery
I77	Other disorders of arteries and arterioles
I77.3	Arterial fibromuscular dysplasia
I77.4	Coeliac artery compression syndrome
I79	Disorders of arteries, arterioles and capillaries in diseases classified elsewhere
I79.0	Aneurysm of aorta in diseases classified elsewhere
I79.2	Peripheral angiopathy in diseases classified elsewhere

Abbreviations: ICD-10: International Statistical Classification of Diseases and Related Health Problems-10.

Supplementary table 5.5 – Classifications of cardiovascular disease admission codes identified in Hospital Episode Statistics prior to cancer diagnosis.

Source	Phenotype	ICD-10 codes	Total (N=102,604) n (%)
Welch et al. Br J Cancer.2020;123(3):471-9.	Cerebrovascular	I60 - I69 (excluding I60.9, I61.3, I61.5, I61.8, I61.8, I61.9, I62.0, I67.3, I67.4, I67.6, I67.7, I68.0, I68.2, I69.1 and I69.2)	20,366 (19.9)
	Stroke (Cerebrovascular subgroup)	I61 - I64 (excluding I60.9, I61.3, I61.5, I61.8 and I62.0), I69.0, I69.3 and I69.4	8,602 (8.4)
	Congestive cardiac failure	I11.0, I13.0, I13.2, I42.0, I42.5, I42.6, I42.7, I42.9, I43.1, I43.8, I50.0, I50.1 and I50.9	21,462 (20.9)
	Ischaemic heart disease	I20.0 - I25 (excluding I20.1 and I24.1)	64,620 (63.0)

	Acute myocardial infarction (Ischaemic heart disease subgroup)	I21 - I23	10,401 (10.1)
	Peripheral artery disease	I70 - I74 (excluding I70.9, I72.4, I73.0 and I73.1), I77.3, I77.4, I79.0, I79.2 and I84.6	20,911 (20.4)
	Valvular heart disease	I105, I106, I108, I27.9, I34, I35, I31.1, I135.2, I35.5 and I35.9	17,770 (17.3)

Abbreviations: ICD-10: International Statistical Classification of Diseases and Related Health Problems-10.

Supplementary table 5.6 – Patient, tumour and treatment characteristics in the breast cancer cohort (N=226,516).

Variable	Category	Overall		Year											
				2013		2014		2015		2016		2017		2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
		226,516		34,226		37,440		38,440		38,480		38,493		39,437	
Age at cancer diagnosis (years)	25-34	4,022	1.8	570	1.7	656	1.8	669	1.7	682	1.8	710	1.8	735	1.9
	35-44	17,286	7.6	2,782	8.1	2,854	7.6	2,945	7.7	2,984	7.8	2,917	7.6	2,804	7.1
	45-54	50,203	22.2	7,889	23.0	8,404	22.4	8,571	22.3	8,589	22.3	8,479	22.0	8,271	21.0
	55-64	51,844	22.9	8,053	23.5	8,388	22.4	8,588	22.3	8,850	23.0	8,900	23.1	9,065	23.0
	65-74	55,876	24.7	8,270	24.2	9,117	24.4	9,487	24.7	9,524	24.8	9,510	24.7	9,968	25.3
	75-84	32,983	14.6	4,782	14.0	5,646	15.1	5,694	14.8	5,381	14.0	5,467	14.2	6,013	15.2
	≥85	14,302	6.3	1,880	5.5	2,375	6.3	2,486	6.5	2,470	6.4	2,510	6.5	2,581	6.5
Ethnicity	White	198,738	87.7	30,839	90.1	33,157	88.6	33,156	86.3	33,662	87.5	33,831	87.9	34,093	86.4
	Mixed	1,184	0.5	179	0.5	169	0.5	189	0.5	209	0.5	229	0.6	209	0.5
	Asian	8,044	3.6	1,152	3.4	1,177	3.1	1,315	3.4	1,420	3.7	1,464	3.8	1,516	3.8
	Black	4,522	2.0	646	1.9	757	2.0	692	1.8	738	1.9	837	2.2	852	2.2
	Other	3,118	1.4	364	1.1	423	1.1	518	1.3	543	1.4	604	1.6	666	1.7

	Missing	10,910	4.8	1,046	3.1	1,757	4.7	2,570	6.7	1,908	5.0	1,528	4.0	2,101	5.3
Income domain of the Index of Multiple Deprivation	1 - Least deprived	51,814	22.9	7,867	23.0	8,639	23.1	8,815	22.9	8,834	23.0	8,612	22.4	9,047	22.9
	2	52,228	23.1	7,873	23.0	8,655	23.1	8,727	22.7	8,903	23.1	8,927	23.2	9,143	23.2
	3	47,406	20.9	7,111	20.8	7,779	20.8	8,097	21.1	8,091	21.0	8,024	20.8	8,304	21.1
	4	40,605	17.9	6,147	18.0	6,644	17.7	6,960	18.1	6,886	17.9	7,023	18.2	6,945	17.6
	5 - Most deprived	34,463	15.2	5,228	15.3	5,723	15.3	5,841	15.2	5,766	15.0	5,907	15.3	5,998	15.2
Charlson comorbidity index excluding CVD[1]	0	106,251	46.9	16,181	47.3	17,598	47.0	18,066	47.0	18,188	47.3	17,925	46.6	18,293	46.4
	1	19,325	8.5	2,920	8.5	3,249	8.7	3,154	8.2	3,301	8.6	3,279	8.5	3,422	8.7
	2	55,420	24.5	8,344	24.4	9,167	24.5	9,531	24.8	9,352	24.3	9,453	24.6	9,573	24.3
	3	23,372	10.3	3,509	10.3	3,851	10.3	3,927	10.2	3,956	10.3	4,038	10.5	4,091	10.4
	≥4	20,238	8.9	3,078	9.0	3,345	8.9	3,505	9.1	3,425	8.9	3,391	8.8	3,494	8.9

[1] Hospital Episode Statistics assessed 5 years before cancer diagnosis.

	Missing[2]	1,910	0.8	194	0.6	230	0.6	257	0.7	258	0.7	407	1.1	564	1.4
Screen-detected	Yes	75,931	33.5	11,494	33.6	12,476	33.3	12,108	31.5	12,571	32.7	13,132	34.1	14,150	35.9
	No	99,072	43.7	13,570	39.6	15,614	41.7	16,210	42.2	16,163	42.0	18,009	46.8	19,506	49.5
	Missing	51,513	22.7	9,162	26.8	9,350	25.0	10,122	26.3	9,746	25.3	7,352	19.1	5,781	14.7
TNM stage	I	10,4899	46.3	15,911	46.5	17,584	47.0	17,713	46.1	17,774	46.2	17,627	45.8	18,290	46.4
	II	98,987	43.7	14,692	42.9	16,075	42.9	16,849	43.8	16,948	44.0	17,059	44.3	17,364	44.0
	III	22,630	10.0	3,623	10.6	3,781	10.1	3,878	10.1	3,758	9.8	3,807	9.9	3,783	9.6
Laterality	Left	115,340	50.9	17,314	50.6	19,060	50.9	19,832	51.6	19,477	50.6	19,676	51.1	19,981	50.7
	Right	108,849	48.1	16,573	48.4	17,999	48.1	18,190	47.3	18,605	48.3	18,421	47.9	19,061	48.3
	Bilateral	2,219	1.0	309	0.9	341	0.9	413	1.1	382	1.0	383	1.0	391	1.0
	Missing	108	0.0	30	0.1	40	0.1	5	0.0	16	0.0	13	0.0	4	0.0
ER status	Positive	147,482	65.1	24,328	71.1	25,519	68.2	26,117	67.9	24,201	62.9	23,608	61.3	23,709	60.1

[2] Missing if not linked to Hospital Episode Statistics.

	Negative	26,438	11.7	4,159	12.2	4,468	11.9	4,516	11.7	4,411	11.5	4,535	11.8	4,349	11.0
	Missing	52,596	23.2	5,739	16.8	7,453	19.9	7,807	20.3	9,868	25.6	10,350	26.9	11,379	28.9
PR status	Positive	70,727	31.2	11,984	35.0	12,284	32.8	11,856	30.8	11,404	29.6	11,290	29.3	11,909	30.2
	Negative	33,913	15.0	5,344	15.6	5,647	15.1	5,787	15.1	5,698	14.8	5,804	15.1	5,633	14.3
	Missing	12,1876	53.8	16,898	49.4	19,509	52.1	20,797	54.1	21,378	55.6	21,399	55.6	21,895	55.5
HER2 status	Positive	24,070	10.6	3,973	11.6	4,181	11.2	4,009	10.4	4,095	10.6	3,967	10.3	3,845	9.7
	Negative	152,262	67.2	23,963	70.0	25,606	68.4	25,706	66.9	26,153	68.0	25,439	66.1	25,395	64.4
	Borderline	14,412	6.4	687	2.0	1,139	3.0	1,881	4.9	2,706	7.0	3,553	9.2	4,446	11.3
	Missing	35,772	15.8	5,603	16.4	6,514	17.4	6,844	17.8	5,526	14.4	5,534	14.4	5,751	14.6
Nottingham prognostic index	≤2.4	20,913	9.2	3,413	10.0	3,516	9.4	3,475	9.0	3,583	9.3	3,373	8.8	3,553	9.0
	>2.4 but ≤3.4	47,868	21.1	7,350	21.5	7,768	20.7	7,867	20.5	8,206	21.3	8,197	21.3	8,480	21.5

	>3.4 but ≤5.4	82,357	36.4	13,196	38.6	13,696	36.6	13,988	36.4	14,041	36.5	13,615	35.4	13,821	35.0
	>5.4	21,497	9.5	3,699	10.8	3,619	9.7	3,692	9.6	3,716	9.7	3,385	8.8	3,386	8.6
	Missing	53,881	23.8	6,568	19.2	8,841	23.6	9,418	24.5	8,934	23.2	9,923	25.8	10,197	25.9
Grade of differentiation	Well differentiated	4,150	1.8	696	2.0	904	2.4	759	2.0	627	1.6	592	1.5	572	1.5
	Moderately differentiated	34,695	15.3	5,584	16.3	5,849	15.6	5,824	15.2	5,789	15.0	5,685	14.8	5,964	15.1
	Poorly differentiated	119,650	52.8	17,215	50.3	19,395	51.8	20,275	52.7	20,491	53.3	20,878	54.2	21,396	54.3
	Undifferentiated / anaplastic	67,146	29.6	10,593	31.0	11,142	29.8	11,444	29.8	11,441	29.7	11,184	29.1	11,342	28.8
	Not appropriate or cannot be assessed	71	0.0	13	0.0	15	0.0	12	0.0	10	0.0	10	0.0	11	0.0
	Missing	804	0.4	125	0.4	135	0.4	126	0.3	122	0.3	144	0.4	152	0.4
Histology	Ductal	177,519	78.4	26,919	78.7	29,464	78.7	29,919	77.8	30,155	78.4	30,145	78.3	30,917	78.4
	Lobular	28,022	12.4	4,087	11.9	4,537	12.1	4,863	12.7	4,652	12.1	4,899	12.7	4,984	12.6
	Mixed	4,899	2.2	766	2.2	802	2.1	814	2.1	884	2.3	795	2.1	838	2.1

	Other	16,076	7.1	2,454	7.2	2,637	7.0	2,844	7.4	2,789	7.2	2,654	6.9	2,698	6.8
Treatment modality[3]	Surgery	201,522	89.0	31,308	91.5	33,580	89.7	34,187	88.9	34,283	89.1	33,752	87.7	34,412	87.3
	Radiotherapy	153,859	67.9	24,427	71.4	26,220	70.0	25,300	65.8	25,684	66.7	25,854	67.2	26,374	66.9
	Chemotherapy	78,877	34.8	11,845	34.6	13,097	35.0	13,583	35.3	13,728	35.7	13,444	34.9	13,180	33.4

Abbreviations: ER: oestrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2.

[3] All treatments identified using National Cancer Registration and Analysis Service treatment standard operating procedure (between 1 month before and 12 months after cancer diagnosis).

Supplementary table 5.7 – Patient, tumour and treatment characteristics in the colon cancer cohort (N=91,210).

Variable	Category	Overall		Year											
				2013		2014		2015		2016		2017		2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
		91,210		13,884		14,850		15,672		15,653		15,432		15,719	
Age at cancer diagnosis (years)	25-34	912	1.0	157	1.1	167	1.1	140	0.9	199	1.3	142	0.9	107	0.7
	35-44	2,036	2.2	290	2.1	329	2.2	323	2.1	359	2.3	354	2.3	381	2.4
	45-54	5,710	6.3	862	6.2	930	6.3	978	6.2	1,001	6.4	931	6.0	1,008	6.4
	55-64	15,385	16.9	2,366	17.0	2,386	16.1	2,606	16.6	2,620	16.7	2,635	17.1	2,772	17.6
	65-74	27,277	29.9	4,222	30.4	4,422	29.8	4,616	29.5	4,697	30.0	4,706	30.5	4,614	29.4
	75-84	28,583	31.3	4,401	31.7	4,717	31.8	5,017	32.0	4,841	30.9	4,720	30.6	4,887	31.1
	≥85	11,307	12.4	1,586	11.4	1,899	12.8	1,992	12.7	1,936	12.4	1,944	12.6	1,950	12.4
Sex	Male	48,431	53.1	7,451	53.7	7,835	52.8	8,291	52.9	8,395	53.6	8,168	52.9	8,291	52.7
	Female	42,779	46.9	6,433	46.3	7,015	47.2	7,381	47.1	7,258	46.4	7,264	47.1	7,428	47.3
Ethnicity	White	83,317	91.3	13,002	93.6	13,695	92.2	14,188	90.5	14,233	90.9	14,073	91.2	14,126	89.9

	Mixed	274	0.3	37	0.3	45	0.3	45	0.3	45	0.3	51	0.3	51	0.3
	Asian	1,883	2.1	252	1.8	301	2.0	313	2.0	309	2.0	354	2.3	354	2.3
	Black	1,339	1.5	184	1.3	199	1.3	226	1.4	239	1.5	240	1.6	251	1.6
	Other	911	1.0	99	0.7	136	0.9	173	1.1	161	1.0	158	1.0	184	1.2
	Missing	3,486	3.8	310	2.2	474	3.2	727	4.6	666	4.3	556	3.6	753	4.8
Income domain of the Index of Multiple Deprivation	1 - Least deprived	20,257	22.2	3,021	21.8	3,293	22.2	3,495	22.3	3,478	22.2	3,471	22.5	3,499	22.3
	2	21,337	23.4	3,221	23.2	3,420	23.0	3,716	23.7	3,765	24.1	3,555	23.0	3,660	23.3
	3	18,932	20.8	2,867	20.6	3,133	21.1	3,267	20.8	3,220	20.6	3,214	20.8	3,231	20.6
	4	16,392	18.0	2,577	18.6	2,686	18.1	2,767	17.7	2,759	17.6	2,791	18.1	2,812	17.9
	5 - Most deprived	14,292	15.7	2,198	15.8	2,318	15.6	2,427	15.5	2,431	15.5	2,401	15.6	2,517	16.0
Charlson comorbidity index excluding CVD[1]	0	43,371	47.6	6,603	47.6	7,094	47.8	7,466	47.6	7,481	47.8	7,333	47.5	7,394	47.0
	1	7,641	8.4	1,131	8.1	1,263	8.5	1,321	8.4	1,315	8.4	1,278	8.3	1,333	8.5
	2	22,466	24.6	3,422	24.6	3,632	24.5	3,852	24.6	3,836	24.5	3,828	24.8	3,896	24.8
	3	9,293	10.2	1,405	10.1	1,519	10.2	1,591	10.2	1,616	10.3	1,529	9.9	1,633	10.4

[1] Hospital Episode Statistics assessed 5 years before cancer diagnosis.

	≥4	8,193	9.0	1,291	9.3	1,304	8.8	1,413	9.0	1,357	8.7	1,399	9.1	1,429	9.1
	Missing[2]	246	0.3	32	0.2	38	0.3	29	0.2	48	0.3	65	0.4	34	0.2
TNM stage	I	19,213	21.1	2,861	20.6	3,011	20.3	3,281	20.9	3,373	21.5	3,278	21.2	3,409	21.7
	II	36,820	40.4	5,835	42.0	6,156	41.5	6,329	40.4	6,233	39.8	6,088	39.5	6,179	39.3
	III	35,177	38.6	5,188	37.4	5,683	38.3	6,062	38.7	6,047	38.6	6,066	39.3	6,131	39.0
Dukes stage	A	11,255	12.3	2,131	15.3	2,098	14.1	2,283	14.6	2,258	14.4	1,997	12.9	488	3.1
	B	28,605	31.4	5,393	38.8	5,585	37.6	5,696	36.3	5,559	35.5	5,088	33.0	1,284	8.2
	C	25,150	27.6	4,507	32.5	4,838	32.6	5,021	32.0	5,107	32.6	4,600	29.8	1,077	6.9
	Missing	26,200	28.7	1,853	13.3	2,329	15.7	2,672	17.0	2,729	17.4	3,747	24.3	12,870	81.9
Grade of differen-tiation	Well differentiated	9,191	10.1	1,248	9.0	1,416	9.5	1,580	10.1	1,503	9.6	1,633	10.6	1,811	11.5
	Moderately differentiated	4,239	4.6	861	6.2	780	5.3	814	5.2	751	4.8	571	3.7	462	2.9

[2] Missing if not linked to Hospital Episode Statistics.

	Poorly differentiated	64,414	70.6	9,689	69.8	10,469	70.5	11,051	70.5	11,101	70.9	10,948	70.9	11,156	71.0
	Undifferentiated / anaplastic	13,030	14.3	2,037	14.7	2,125	14.3	2,160	13.8	2,232	14.3	2,234	14.5	2,242	14.3
	Not appropriate or cannot be assessed	85	0.1	15	0.1	20	0.1	13	0.1	14	0.1	10	0.1	13	0.1
	Missing	251	0.3	34	0.2	40	0.3	54	0.3	52	0.3	36	0.2	35	0.2
Histology	Adenocarcinoma	85,224	93.4	13,059	94.1	13,904	93.6	14,640	93.4	14,556	93.0	14,465	93.7	14,600	92.9
	Other	5,986	6.6	825	5.9	946	6.4	1,032	6.6	1,097	7.0	967	6.3	1,119	7.1
Treatment modality[3]	Surgery	84,211	92.3	12,911	93.0	13,748	92.6	14,485	92.4	14,474	92.5	14,256	92.4	14,337	91.2
	Chemotherapy	27,259	29.9	4,014	28.9	4,461	30.0	4,701	30.0	4,654	29.7	4,687	30.4	4,742	30.2

Abbreviations: CVD: cardiovascular disease.

[3] All treatments identified using National Cancer Registration and Analysis Service treatment standard operating procedure (between 1 month before and 12 months after cancer diagnosis).

Supplementary table 5.8 – Patient, tumour and treatment characteristics in the rectal cancer cohort (N=39,688).

Variable	Category	Overall		Year											
				2013		2014		2015		2016		2017		2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
		39,688	100.0	6,130	100.0	6,408	100.0	6,672	100.0	6,816	100.0	6,749	100.0	6,913	100.0
Age at cancer diagnosis (years)	25-34	371	0.9	56	0.9	57	0.9	57	0.9	65	1.0	61	0.9	75	1.1
	35-44	999	2.5	127	2.1	125	2.0	158	2.4	194	2.8	194	2.9	201	2.9
	45-54	3,527	8.9	585	9.5	576	9.0	580	8.7	561	8.2	579	8.6	646	9.3
	55-64	8,860	22.3	1,329	21.7	1,435	22.4	1,484	22.2	1,485	21.8	1,486	22.0	1,641	23.7
	65-74	12,630	31.8	1,965	32.1	1,956	30.5	2,136	32.0	2,236	32.8	2,209	32.7	2,128	30.8
	75-84	9,995	25.2	1,583	25.8	1,708	26.7	1,721	25.8	1,695	24.9	1,646	24.4	1,642	23.8
	≥85	3,306	8.3	485	7.9	551	8.6	536	8.0	580	8.5	574	8.5	580	8.4
Sex	Male	25,420	64.0	3,949	64.4	4,049	63.2	4,228	63.4	4,394	64.5	4,357	64.6	4,443	64.3
	Female	14,268	36.0	2,181	35.6	2,359	36.8	2,444	36.6	2,422	35.5	2,392	35.4	2,470	35.7
Ethnicity	White	36,153	91.1	5,706	93.1	5,902	92.1	6,050	90.7	6,197	90.9	6,118	90.7	6,180	89.4
	Mixed	131	0.3	17	0.3	17	0.3	20	0.3	20	0.3	32	0.5	25	0.4
	Asian	1,066	2.7	137	2.2	152	2.4	198	3.0	195	2.9	187	2.8	197	2.8
	Black	418	1.1	74	1.2	62	1.0	55	0.8	76	1.1	83	1.2	68	1.0

	Other	388	1.0	43	0.7	70	1.1	64	1.0	57	0.8	83	1.2	71	1.0
	Missing	1,532	3.9	153	2.5	205	3.2	285	4.3	271	4.0	246	3.6	372	5.4
Income domain of the Index of Multiple Deprivation	1 - Least deprived	8,776	22.1	1,347	22.0	1,371	21.4	1,471	22.0	1,560	22.9	1,510	22.4	1,517	21.9
	2	9,039	22.8	1,389	22.7	1,501	23.4	1,524	22.8	1,517	22.3	1,540	22.8	1,568	22.7
	3	8,361	21.1	1,248	20.4	1,340	20.9	1,422	21.3	1,437	21.1	1,416	21.0	1,498	21.7
	4	7,171	18.1	1,112	18.1	1,152	18.0	1,163	17.4	1,272	18.7	1,236	18.3	1,236	17.9
	5 - Most deprived	6,341	16.0	1,034	16.9	1,044	16.3	1,092	16.4	1,030	15.1	1,047	15.5	1,094	15.8
Charlson comorbidity index excluding CVD[1]	0	18,900	47.6	2,909	47.5	3,049	47.6	3,183	47.7	3,249	47.7	3234	47.9	3,276	47.4
	1	3,364	8.5	523	8.5	530	8.3	535	8.0	571	8.4	564	8.4	641	9.3
	2	9,708	24.5	1,493	24.4	1,601	25.0	1,665	25.0	1,658	24.3	1,588	23.5	1,703	24.6
	3	4,078	10.3	649	10.6	641	10.0	681	10.2	728	10.7	708	10.5	671	9.7
	≥4	3,533	8.9	545	8.9	571	8.9	589	8.8	593	8.7	634	9.4	601	8.7
	Missing[2]	105	0.3	11	0.2	16	0.2	19	0.3	17	0.2	21	0.3	21	0.3
TNM stage	I	12,357	31.1	1,862	30.4	1,943	30.3	2,087	31.3	2,149	31.5	2,115	31.3	2,201	31.8
	II	9,365	23.6	1,528	24.9	1,542	24.1	1,561	23.4	1,595	23.4	1,581	23.4	1,558	22.5

[1] Hospital Episode Statistics assessed 5 years before cancer diagnosis.

[2] Missing if not linked to Hospital Episode Statistics.

	III	17,966	45.3	2,740	44.7	2,923	45.6	3,024	45.3	3,072	45.1	3,053	45.2	3,154	45.6
Dukes' stage	A	7,109	17.9	1,389	22.7	1,384	21.6	1,411	21.1	1,507	22.1	1,146	17.0	272	3.9
	B	6,745	17.0	1,325	21.6	1,293	20.2	1,360	20.4	1,345	19.7	1,156	17.1	266	3.8
	C	8,772	22.1	1,785	29.1	1,736	27.1	1,776	26.6	1,833	26.9	1,358	20.1	284	4.1
	Missing	17,062	43.0	1,631	26.6	1,995	31.1	2,125	31.8	2,131	31.3	3,089	45.8	6,091	88.1
Grade of differentiation	Well differentiated	5,119	12.9	820	13.4	918	14.3	801	12.0	756	11.1	914	13.5	910	13.2
	Moderately differentiated	1,803	4.5	297	4.8	293	4.6	295	4.4	330	4.8	301	4.5	287	4.2
	Poorly differentiated	2,919 6	73.6	4,463	72.8	4,612	72.0	4,983	74.7	5,092	74.7	4,935	73.1	5,111	73.9
	Undifferentiated / anaplastic	3,358	8.5	516	8.4	537	8.4	545	8.2	604	8.9	573	8.5	583	8.4
	Not appropriate or cannot be assessed	25	0.1	8	0.1	3	0.0	4	0.1	2	0.0	5	0.1	3	0.0
	Missing	187	0.5	26	0.4	45	0.7	44	0.7	32	0.5	21	0.3	19	0.3
Histology	Adenocarcinoma	3,777 1	95.2	5,867	95.7	6,130	95.7	6,353	95.2	6,505	95.4	6,386	94.6	6,530	94.5
	Other	1,917	4.8	263	4.3	278	4.3	319	4.8	311	4.6	363	5.4	383	5.5

Treatment modality[3]	Surgery	27,258	68.7	4,420	72.1	4,545	70.9	4,589	68.8	4,655	68.3	4,523	67.0	4,526	65.5
	Radiotherapy	17,165	43.2	2,844	46.4	2,892	45.1	2,861	42.9	2,878	42.2	2,808	41.6	2,882	41.7
	Chemotherapy	15,709	39.6	2,317	37.8	2,556	39.9	2,597	38.9	2,606	38.2	2,735	40.5	2,898	41.9

Abbreviations: CVD: cardiovascular disease.

[3] All treatments identified using National Cancer Registration and Analysis Service treatment standard operating procedure (between 1 month before and 12 months after cancer diagnosis).

Supplementary table 5.9 – Patient, tumour and treatment characteristics in the prostate cancer cohort (N=175,639).

Variable	Category	Overall		Years											
				2013		2014		2015		2016		2017		2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
		175,639	100.0	26,502	100.0	27,554	100.0	28,576	100.0	28,443	100.0	28,617	100.0	35,947	100.0
Age at cancer diagnosis (years)	25-34	4	0.0	0	0.0	1	0.0	2	0.0	1	0.0	0	0.0	0	0.0
	35-44	366	0.2	49	0.2	53	0.2	66	0.2	63	0.2	62	0.2	73	0.2
	45-54	8,534	4.9	1,135	4.3	1,299	4.7	1,349	4.7	1,442	5.1	1,491	5.2	1,818	5.1
	55-64	39,927	22.7	5,968	22.5	6,208	22.5	6,405	22.4	6,236	21.9	6,600	23.1	8,510	23.7
	65-74	79,141	45.1	11,829	44.6	12,066	43.8	13,007	45.5	12,918	45.4	12,970	45.3	16,351	45.5
	75-84	41,980	23.9	6,572	24.8	6,877	25.0	6,816	23.9	6,905	24.3	6,610	23.1	8,200	22.8
	≥85	5,687	3.2	949	3.6	1,050	3.8	931	3.3	878	3.1	884	3.1	995	2.8
Ethnicity	White	153,282	87.3	24,042	90.7	24,406	88.6	24,413	85.4	24,553	86.3	25,080	87.6	30,788	85.6
	Mixed	762	0.4	114	0.4	102	0.4	113	0.4	134	0.5	141	0.5	158	0.4
	Asian	3,309	1.9	436	1.6	520	1.9	542	1.9	550	1.9	572	2.0	689	1.9
	Black	6,093	3.5	845	3.2	889	3.2	973	3.4	949	3.3	1,147	4.0	1,290	3.6
	Other	1,723	1.0	201	0.8	234	0.8	280	1.0	297	1.0	293	1.0	418	1.2
	Missing	10470	6.0	864	3.3	1,403	5.1	2,255	7.9	1,960	6.9	1,384	4.8	2,604	7.2
Income domain of the Index of Multiple Deprivation	1 - Least deprived	43,793	24.9	6,600	24.9	6,736	24.4	7,024	24.6	7,052	24.8	7,162	25.0	9,219	25.6
	2	43,060	24.5	6,499	24.5	6,705	24.3	7,016	24.6	6,937	24.4	7,014	24.5	8,889	24.7
	3	36888	21.0	5,533	20.9	5,899	21.4	6,028	21.1	5,969	21.0	5,987	20.9	7,472	20.8
	4	28899	16.5	4,284	16.2	4,548	16.5	4,680	16.4	4,683	16.5	4,797	16.8	5,907	16.4

	5 - Most deprived	22,999	13.1	3,586	13.5	3,666	13.3	3,828	13.4	3,802	13.4	3,657	12.8	4,460	12.4
Charlson comorbidity index excluding CVD[1]	0	79,618	45.3	12,433	46.9	12,695	46.1	13,048	45.7	13,013	45.8	12,762	44.6	15,667	43.6
	1	14,857	8.5	2,277	8.6	2,285	8.3	2,510	8.8	2,432	8.6	2,409	8.4	2,944	8.2
	2	43,368	24.7	6,443	24.3	6,817	24.7	7,095	24.8	7,113	25.0	7,049	24.6	8,851	24.6
	3	18,266	10.4	2,723	10.3	2,943	10.7	2,893	10.1	2,902	10.2	2,952	10.3	3,853	10.7
	≥4	15,547	8.9	2,294	8.7	2,446	8.9	2,580	9.0	2,451	8.6	2,624	9.2	3,152	8.8
	Missing[2]	3,983	2.3	332	1.3	368	1.3	450	1.6	532	1.9	821	2.9	1,480	4.1
TNM stage	I	79,477	45.3	11,868	44.8	11,989	43.5	12,530	43.8	12,223	43.0	13,364	46.7	17,503	48.7
	II	44,469	25.3	7,758	29.3	7,985	29.0	8,078	28.3	7,662	26.9	6,284	22.0	6,702	18.6
	III	51,693	29.4	6,876	25.9	7,580	27.5	7,968	27.9	8,558	30.1	8,969	31.3	11,742	32.7
Gleason score	Group 1 (3+3)	42,774	24.4	8,254	31.1	7,935	28.8	6,666	23.3	6,292	22.1	6,220	21.7	7,407	20.6
	Group 2 (3+4)	57,810	32.9	7,925	29.9	8,614	31.3	9,684	33.9	9,755	34.3	9,586	33.5	12,246	34.1
	Group 3 (4+3)	29,644	16.9	3,983	15.0	4,207	15.3	4,928	17.2	4,862	17.1	5,129	17.9	6,535	18.2
	Group 4 (4+4, 3+5, 5+3)	14,966	8.5	2,107	8.0	2,161	7.8	2,413	8.4	2,550	9.0	2,625	9.2	3,110	8.7
	Group 5 (4+5, 5+4, 5+5)	18,623	10.6	2,513	9.5	2,622	9.5	2,953	10.3	3,215	11.3	3,196	11.2	4,124	11.5
	Missing	11,822	6.7	1,720	6.5	2,015	7.3	1,932	6.8	1,769	6.2	1,861	6.5	2,525	7.0

[1] Hospital Episode Statistics assessed 5 years before cancer diagnosis.

[2] Missing if not linked to Hospital Episode Statistics.

Grade of differentiation	Well differentiated	116,616	66.4	1,646	6.2	5,073	18.4	23,686	82.9	24,459	86.0	26,736	93.4	35,016	97.4
	Moderately differentiated	1,516	0.9	22	0.1	49	0.2	504	1.8	551	1.9	254	0.9	136	0.4
	Poorly differentiated	20,965	11.9	8,282	31.3	7,222	26.2	2,421	8.5	1,916	6.7	814	2.8	310	0.9
	Undifferentiated / anaplastic	31,063	17.7	14,041	53.0	12,932	46.9	1,738	6.1	1,381	4.9	691	2.4	280	0.8
	Not appropriate or cannot be assessed	5,134	2.9	2,506	9.5	2,270	8.2	168	0.6	78	0.3	61	0.2	51	0.1
	Missing	345	0.2	5	0.0	8	0.0	59	0.2	58	0.2	61	0.2	154	0.4
Histology	Adenocarcinoma	170,221	96.9	25,953	97.9	26,873	97.5	27,813	97.3	27,480	96.6	27,515	96.1	34,587	96.2
	Other	5,418	3.1	549	2.1	681	2.5	763	2.7	963	3.4	1,102	3.9	1,360	3.8
Treatment modality[3]	Surgery	37,676	21.5	4,979	18.8	5,456	19.8	6,224	21.8	6,214	21.8	6,516	22.8	8,287	23.1
	Radiotherapy	62,070	35.3	9,784	36.9	9,879	35.9	9,373	32.8	9,833	34.6	9,884	34.5	13,317	37.0
	Chemotherapy	7,039	4.0	222	0.8	885	3.2	1,442	5.0	1,423	5.0	1,412	4.9	1,655	4.6

Abbreviations: CVD: cardiovascular disease.

[3] All treatments identified using National Cancer Registration and Analysis Service treatment standard operating procedure (between 1 month before and 12 months after cancer diagnosis).

Supplementary table 5.10 – Patient, tumour and treatment characteristics in the non-small-cell lung cancer cohort (N=70,458).

Variable	Category	Overall		Years											
				2013		2014		2015		2016		2017		2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
		70,458	100.0	10,745	100.0	11,780	100.0	11,931	100.0	12,128	100.0	12,444	100.0	11,430	100.0
Age at cancer diagnosis (years)	25-34	155	0.2	21	0.2	23	0.2	29	0.2	27	0.2	28	0.2	27	0.2
	35-44	444	0.6	65	0.6	67	0.6	83	0.7	77	0.6	71	0.6	81	0.7
	45-54	2,655	3.8	406	3.8	483	4.1	466	3.9	437	3.6	445	3.6	418	3.7
	55-64	10,327	14.7	1,678	15.6	1,749	14.8	1,866	15.6	1,706	14.1	1,777	14.3	1,551	13.6
	65-74	24,292	34.5	3,745	34.9	4,045	34.3	4,042	33.9	4,230	34.9	4,267	34.3	3,963	34.7
	75-84	23,882	33.9	3,607	33.6	3,954	33.6	3,975	33.3	4,159	34.3	4,252	34.2	3,935	34.4
	≥85	8,703	12.4	1,223	11.4	1,459	12.4	1,470	12.3	1,492	12.3	1,604	12.9	1,455	12.7
Sex	Male	36,229	51.4	5,702	53.1	6,074	51.6	6,217	52.1	6,303	52.0	6,279	50.5	5,654	49.5
	Female	34,229	48.6	5,043	46.9	5,706	48.4	5,714	47.9	5,825	48.0	6,165	49.5	5,776	50.5
Ethnicity	White	66,312	94.1	10,207	95.0	11,118	94.4	11,159	93.5	11,355	93.6	11,753	94.4	10,720	93.8
	Mixed	163	0.2	25	0.2	25	0.2	21	0.2	30	0.2	30	0.2	32	0.3

	Asian	1,183	1.7	178	1.7	187	1.6	186	1.6	199	1.6	233	1.9	200	1.7
	Black	625	0.9	77	0.7	100	0.8	104	0.9	108	0.9	115	0.9	121	1.1
	Other	518	0.7	67	0.6	85	0.7	75	0.6	80	0.7	111	0.9	100	0.9
	Missing	1,657	2.4	191	1.8	265	2.2	386	3.2	356	2.9	202	1.6	257	2.2
Income domain of the Index of Multiple Deprivation	1 - Least deprived	9,891	14.0	1,458	13.6	1,662	14.1	1,653	13.9	1,649	13.6	1,801	14.5	1,668	14.6
	2	12,467	17.7	1,837	17.1	2,112	17.9	2,118	17.8	2,132	17.6	2,257	18.1	2,011	17.6
	3	13,612	19.3	2,092	19.5	2,196	18.6	2,360	19.8	2,387	19.7	2,332	18.7	2,245	19.6
	4	15,262	21.7	2,378	22.1	2,610	22.2	2,515	21.1	2,620	21.6	2,689	21.6	2,450	21.4
	5 - Most deprived	19,226	27.3	2,980	27.7	3,200	27.2	3,285	27.5	3,340	27.5	3,365	27.0	3,056	26.7
Charlson comorbidity index excluding CVD[1]	0	33,258	47.2	5,034	46.8	5,573	47.3	5,643	47.3	5,790	47.7	5,790	46.5	5,428	47.5
	1	6,020	8.5	970	9.0	1,058	9.0	1,054	8.8	999	8.2	1,010	8.1	929	8.1
	2	17,203	24.4	2,589	24.1	2,856	24.2	2,926	24.5	2,953	24.3	3,076	24.7	2,803	24.5
	3	7,278	10.3	1,111	10.3	1,237	10.5	1,187	9.9	1,256	10.4	1,315	10.6	1,172	10.3
	≥4	6,283	8.9	1,004	9.3	1,031	8.8	1,084	9.1	1,074	8.9	1,087	8.7	1,003	8.8

[1] Hospital Episode Statistics assessed 5 years before cancer diagnosis.

	Missing[2]	416	0.6	37	0.3	25	0.2	37	0.3	56	0.5	166	1.3	95	0.8
TNM stage	I	33,890	48.1	4,704	43.8	5,418	46.0	5,649	47.3	5,857	48.3	6,252	50.2	6,010	52.6
	II	15,322	21.7	2,491	23.2	2,614	22.2	2,620	22.0	2,575	21.2	2,557	20.5	2,465	21.6
	IIIA	21,246	30.2	3,550	33.0	3,748	31.8	3,662	30.7	3,696	30.5	3,635	29.2	2,955	25.9
Laterality	Left	29,043	41.2	4,353	40.5	4,876	41.4	4,905	41.1	5,049	41.6	5,048	40.6	4,812	42.1
	Right	40,480	57.5	6,094	56.7	6,665	56.6	6,897	57.8	6,974	57.5	7,316	58.8	6,534	57.2
	Bilateral	122	0.2	12	0.1	30	0.3	16	0.1	21	0.2	21	0.2	22	0.2
	Missing	813	1.2	286	2.7	209	1.8	113	0.9	84	0.7	59	0.5	62	0.5
Grade of differen-tiation	Well differentiated	45,189	64.1	6,286	58.5	7,196	61.1	7,490	62.8	7,874	64.9	8,440	67.8	7,903	69.1
	Moderately differentiated	2,878	4.1	459	4.3	499	4.2	490	4.1	515	4.2	484	3.9	431	3.8
	Poorly differentiated	10,263	14.6	1,847	17.2	1,905	16.2	1,836	15.4	1,670	13.8	1,573	12.6	1,432	12.5
	Undifferentiated / anaplastic	11,560	16.4	2,056	19.1	2,079	17.6	2,006	16.8	1,980	16.3	1,856	14.9	1,583	13.8

[2] Missing if not linked to Hospital Episode Statistics.

	Not appropriate or cannot be assessed	270	0.4	60	0.6	42	0.4	46	0.4	41	0.3	38	0.3	43	0.4
	Missing	298	0.4	37	0.3	59	0.5	63	0.5	48	0.4	53	0.4	38	0.3
Histology	Adenocarcinoma	21,863	31.0	3,488	32.5	3,884	33.0	3,911	32.8	3,526	29.1	3,627	29.1	3,427	30.0
	Squamous cell carcinoma	19,616	27.8	3,233	30.1	3,332	28.3	3,334	27.9	3,453	28.5	3,392	27.3	2,872	25.1
	Other	28,979	41.1	4,024	37.4	4,564	38.7	4,686	39.3	5,149	42.5	5,425	43.6	5,131	44.9
Treatment modality[3]	Surgery	27,819	39.5	4,334	40.3	4,679	39.7	4,818	40.4	4,585	37.8	4,784	38.4	4,619	40.4
	Radiotherapy	20,196	28.7	3,087	28.7	3,435	29.2	3,519	29.5	3,519	29.0	3,448	27.7	3,188	27.9
	Chemotherapy	13,691	19.4	2,294	21.3	2,462	20.9	2,490	20.9	2,224	18.3	2,327	18.7	1,894	16.6

Abbreviations: CVD: cardiovascular disease.

[3] All treatments identified using National Cancer Registration and Analysis Service treatment standard operating procedure (between 1 month before and 12 months after cancer diagnosis).

Supplementary table 5.11 – Patient, tumour and treatment characteristics in the diffuse large B cell lymphoma cohort (N=23,426).[1]

Variable	Category	Overall		Years											
				2013		2014		2015		2016		2017		2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
		23,426	100.0	3,366	100.0	3,723	100.0	4,112	100.0	4,248	100.0	4,246	100.0	3,731	100.0
Age at cancer diagnosis (years)	25-34	652	2.8	72	2.1	105	2.8	118	2.9	115	2.7	119	2.8	123	3.3
	35-44	994	4.2	131	3.9	184	4.9	180	4.4	170	4.0	165	3.9	164	4.4
	45-54	2,214	9.5	333	9.9	360	9.7	361	8.8	425	10.0	381	9.0	354	9.5
	55-64	3,975	17.0	590	17.5	643	17.3	705	17.1	702	16.5	697	16.4	638	17.1
	65-74	7,138	30.5	1,039	30.9	1,113	29.9	1,232	30.0	1,281	30.2	1,352	31.8	1,121	30.0
	75-84	6,364	27.2	909	27.0	972	26.1	1,174	28.6	1,136	26.7	1,172	27.6	1,001	26.8
	≥85	2,089	8.9	292	8.7	346	9.3	342	8.3	419	9.9	360	8.5	330	8.8
Sex	Male	12,981	55.4	1,833	54.5	2,060	55.3	2,286	55.6	2,383	56.1	2,316	54.5	2,103	56.4
	Female	10,445	44.6	1,533	45.5	1,663	44.7	1,826	44.4	1,865	43.9	1,930	45.5	1,628	43.6
Ethnicity	White	20,921	89.3	3,085	91.7	3,340	89.7	3,632	88.3	3,772	88.8	3,779	89.0	3,313	88.8

[1] No specific histology categories are included in National Cancer Registration and Analysis Service for DLBCL cases.

	Mixed	99	0.4	14	0.4	9	0.2	19	0.5	17	0.4	26	0.6	14	0.4
	Asian	952	4.1	114	3.4	144	3.9	163	4.0	177	4.2	191	4.5	163	4.4
	Black	351	1.5	42	1.2	68	1.8	69	1.7	61	1.4	60	1.4	51	1.4
	Other	311	1.3	33	1.0	43	1.2	55	1.3	65	1.5	64	1.5	51	1.4
	Missing	792	3.4	78	2.3	119	3.2	174	4.2	156	3.7	126	3.0	139	3.7
Income domain of the Index of Multiple Deprivation	1 - Least deprived	5,020	21.4	739	22.0	772	20.7	939	22.8	911	21.4	882	20.8	777	20.8
	2	5,317	22.7	784	23.3	867	23.3	889	21.6	938	22.1	1,010	23.8	829	22.2
	3	4,880	20.8	710	21.1	792	21.3	869	21.1	868	20.4	856	20.2	785	21.0
	4	4,371	18.7	649	19.3	684	18.4	754	18.3	787	18.5	794	18.7	703	18.8
	5 - Most deprived	3,838	16.4	484	14.4	608	16.3	661	16.1	744	17.5	704	16.6	637	17.1
Charlson comorbidity index excluding CVD[2]	0	11,051	47.2	1,570	46.6	1,727	46.4	1953	47.5	2,017	47.5	1996	47.0	1,788	47.9
	1	1,840	7.9	295	8.8	296	8.0	326	7.9	294	6.9	306	7.2	323	8.7
	2	5,805	24.8	831	24.7	950	25.5	1,021	24.8	1,053	24.8	1,064	25.1	886	23.7
	3	2,504	10.7	366	10.9	400	10.7	429	10.4	472	11.1	458	10.8	379	10.2
	≥4	2,126	9.1	292	8.7	336	9.0	368	8.9	400	9.4	391	9.2	339	9.1

[2] Hospital Episode Statistics assessed 5 years before cancer diagnosis.

	Missing[3]	100	0.4	12	0.4	14	0.4	15	0.4	12	0.3	31	0.7	16	0.4
TNM stage	I	4,478	19.1	790	23.5	842	22.6	790	19.2	708	16.7	717	16.9	631	16.9
	II	3,973	17.0	601	17.9	720	19.3	772	18.8	722	17.0	619	14.6	539	14.4
	III	4,066	17.4	619	18.4	683	18.3	737	17.9	734	17.3	710	16.7	583	15.6
	IV	10,909	46.6	1,356	40.3	1,478	39.7	1,813	44.1	2,084	49.1	2,200	51.8	1,978	53.0
Grade of differentiation	Well differentiated	14,589	62.3	2,353	69.9	2,236	60.1	2,375	57.8	2,625	61.8	2,758	65.0	2,242	60.1
	Moderately differentiated	13	0.1	4	0.1	3	0.1	4	0.1	0	0.0	2	0.0	0	0.0
	Poorly differentiated	28	0.1	11	0.3	7	0.2	2	0.0	2	0.0	4	0.1	2	0.1
	Undifferentiated / anaplastic	1,260	5.4	411	12.2	277	7.4	287	7.0	187	4.4	60	1.4	38	1.0
	Not appropriate or cannot be assessed	53	0.2	13	0.4	10	0.3	9	0.2	4	0.1	7	0.2	10	0.3
	Missing	7,483	31.9	574	17.1	1,190	32.0	1,435	34.9	1,430	33.7	1,415	33.3	1,439	38.6
	Radiotherapy	6,564	28.0	891	26.5	1,087	29.2	1,098	26.7	1,177	27.7	1,199	28.2	1,112	29.8

[3] Missing if not linked to Hospital Episode Statistics.

Treatment modality[4]	Chemotherapy	19,861	84.8	2,804	83.3	3,169	85.1	3,478	84.6	3,594	84.6	3,611	85.0	3,205	85.9

Abbreviations: CVD: cardiovascular disease.

[4] All treatments identified using National Cancer Registration and Analysis Service treatment standard operating procedure (between 1 month before and 12 months after cancer diagnosis).

Supplementary table 5.12 – Patient, tumour and treatment characteristics in the Hodgkin lymphoma cohort (N=7,303).

Variable	Category	Overall		Years											
				2013		2014		2015		2016		2017		2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
		7,303	100.0	1,016	100.0	1,186	100.0	1,306	100.0	1,236	100.0	1,331	100.0	1,228	100.0
Age at cancer diagnosis (years)	25-34	1,686	23.1	225	22.1	260	21.9	299	22.9	302	24.4	329	24.7	271	22.1
	35-44	1,170	16.0	177	17.4	190	16.0	204	15.6	196	15.9	226	17.0	177	14.4
	45-54	1,125	15.4	164	16.1	172	14.5	212	16.2	184	14.9	193	14.5	200	16.3
	55-64	1,076	14.7	153	15.1	187	15.8	181	13.9	179	14.5	187	14.0	189	15.4
	65-74	1,158	15.9	139	13.7	201	16.9	212	16.2	196	15.9	211	15.9	199	16.2
	75-84	883	12.1	127	12.5	141	11.9	161	12.3	150	12.1	153	11.5	151	12.3
	≥85	205	2.8	31	3.1	35	3.0	37	2.8	29	2.3	32	2.4	41	3.3
Sex	Male	4,321	59.2	580	57.1	687	57.9	795	60.9	717	58.0	810	60.9	732	59.6
	Female	2,982	40.8	436	42.9	499	42.1	511	39.1	519	42.0	521	39.1	496	40.4
Ethnicity	White	5,964	81.7	847	83.4	994	83.8	1,047	80.2	996	80.6	1,086	81.6	994	80.9
	Mixed	81	1.1	12	1.2	7	0.6	17	1.3	17	1.4	19	1.4	9	0.7
	Asian	486	6.7	65	6.4	61	5.1	75	5.7	86	7.0	111	8.3	88	7.2
	Black	231	3.2	34	3.3	33	2.8	42	3.2	37	3.0	43	3.2	42	3.4
	Other	155	2.1	18	1.8	35	3.0	30	2.3	21	1.7	28	2.1	23	1.9
	Missing	386	5.3	40	3.9	56	4.7	95	7.3	79	6.4	44	3.3	72	5.9
Income domain of the Index of	1 - Least deprived	1,322	18.1	199	19.6	206	17.4	232	17.8	224	18.1	237	17.8	224	18.2
	2	1,463	20.0	201	19.8	252	21.2	259	19.8	242	19.6	267	20.1	242	19.7

Multiple Deprivation	3	1,544	21.1	188	18.5	251	21.2	275	21.1	278	22.5	284	21.3	268	21.8
	4	1,531	21.0	242	23.8	237	20.0	273	20.9	251	20.3	270	20.3	258	21.0
	5 - Most deprived	1,443	19.8	186	18.3	240	20.2	267	20.4	241	19.5	273	20.5	236	19.2
Charlson comorbidity index excluding CVD[1]	0	3,512	48.1	493	48.5	554	46.7	610	46.7	606	49.0	649	48.8	600	48.9
	1	608	8.3	90	8.9	98	8.3	124	9.5	105	8.5	109	8.2	82	6.7
	2	1,729	23.7	261	25.7	280	23.6	324	24.8	265	21.4	296	22.2	303	24.7
	3	736	10.1	95	9.4	128	10.8	126	9.6	135	10.9	141	10.6	111	9.0
	≥4	641	8.8	73	7.2	116	9.8	113	8.7	115	9.3	114	8.6	110	9.0
	Missing[2]	77	1.1	4	0.4	10	0.8	9	0.7	10	0.8	22	1.7	22	1.8
TNM stage	I	1,006	13.8	140	13.8	178	15.0	185	14.2	157	12.7	177	13.3	169	13.8
	II	2,380	32.6	354	34.8	386	32.5	427	32.7	436	35.3	427	32.1	350	28.5
	III	1,571	21.5	205	20.2	246	20.7	297	22.7	271	21.9	276	20.7	276	22.5
	IV	2,346	32.1	317	31.2	376	31.7	397	30.4	372	30.1	451	33.9	433	35.3
Grade of differentiation	Well differentiated	6,051	82.9	921	90.6	968	81.6	1,063	81.4	1,006	81.4	1,094	82.2	999	81.4
	Moderately differentiated	145	2.0	53	5.2	27	2.3	22	1.7	27	2.2	12	0.9	4	0.3
	Poorly differentiated	58	0.8	16	1.6	16	1.3	14	1.1	7	0.6	1	0.1	4	0.3

[1] Hospital Episode Statistics assessed 5 years before cancer diagnosis.

[2] Missing if not linked to Hospital Episode Statistics.

	Undifferentiated / anaplastic	10	0.1	2	0.2	2	0.2	2	0.2	2	0.2	1	0.1	1	0.1
	Not appropriate or cannot be assessed	14	0.2	3	0.3	1	0.1	1	0.1	3	0.2	3	0.2	3	0.2
	Missing	1,025	14.0	21	2.1	172	14.5	204	15.6	191	15.5	220	16.5	217	17.7
Histology	Classic	3,739	51.2	572	56.3	647	54.6	685	52.5	622	50.3	638	47.9	575	46.8
	Nodular lymphocyte predominant	859	11.8	107	10.5	124	10.5	152	11.6	156	12.6	146	11.0	174	14.2
	Not otherwise specified	2,705	37.0	337	33.2	415	35.0	469	35.9	458	37.1	547	41.1	479	39.0
Treatment modality[3]	Radiotherapy	1,809	24.8	255	25.1	301	25.4	354	27.1	306	24.8	299	22.5	294	23.9
	Chemotherapy	6,212	85.1	869	85.5	1,013	85.4	1,096	83.9	1,048	84.8	1,143	85.9	1,043	84.9

Abbreviations: CVD: cardiovascular disease.

[3] All treatments identified using National Cancer Registration and Analysis Service treatment standard operating procedure (between 1 month before and 12 months after cancer diagnosis).

Supplementary table 5.13 – Summary of patients with hospitalised CVD categories identified using ICD-10 diagnosis code list[1] in HES only or HES and a record found in a NICOR dataset.[2]

	HES only n	HES and MINAP n	HES and NACSA n	HES and PCI n	HES and NHFA n	HES and NICOR n	NICOR only n	Total N
Hospitalised CVD[3]	84,424	8,359	4,020	9,250	3,108	18,182	230	102,834[4]
CVD category								
Cerebrovascular	18,584	775	473	633	479	1,782	-	20,366
Stroke	7,948	273	158	240	184	654	-	8,602
Congestive cardiac failure	15,393	2,325	1,044	1,722	3,024	6,069	-	21,462
Ischaemic heart disease	48,138	8,290	3,475	9,240	1,995	16,482	-	64,620
Acute myocardial infarction	2,122	7,099	955	5,251	555	8,279	-	10,401
Peripheral artery disease	18,090	1,214	866	1,187	560	2,821	-	20,911
Valvular heart disease	12,376	1,944	2,235	1,545	1,381	5,398	-	17,775

[1] ICD-10 codes for each CVD category found in Table 5.4.

[2] Occurrences are reported, therefore rows and columns do not add up to the totals.

[3] CVD categories are retrieved from HES ICD-10 codes and not from a NICOR diagnosis.

[4] This table only reports CVD records identified in HES which excludes 230 identified only in NICOR. Therefore, the total number of records does not include 203 records identified only in NICOR.

Abbreviations: CVD: cardiovascular disease; HES: Hospital Episode Statistics; NICOR: National Institute for Cardiovascular Outcomes Research; MINAP: Myocardial Ischaemia National Audit Project; NACSA: National Adult Cardiac Surgery Audit; PCI: Percutaneous Coronary Intervention audit; NHFA: National Heart Failure Audit

Supplementary table 5.14 – Unadjusted odds of hospitalisation with cardiovascular disease in the individual tumour cohorts using logistic regression analysis with interaction between each covariate and the income domain of Index of Multiple Deprivation (N = 634,240).

Income domain of the Index of Multiple Deprivation	1 - least	2	3	4	5 – most
Breast cancer, N (226516)	51,814	52,228	47,406	40,605	34,463
Prior CVD, n (%) 17452 (7.7)	3,153 (6.1)	3,577 (6.8)	3,714 (7.8)	3,534 (8.7)	3,474 (10.1)
TNM stage, OR (95% CI)					
I	1 (Reference)	1.12 (1.03, 1.20)	1.32 (1.23, 1.42)	1.54 (1.42, 1.66)	1.84 (1.69, 1.98)
II	1.26 (1.17, 1.36)	1.46 (1.35, 1.57)	1.60 (1.48, 1.71)	1.76 (1.63, 1.90)	2.09 (1.93, 2.24)
III	1.07 (0.93, 1.21)	1.18 (1.03, 1.33)	1.56 (1.38, 1.74)	1.58 (1.39, 1.77)	1.72 (1.51, 1.93)
Treatment modality (Reference: "No" treatment* and Index of Multiple Deprivation "1")[82], OR (95% CI)					
Surgery	0.16 (0.15, 0.18)	0.18 (0.17, 0.20)	0.21 (0.19, 0.22)	0.23 (0.21, 0.25)	0.28 (0.26, 0.30)
Radiotherapy	0.33 (0.31, 0.36)	0.36 (0.33, 0.38)	0.42 (0.39, 0.45)	0.47 (0.43, 0.50)	0.56 (0.52, 0.60)
Chemotherapy	0.25 (0.22, 0.27)	0.28 (0.25, 0.31)	0.33 (0.30, 0.37)	0.39 (0.35, 0.43)	0.44 (0.40, 0.48)
Colon cancer, N (91210)	20,257	21,337	18,932	16,392	14,292
Prior CVD, n (%) 20161 (22.1)	3,990 (19.7)	4,386 (20.6)	4,202 (22.2)	3,877 (23.7)	3,706 (25.9)
TNM stage, OR (95% CI)					
I	1 (Reference)	1.13 (1.01, 1.24)	1.21 (1.08, 1.33)	1.39 (1.24, 1.54)	1.50 (1.34, 1.67)
II	1.03 (0.93, 1.12)	1.05 (0.95, 1.14)	1.16 (1.06, 1.27)	1.28 (1.16, 1.40)	1.43 (1.29, 1.56)
III	0.92 (0.84, 1.01)	0.98 (0.89, 1.07)	1.09 (0.98, 1.19)	1.13 (1.02, 1.23)	1.33 (1.20, 1.46)

[82] The three treatment modalities are not mutually exclusive, and reference includes either "No surgery" or "No chemotherapy" or "No radiotherapy".

Treatment modality (Reference: “No” treatment* and Index of Multiple Deprivation “1”), OR (95% CI)					
Surgery	0.67 (0.59, 0.75)	0.70 (0.62, 0.79)	0.76 (0.67, 0.85)	0.84 (0.74, 0.94)	0.94 (0.83, 1.06)
Chemotherapy	0.37 (0.34, 0.41)	0.39 (0.35, 0.42)	0.40 (0.36, 0.43)	0.42 (0.38, 0.46)	0.49 (0.44, 0.53)
Rectal cancer, N (39688)	8,776	9,039	8,361	7,171	6,341
Prior CVD, n (%) 6699 (16.9)	1,306 (14.9)	1,367 (15.1)	1,403 (16.8)	13,31 (18.6)	1,292 (20.4)
TNM stage, OR (95% CI)					
I	1 (Reference)	0.98 (0.84, 1.11)	1.15 (0.99, 1.30)	1.32 (1.13, 1.50)	1.48 (1.26, 1.69)
II	0.91 (0.77, 1.05)	0.91 (0.77, 1.04)	1.05 (0.89, 1.20)	1.20 (1.02, 1.38)	1.38 (1.16, 1.59)
III	0.65 (0.56, 0.74)	0.71 (0.62, 0.80)	0.77 (0.67, 0.87)	0.86 (0.75, 0.98)	0.98 (0.85, 1.11)
Treatment modality (Reference: “No” treatment* and Index of Multiple Deprivation “1”), OR (95% CI)					
Surgery	0.49 (0.43, 0.55)	0.48 (0.42, 0.54)	0.51 (0.45, 0.57)	0.60 (0.53, 0.68)	0.66 (0.58, 0.75)
Radiotherapy	0.91 (0.80, 1.03)	0.98 (0.86, 1.09)	1.08 (0.95, 1.21)	1.10 (0.97, 1.23)	1.29 (1.14, 1.44)
Chemotherapy	0.40 (0.34, 0.45)	0.43 (0.37, 0.48)	0.41 (0.35, 0.47)	0.47 (0.40, 0.54)	0.54 (0.46, 0.62)
Prostate cancer, N (175639)	43,793	43,060	36,888	28,899	22,999
Prior CVD, n (%) 27123 (15.4)	5,903 (13.5)	6392 (14.8)	5,,729 (15.5)	4,758 (16.5)	4,341 (18.9)
TNM stage, OR (95% CI)					
I	1 (Reference)	1.16 (1.09, 1.22)	1.22 (1.15, 1.29)	1.27 (1.19, 1.35)	1.53 (1.44, 1.63)
II	0.86 (0.80, 0.92)	0.94 (0.88, 1.01)	1.01 (0.94, 1.08)	1.20 (1.11, 1.28)	1.26 (1.16, 1.36)
III	1.05 (0.98, 1.11)	1.13 (1.06, 1.21)	1.18 (1.10, 1.26)	1.22 (1.13, 1.30)	1.52 (1.41, 1.63)
Treatment modality (Reference: “No” treatment* and Index of Multiple Deprivation “1”), OR (95% CI)					
Surgery	0.40 (0.37, 0.44)	0.44 (0.40, 0.48)	0.43 (0.39, 0.47)	0.47 (0.43, 0.52)	0.56 (0.51, 0.62)
Radiotherapy	1.14 (1.07, 1.20)	1.21 (1.14, 1.27)	1.24 (1.17, 1.32)	1.39 (1.30, 1.47)	1.53 (1.43, 1.64)
Chemotherapy	1.21 (1.04, 1.38)	1.26 (1.09, 1.43)	1.39 (1.20, 1.58)	1.44 (1.23, 1.65)	1.74 (1.50, 1.98)

NSCLC, N (70458)	9,891	12,467	13,612	15,262	19,226
Prior CVD, n (%) 25458 (36.1)	3,227 (32.6)	4,403 (35.3)	4,808 (35.3)	5,631 (36.9)	7,389 (38.4)
TNM stage, OR (95% CI)					
I	1 (Reference)	1.16 (1.07, 1.25)	1.17 (1.08, 1.26)	1.24 (1.14, 1.33)	1.37 (1.28, 1.47)
II	0.99 (0.88, 1.10)	1.04 (0.94, 1.14)	0.99 (0.89, 1.08)	1.06 (0.96, 1.16)	1.13 (1.03, 1.22)
III	0.84 (0.75, 0.92)	0.95 (0.87, 1.04)	0.99 (0.90, 1.08)	1.07 (0.98, 1.16)	1.08 (0.99, 1.16)
Treatment modality (Reference: “No” treatment* and Index of Multiple Deprivation “1”), OR (95% CI)					
Surgery	0.46 (0.42, 0.50)	0.52 (0.48, 0.57)	0.52 (0.48, 0.56)	0.53 (0.49, 0.58)	0.62 (0.57, 0.66)
Radiotherapy	1.19 (1.08, 1.30)	1.22 (1.11, 1.32)	1.28 (1.17, 1.38)	1.33 (1.22, 1.43)	1.35 (1.26, 1.45)
Chemotherapy	0.40 (0.35, 0.44)	0.49 (0.44, 0.54)	0.47 (0.42, 0.52)	0.50 (0.45, 0.54)	0.48 (0.44, 0.53)
DLBCL cancer, N (23426)	5,020	5,317	4,880	4,371	3,838
Prior CVD, n (%) 5091 (21.7)	986 (19.6)	1,147 (21.6)	1,066 (21.8)	995 (22.8)	897 (23.4)
TNM stage, OR (95% CI)					
I	1 (Reference)	1.03 (0.80, 1.25)	1.10 (0.86, 1.35)	1.22 (0.94, 1.50)	1.08 (0.82, 1.35)
II	0.80 (0.61, 0.99)	0.95 (0.73, 1.17)	1.00 (0.76, 1.23)	1.04 (0.79, 1.29)	1.10 (0.83, 1.37)
III	1.08 (0.84, 1.33)	1.36 (1.06, 1.65)	1.24 (0.96, 1.51)	1.27 (0.97, 1.56)	1.29 (0.98, 1.60)
IV	1.08 (0.88, 1.28)	1.19 (0.97, 1.41)	1.22 (0.99, 1.44)	1.27 (1.03, 1.51)	1.39 (1.13, 1.65)
Treatment modality (Reference: “No” treatment* and Index of Multiple Deprivation “1”), OR (95% CI)					
Radiotherapy	0.81 (0.68, 0.94)	0.85 (0.72, 0.97)	0.82 (0.69, 0.95)	0.89 (0.74, 1.04)	0.87 (0.72, 1.03)
Chemotherapy	0.34 (0.28, 0.40)	0.39 (0.32, 0.45)	0.40 (0.33, 0.47)	0.41 (0.34, 0.48)	0.44 (0.36, 0.51)
Hodgkin Lymphoma, N (7303)	1,322	1,463	1,544	1,531	1,443
Prior CVD, n (%) 850 (11.6)	149 (11.3)	161 (11.0)	167 (10.8)	195 (12.7)	178 (12.3)

TNM stage, OR (95% CI)					
I	1 (Reference)	1.01 (0.33, 1.69)	0.92 (0.30, 1.55)	1.21 (0.42, 1.99)	1.24 (0.44, 2.05)
II	0.72 (0.28, 1.16)	0.71 (0.29, 1.14)	0.74 (0.31, 1.18)	0.81 (0.34, 1.29)	0.99 (0.41, 1.56)
III	1.66 (0.69, 2.63)	1.49 (0.60, 2.38)	1.22 (0.50, 1.94)	1.82 (0.80, 2.85)	1.76 (0.75, 2.77)
IV	1.47 (0.65, 2.30)	1.53 (0.69, 2.37)	1.63 (0.73, 2.52)	1.69 (0.77, 2.62)	1.38 (0.62, 2.14)
Treatment modality (Reference: “No” treatment* and Index of Multiple Deprivation “1”), OR (95% CI)					
Radiotherapy	0.76 (0.44, 1.08)	0.61 (0.36, 0.87)	0.42 (0.21, 0.62)	0.66 (0.39, 0.93)	0.85 (0.50, 1.19)
Chemotherapy	0.46 (0.28, 0.65)	0.42 (0.25, 0.59)	0.45 (0.28, 0.63)	0.49 (0.30, 0.68)	0.53 (0.32, 0.73)

Abbreviations: OR: odds ratio; CI: confidence interval; CVD: cardiovascular disease; NSCLC: non-small cell lung cancer; DLBCL: diffuse large B-cell lymphoma.

Supplementary table 5.16 – Prevalence of each CVD subgroup overall and with for Cancer Alliances grouped in tertiles of CVD prevalence identified in HES only.

Cancer Alliance tertile	Minimum	Middle	Maximum	All
Total	213,332	209,560	211,348	634,240
Number of Cancer Alliances	7	5	8	20
CVD prevalence, n (%; 95% CI)	30,745 (14.4; 14.3, 14.6)	32,496 (15.5; 15.4, 15.7)	39,363 (18.6; 18.5, 18.8)	102,604 (16.2; 16.1, 16.3)
CVD category				
Cerebrovascular	6,387 (3.0; 2.9, 3.1)	6,702 (3.2; 3.1, 3.3)	7,277 (3.4; 3.4, 3.5)	20,366 (3.2; 3.2, 3.3)
Stroke	2,651 (1.2; 1.2, 1.3)	2,723 (1.3; 1.3, 1.3)	3,228 (1.5; 1.5, 1.6)	8,602 (1.4; 1.3, 1.4)
Congestive cardiac failure	6,255 (2.9; 2.9, 3.0)	6,670 (3.2; 3.1, 3.3)	8,537 (4.0; 4.0, 4.1)	21,462 (3.4; 3.3, 3.4)
Ischaemic heart disease	19,112 (9.0; 8.8, 9.1)	20,321 (9.7; 9.6, 9.8)	25,187 (11.9; 11.8, 12.1)	64,620 (10.2; 10.1, 10.3)
Acute myocardial infarction	3,113 (1.5; 1.4, 1.5)	3,233 (1.5; 1.5, 1.6)	4,055 (1.9; 1.9, 2)	10,401 (1.6; 1.6, 1.7)
Peripheral artery disease	5,965 (2.8; 2.7, 2.9)	6,243 (3.0; 2.9, 3.1)	8,703 (4.1; 4.0, 4.2)	20,911 (3.3; 3.3, 3.3)
Valvular heart disease	5,142 (2.4; 2.3, 2.5)	5,774 (2.8; 2.7, 2.8)	6,854 (3.2; 3.2, 3.3)	17,770 (2.8; 2.8, 2.8)

Abbreviations: CVD: cardiovascular disease.

Supplementary table 5.17 – Counts of CVD records identified from different sources.[1]

Cancer Alliance tertile	Minimum	Middle	Maximum	All
Total	30,844	32,585	39,405	102,834
Number of cancer alliances	7	5	8	20
HES only	24,969	26,631	32,822	84,422
HES and MINAP	2,424	2,655	3,400	8,479
HES and NACSA	1,296	1,330	1,432	4,058
HES and PCI	3,159	3,076	3,069	9,304
HES and NHFA	959	943	1,236	3,138

Abbreviations: CVD: cardiovascular disease; HES: Hospital Episode Statistics; NICOR: National Institute for Cardiovascular Outcomes Research; MINAP: Myocardial Ischaemia National Audit Project; NACSA: National Adult Cardiac Surgery Audit; PCI: Percutaneous Coronary Intervention audit; NHFA: National Heart Failure Audit.

[1] Occurrences reported, so row and columns do not add up to the totals.

Supplementary table 5.18 – CVD prevalence for each Cancer Alliance and for each cancer site.

Cancer Alliance	All cancer sites		Breast cancer		Colon cancer		Rectal cancer	
	N	CVD, n (%; 95% CI)	N	CVD, n (%; 95% CI)	N	CVD, n (%; 95% CI)	N	CVD, n (%; 95% CI)
All	634,240	102,834 (16.2; 16.1, 16.3)	226,516	17,452 (7.7; 7.6, 7.8)	91,210	20,161 (22.1; 21.8, 22.4)	39,688	6,699 (16.9; 16.5, 17.2)
1	15,374	2,058 (13.4; 12.8, 13.9)	5,640	383 (6.8; 6.1, 7.4)	1,955	412 (21.1; 19.3, 22.9)	797	127 (15.9; 13.4, 18.5)
2	24,489	3,293 (13.4; 13.0, 13.9)	9,248	556 (6.0; 5.5, 6.5)	3,509	698 (19.9; 18.6, 21.2)	1,504	226 (15.0; 13.2, 16.8)
3	50,496	7,254 (14.4; 14.1, 14.7)	18,301	1,202 (6.6; 6.2, 6.9)	7,201	1,381 (19.2; 18.3, 20.1)	3361	524 (15.6; 14.4, 16.8)
4	36,440	5,274 (14.5; 14.1, 14.8)	13,375	949 (7.1; 6.7, 7.5)	5,419	1,118 (20.6; 19.6, 21.7)	2,095	296 (14.1; 12.6, 15.6)
5	22,647	3,343 (14.8; 14.3, 15.2)	7,957	617 (7.8; 7.2, 8.3)	3,014	629 (20.9; 19.4, 22.3)	1,271	195 (15.3; 13.4, 17.3)
6	35,055	5,267 (15.0; 14.7, 15.4)	13,144	987 (7.5; 7.1, 8)	5,217	1,112 (21.3; 20.2, 22.4)	2,280	358 (15.7; 14.2, 17.2)
7	28,831	4,355 (15.1; 14.7, 15.5)	11,168	882 (7.9; 7.4, 8.4)	3,899	854 (21.9; 20.6, 23.2)	1,648	263 (16.0; 14.2, 17.7)
8	41,698	6,336 (15.2; 14.9, 15.5)	15,308	1,151 (7.5; 7.1, 7.9)	5,737	1,153 (20.1; 19.1, 21.1)	2,412	364 (15.1; 13.7, 16.5)
9	25,643	3,944 (15.4; 14.9, 15.8)	9,502	724 (7.6; 7.1, 8.2)	3,300	748 (22.7; 21.2, 24.1)	1,368	257 (18.8; 16.7, 20.9)
10	34,899	5,400 (15.5; 15.1, 15.9)	12,300	974 (7.9; 7.4, 8.4)	5,109	1,149 (22.5; 21.3, 23.6)	2,200	363 (16.5; 14.9, 18.1)
11	40,232	6,276 (15.6; 15.2, 16.0)	13,657	996 (7.3; 6.9, 7.7)	5,767	1,218 (21.1; 20.1, 22.2)	2,418	354 (14.6; 13.2, 16.0)
12	67,088	10,629 (15.8; 15.6, 16.1)	23676	1,744 (7.4; 7, 7.7)	9,884	2,147 (21.7; 20.9, 22.5)	4,487	764 (17.0; 15.9, 18.1)

13	25,285	4,126 (16.3; 15.9, 16.8)	8,777	720 (8.2; 7.6, 8.8)	3,719	811 (21.8; 20.5, 23.1)	1,590	256 (16.1; 14.3, 17.9)
14	28,546	5,081 (17.8; 17.4, 18.2)	9,773	792 (8.1; 7.6, 8.6)	3,954	929 (23.5; 22.2, 24.8)	1,831	347 (19.0; 17.2, 20.7)
15	18,068	3,237 (17.9; 17.4, 18.5)	5,998	474 (7.9; 7.2, 8.6)	2,719	701 (25.8; 24.1, 27.4)	1,249	240 (19.2; 17.0, 21.4)
16	16,281	2,967 (18.2; 17.6, 18.8)	5,740	497 (8.7; 7.9, 9.4)	2,299	487 (21.2; 19.5, 22.9)	1,027	165 (16.1; 13.8, 18.3)
17	31,884	6,107 (19.2; 18.7, 19.6)	10,909	878 (8.0; 7.5, 8.6)	5,048	1,284 (25.4; 24.2, 26.6)	2,036	365 (17.9; 16.3, 19.6)
18	39,852	7,818 (19.6; 19.2, 20.0)	13,812	1,264 (9.2; 8.7, 9.6)	5,923	1,439 (24.3; 23.2, 25.4)	2,784	560 (20.1; 18.6, 21.6)
19	20,368	3,995 (19.6; 19.1, 20.2)	7,414	703 (9.5; 8.8, 10.1)	3,073	824 (26.8; 25.2, 28.4)	1,396	285 (20.4; 18.3, 22.5)
20	31,064	6,074 (19.6; 19.1, 20.0)	10,817	959 (8.9; 8.3, 9.4)	4,464	1,067 (23.9; 22.7, 25.2)	1,934	390 (20.2; 18.4, 22.0)

Cancer	Prostate cancer		NSCLC		DLBCL		Hodgkin lymphoma	
Alliance	N	CVD, n (%)	N	CVD, n (%)	N	CVD, n (%)	N	CVD, n (%)
All	175,639	27123 (15.4; 15.3, 15.6)	70,458	2458 (36.1; 35.8, 36.5)	23,426	5,091 (21.7; 21.2, 22.3)	7,303	850 (11.6; 10.9, 12.4)
1	4,771	552 (11.6; 10.7, 12.5)	1,492	469 (31.4; 29.1, 33.8)	525	102 (19.4; 16.0, 22.8)	194	13 (6.7; 3.2, 10.2)
2	6,823	863 (12.6; 11.9, 13.4)	2,269	756 (33.3; 31.4, 35.3)	854	169 (19.8; 17.1, 22.5)	282	25 (8.9; 5.5, 12.2)
3	13,800	1,921 (13.9; 13.3, 14.5)	5,220	1,767 (33.9; 32.6, 351.)	2,033	404 (19.9; 18.1, 21.6)	580	55 (9.5; 7.1, 11.9)
4	10,508	1,447 (13.8; 13.1, 14.4)	3,383	1,120 (33.1; 31.5, 34.7)	1,289	295 (22.9; 20.6, 25.2)	371	49 (13.2; 9.8, 16.7)
5	7,269	1,014 (13.9; 13.2, 14.7)	2,143	688 (32.1; 30.1, 341.)	755	164 (21.7; 18.8, 24.7)	238	36 (15.1; 10.6, 19.7)

6	9,568	1,455 (15.2; 14.5, 15.9)	3,079	1,025 (33.3; 31.6, 35.0)	1,391	291 (20.9; 18.8, 23.1)	376	39 (10.4; 7.3, 13.5)
7	7,925	1,144 (14.4; 13.7, 15.2)	2,734	953 (34.9; 33.1, 36.6)	970	199 (20.5; 18.0, 23.1)	487	60 (12.3; 9.4, 15.2)
8	12,394	1,979 (16.0; 15.3, 16.6)	3,839	1,323 (34.5; 33, 36.0)	1,531	312 (20.4; 18.4, 22.4)	477	54 (11.3; 8.5, 14.2)
9	7,323	1,046 (14.3; 13.5, 15.1)	2,670	921 (34.5; 32.7, 36.3)	1,031	216 (21.0; 18.5, 23.4)	449	32 (7.1; 4.7, 9.5)
10	10,532	1,523 (14.5; 13.8, 15.1)	2,982	1,039 (34.8; 33.1, 36.6)	1,399	308 (22.0; 19.8, 24.2)	377	44 (11.7; 8.4, 14.9)
11	12,605	2,026 (16.1; 15.4, 16.7)	3,735	1,297 (34.7; 33.2, 36.3)	1,623	332 (20.5; 18.5, 22.4)	427	53 (12.4; 9.3, 15.5)
12	19,001	2,864 (15.1; 14.6, 15.6)	7,066	2,540 (35.9; 34.8, 37.1)	2,214	492 (22.2; 20.5, 24.0)	760	78 (10.3; 8.1, 12.4)
13	7,595	1,248 (16.4; 15.6, 17.3)	2,353	829 (35.2; 33.3, 37.2)	967	221 (22.9; 20.2, 25.5)	284	41 (14.4; 10.3, 18.5)
14	7,297	1,157 (15.9; 15.0, 16.7)	4,298	1,582 (36.8; 35.4, 38.2)	1,044	233 (22.3; 19.8, 24.8)	349	41 (11.7; 8.4, 15.1)
15	4,743	787 (16.6; 15.5, 17.7)	2,394	834 (34.8; 32.9, 36.7)	782	170 (21.7; 18.8, 24.6)	183	31 (16.9; 11.5, 22.4)
16	3,937	661 (16.8; 15.6, 18.0)	2,581	1,014 (39.3; 37.4, 41.2)	543	118 (21.7; 18.3, 25.2)	154	25 (16.2; 10.4, 22.1)
17	7,870	1,485 (18.9; 18.0, 19.7)	4,646	1,825 (39.3; 37.9, 40.7)	1,045	234 (22.4; 19.9, 24.9)	330	36 (10.9; 7.5, 14.3)

18	9,228	1,587 (17.2; 16.4, 18.0)	6,009	2,472 (41.1; 39.9, 42.4)	1,649	424 (25.7; 23.6, 27.8)	447	72 (16.1; 12.7, 19.5)
19	5,114	1,004 (19.6; 18.5, 20.7)	2,488	995 (40.0; 38.1, 41.9)	696	164 (23.6; 20.4, 26.7)	187	20 (10.7; 6.3, 15.1)
20	7,336	1,360 (18.5; 17.6, 19.4)	5,077	2,009 (39.6; 38.2, 40.9)	1,085	243 (22.4; 19.9, 24.9)	351	46 (13.1; 9.6, 16.6)

Abbreviations: CVD: cardiovascular disease; CI: confidence interval; NSCLC: non-small cell lung cancer; DLBCL: diffuse large B-cell lymphoma.

Supplementary table 5.19 – Cancer Alliances corresponding to the outlier ID in Figure 5.15.[1]

ID	Cancer Alliance
1	North East and Cumbria
2	Lancashire and South Cumbria
3	Greater Manchester
4	East Midlands
5	Surrey and Sussex
6	Cheshire and Merseyside
7	Thames Valley
8	East of England - North
9	South East London
10	Humber, Coast and Vale
11	Kent and Medway
12	Wessex
13	West Midlands

[1] Cancer Alliances ordered by frequency that they appear as an outlier in the funnel plots.

Chapter 6

Supplementary table 6.1 – Management of trastuzumab-related cardiac toxicity in the overall population and according to age group and Heart Failure Association-International Cardio-Oncology Society risk group.

Variable	Category	Overall		Age group				p value	HFA-ICOS risk group								p value
		N = 931		<65 years N = 736		≥65 years N = 195			Low N = 401		Medium N = 454		High N = 70		Very high N = 6		
		N	%	N	%	N	%		N	%	N	%	N	%	N	%	
Referral to cardiologist		166	17.8	129	17.5	37	19.0	0.674	54	13.5	86	18.9	20	28.6	6	100.0	0.001
Referral	Baseline	49	5.2	33	4.5	16	8.2	0.047	13	3.2	21	4.6	11	15.7	4	66.7	0.001
	Reactive (due to cardiac problems)	117	12.6	96	13.0	21	10.8	0.466	41	10.2	65	14.3	9	12.9	2	33.3	0.131
Medications prescribed	Beta-blocker	57	6.1	42	5.7	15	7.7	0.314	11	2.7	38	8.4	7	10.0	1	16.7	0.002
	ACE inhibitor	81	8.7	63	8.6	18	9.2	0.775	25	6.2	41	9.0	12	17.1	3	50.0	0.001
	Angiotensin receptor blocker	18	1.9	14	1.9	4	2.0	0.778	6	1.5	10	2.2	2	2.9	0	0.0	0.799
	Mineralcorticoid receptor blocker	5	0.5	5	0.7	0	0.0	0.590	1	0.2	4	0.9	0	0.0	0	0.0	0.565
	Diuretic	16	1.7	13	1.8	3	1.5	0.999	1	0.2	14	3.1	1	1.4	0	0.0	0.016
	Ivabradine	3	0.3	3	0.4	0	0.0	0.999	1	0.2	2	0.4	0	0.0	0	0.0	0.917
	Digitalis	2	0.2	1	0.1	1	0.5	0.375	0	0.0	0	0.0	1	1.4	1	16.7	0.001
	Calcium channel blocker	4	0.4	3	0.4	1	0.5	0.999	0	0.0	2	0.4	2	2.9	0	0.0	0.010
	Antiplatelets	17	1.8	12	1.6	5	2.6	0.373	3	0.7	10	2.2	4	5.7	0	0.0	0.030

Variable	Category	Overall		Age group				p value	HFA-ICOS risk group								p value
		N = 931		<65 years N = 736		≥65 years N = 195			Low N = 401		Medium N = 454		High N = 70		Very high N = 6		
		N	%	N	%	N	%		N	%	N	%	N	%	N	%	
	Anticoagulants	8	0.9	3	0.4	5	2.6	0.012	0	0.0	6	1.3	2	2.9	0	0.0	0.047
	Statins	17	1.8	10	1.4	7	3.6	0.063	1	0.2	11	2.4	5	7.1	0	0.0	0.001

Abbreviations: HFA: Heart Failure Association; ICOS: International Cardio-Oncology Society; ACE: angiotensin-converting enzyme.

BJC British Journal of Cancer

www.nature.com/bjc

ARTICLE

Clinical Study

Bridging The Age Gap: observational cohort study of effects of chemotherapy and trastuzumab on recurrence, survival and quality of life in older women with early breast cancer

Alistair Ring[1], Nicolò Matteo Luca Battisti[1], Malcolm W. R. Reed[2], Esther Herbert[3], Jenna L. Morgan[4], Michael Bradburn[3], Stephen J. Walters[3], Karen A. Collins[5], Sue E. Ward[6], Geoffrey R. Holmes[6], Maria Burton[5], Kate Lifford[7], Adrian Edwards[7], Thompson G. Robinson[8], Charlene Martin[4], Tim Chater[3], Kirsty J. Pemberton[3], Alan Brennan[6], Kwok Leung Cheung[9], Annaliza Todd[4], Riccardo A. Audisio[10], Juliet Wright[2], Richard Simcock[11], Tracey Green[12], Deirdre Revell[12], Jacqui Gath[12], Kieran Horgan[13], Chris Holcombe[14], Matthew C. Winter[15], Jay Naik[16], Rishi Parmeshwar[17], Margot A. Gosney[18], Matthew Q. Hatton[15], Alastair M. Thompson[19], Lynda Wyld[4] and on behalf of the Age Gap TMG

BACKGROUND: Chemotherapy improves outcomes for high risk early breast cancer (EBC) patients but is infrequently offered to older individuals. This study determined if there are fit older patients with high-risk disease who may benefit from chemotherapy.
METHODS: A multicentre, prospective, observational study was performed to determine chemotherapy (±trastuzumab) usage and survival and quality-of-life outcomes in EBC patients aged ≥70 years. Propensity score-matching adjusted for variation in baseline age, fitness and tumour stage.
RESULTS: Three thousands four hundred sixteen women were recruited from 56 UK centres between 2013 and 2018. Two thousands eight hundred eleven (82%) had surgery. 1520/2811 (54%) had high-risk EBC and 2059/2811 (73%) were fit. Chemotherapy was given to 306/1100 (27.8%) fit patients with high-risk EBC. Unmatched comparison of chemotherapy versus no chemotherapy demonstrated reduced metastatic recurrence risk in high-risk patients(hazard ratio [HR] 0.36 [95% CI 0.19–0.68]) and in 541 age, stage and fitness-matched patients(adjusted HR 0.43 [95% CI 0.20–0.92]) but no benefit to overall survival (OS) or breast cancer-specific survival (BCSS) in either group. Chemotherapy improved survival in women with oestrogen receptor (ER)-negative cancer (OS: HR 0.20 [95% CI 0.08–0.49];BCSS: HR 0.12 [95% CI 0.03–0.44]).Transient negative quality-of-life impacts were observed.
CONCLUSIONS: Chemotherapy was associated with reduced risk of metastatic recurrence, but survival benefits were only seen in patients with ER-negative cancer. Quality-of-life impacts were significant but transient.
TRIAL REGISTRATION: ISRCTN 46099296

British Journal of Cancer https://doi.org/10.1038/s41416-021-01388-9

BACKGROUND

In 2014–2016 over 18,500 women per year aged ≥70 years were diagnosed with breast cancer in the UK, representing 34% of all diagnoses.[1] Breast cancer survival is worse in older patients[2] who have not experienced similar outcome improvements compared with younger individuals in the past three decades.[3] This may reflect late presentation, more comorbidities or undertreatment. Significant treatment variations between centres are frequently reported in older adults.[4,5] However, interpreting such data can be challenging without information on fitness, which may mitigate treatment benefits, due to competing mortality risks and increased treatment-related toxicity.

Chemotherapy benefit in older women is controversial. While there have been many high-quality randomised clinical trials

[1]Department of Medicine, Breast Unit, The Royal Marsden Hospital NHS Foundation Trust, London, UK & Breast Cancer Research Division, The Institute of Cancer Research, London, UK; [2]Brighton and Sussex Medical School, Brighton, UK; [3]Clinical Trials Research Unit, School for Health and Related Research, University of Sheffield, Sheffield, UK; [4]Department of Oncology and Metabolism, University of Sheffield Medical School, Sheffield, UK; [5]College of Health, Wellbeing and Life Sciences, Department of Allied Health Professions, Sheffield Hallam University, Sheffield, UK; [6]Department of Health Economics and Decision Science, School for Health and Related Research (ScHARR), University of Sheffield, Sheffield, UK; [7]Division of Population Medicine, Cardiff University, Cardiff, UK; [8]Department of Cardiovascular Sciences and NIHR Biomedical Research Centre, University of Leicester, Cardiovascular Research Centre, Leicester, UK; [9]School of Medicine, University of Nottingham, Royal Derby Hospital, Derby, UK; [10]University of Gothenberg, Sahlgrenska Universitetssjukhuset, Göteborg, Sweden; [11]Sussex Cancer Centre, Royal Sussex County Hospital, Brighton, UK; [12]Yorkshire and Humber Consumer Research Panel, Cottingham, UK; [13]Department of Breast Surgery, Bexley Cancer Centre, St James's University Hospital, Leeds, UK; [14]Liverpool University Hospitals Foundation Trust, Liverpool, UK; [15]Weston Park Hospital, Sheffield, UK; [16]Pinderfields Hospital, Mid Yorkshire NHS Foundation Trust, Wakefield, UK; [17]University Hospitals of Morecambe Bay, Royal Lancashire Infirmary, Lancaster, Lancashire, UK; [18]Royal Berkshire NHS Foundation Trust, Reading, UK and [19]Department of Surgery, Baylor College of Medicine, Houston, TX, USA
Correspondence: Lynda Wyld (l.wyld@sheffield.ac.uk)
These authors contributed equally: Alistair Ring, Nicolò Matteo Luca Battisti.
Members of the Age Gap TMG are listed above Acknowledgements.

Received: 29 October 2020 Revised: 20 February 2021 Accepted: 31 March 2021
Published online: 10 May 2021

Published by Springer Nature on behalf of Cancer Research UK

(RCTs) to evaluate the impact of systemic chemotherapy, the majority of trials excluded or recruited poorly amongst older patients, and tended to enrol fitter individuals.[6] This reflects clinicians' and patients' toxicity concerns and reticence from trialists about diluting the study power by introducing higher morbidity rates and competing causes of death in less fit older patients.

Older adults derive less benefit from chemotherapy compared to younger patients. Benefit is present between the ages of 70 and 80, although data for women aged over 80 years are scarce.[7] The Bridging the Age Gap study was designed to recruit a large, real-world, cohort of older women with breast cancer including detailed baseline fitness data and information about the cancer, treatment received and outcomes. The objectives of this study analysis were to determine health status-stratified outcomes for EBC patients aged ≥70 according to whether they received guideline concordant or non-concordant care with a particular focus on chemotherapy use. In this paper, the age- and risk-stratified patterns of receipt of adjuvant systemic therapy are described in older EBC patients, with propensity score-matched analysis of disease recurrence, survival and quality-of-life outcomes.

METHODS

Study design

Bridging the Age Gap is a prospective multicentre, observational cohort study. Patients were recruited from 56 UK centres in England and Wales (Supplementary Table 1). Eligible patients were women ≥70 years at diagnosis of primary operable invasive breast cancer (TNM stages: T1-3 (plus some T4b), N0-1, M0). Those unsuitable for surgery or with previous EBC within five years were not eligible.

Baseline data collection

Patients were recruited at the time of EBC diagnosis and before commencing treatment and could participate at three levels: full, partial (no requirement to complete quality of life [QoL] assessments) or by proxy (simple third-party data collection for those with cognitive impairment).

Baseline data were collected about the primary tumour including; cancer type, grade, nodal status, tumour size, oestrogen (ER), progesterone (PR) and human epidermal growth factor receptor 2 (HER2) status. Staging was performed if clinically indicated. Surgical, radiotherapy and systemic therapy data were collected.

At baseline, patients underwent assessments using validated tools including: comorbidities (Charlson comorbidity index [CCI]),[8] nutrition (Abridged Patient Generated Subjective Global Assessment [aPG-SGA]),[9,10] functional status (Activities of Daily Living [ADL]),[11] advanced functional status (Instrumental Activities of Daily Living [IADL]),[12] dementia (Mini Mental State Examination [MMSE]),[13] Eastern Cooperative Oncology Group Performance Status (ECOG PS) and medication list.

Quality-of-life was assessed using the EuroQol-5D-5L (EQ-5D-5L).[14] Assessments on the European Organisation for the Research and Treatment of Cancer QoL Questionnaire (EORTC-QLQ)-C30,[15] EORTC-QLQ-BR23,[16] EORTC-QLQ-ELD15[17] were also collected but are presented elsewhere.[18]

Follow-up and outcomes

Patients were followed up at 6 weeks, and 6, 12, 18 and 24 months. Survival outcomes (date and cause of death) were obtained at 52 months median follow-up from the UK cancer registry. All patients were assessed for recurrence and QoL at each visit. Complications were categorised using the Common Terminology Criteria for Adverse Events system (CTCAE v4.0).

Chemotherapy-related mortality was defined as death within 30 days of chemotherapy or if chemotherapy was documented as a contributing cause. Deaths were categorised as disease related or other causes. Deaths were reviewed by the chief investigator blind to treatment decisions. Deaths were classified as disease related if the death was related to the initial breast cancer. Patients for whom the cause could not be established were excluded from cause-specific analyses.

Statistical analyses

Analyses were performed in IBM SPSS statistics version 24 and R version 3.6.3.[19] A $p < 0.05$ was considered statistically significant.

The relationships between systemic therapy use and tumour and patient characteristics were evaluated using uni- and multivariable logistic regression. High-risk EBC was defined if any of the following criteria were present: node-positive, ER-negative, HER2 positive, grade 3 or Recurrence Score ≥25. (Supplementary Table 2a). Additional analyses were conducted in patients with ER-negative and HER2-positive tumours, where the benefits from chemotherapy might be anticipated. Fitness was defined based on geriatric assessments and categorised into fit, vulnerable and frail according to a cumulative score including measures of functional status, comorbidities, polypharmacy, nutritional status and cognitive status (Supplementary Table 2b).

Both overall survival (OS) and breast cancer-specific survival (BCSS) were compared in treated and untreated patients. A Cox proportional hazards model was fitted using regression-based adjustment based on covariates of: treatment; age; categories of aPG-SGA, ADL, IADL, CCI, MMSE, ECOG, medications and Nottingham Prognostic Index (NPI)[20] and HER2 for all high-risk patients. Hazard ratios (HR) and corresponding 95% confidence intervals (CIs) were calculated.

A propensity score adjustment among sufficiently similar high-risk patients was fitted using a Cox model with a shared frailty term (or random effect) for matched patients. Participants were matched exactly on NPI category and HER2 status, and logistic regression was used to calculate propensity scores for treatment in relation to age, aPG-SGA category, ADL category, IADL category, MMSE category, CCI category, ECOG PS category and number of medications. The ratio and calliper widths of the propensity scores were chosen following examination of the propensity score overlaps for several combinations of ratios and callipers. A 1:3 ratio for chemotherapy versus no chemotherapy and a calliper of 0.25 times the propensity scores' standard deviation was used to ensure participants were closely matched whilst retaining as many patients as possible.

The QoL questionnaires were scored according to the EQ-5D-5L User Guide (Version 3.0).[21] Missing data were managed accordingly. The QoL analysis included only patients with high-risk EBC as detailed in Supplementary Table 2a and where questionnaires were available. The mean difference (95% CI) of the domain scores at each time-point, adjusted for baseline scores, was calculated with linear regression models for high-risk participants. Propensity score-matching was also performed, as detailed above, to compare the EQ-5D-5L usual activities score in a matched cohort receiving chemotherapy versus patients not receiving it.

RESULTS

Between January 2013 and June 2018, 3456 women were recruited from 56 centres in England and Wales. This analysis was restricted to the 2811 women who underwent surgery within 6 months of diagnosis (STROBE diagram [Fig. 1]).[22] Patients' characteristics according to geriatric assessments, tumour characteristics, postoperative histology and surgery performed are shown in Table 1.

Of the 2811 patients, 397 (14.1%) received chemotherapy (365 [92%] in the adjuvant setting, 30 [8%] in neoadjuvant setting, and 2 [0.5%] unknown). Of those 380 patients for whom the

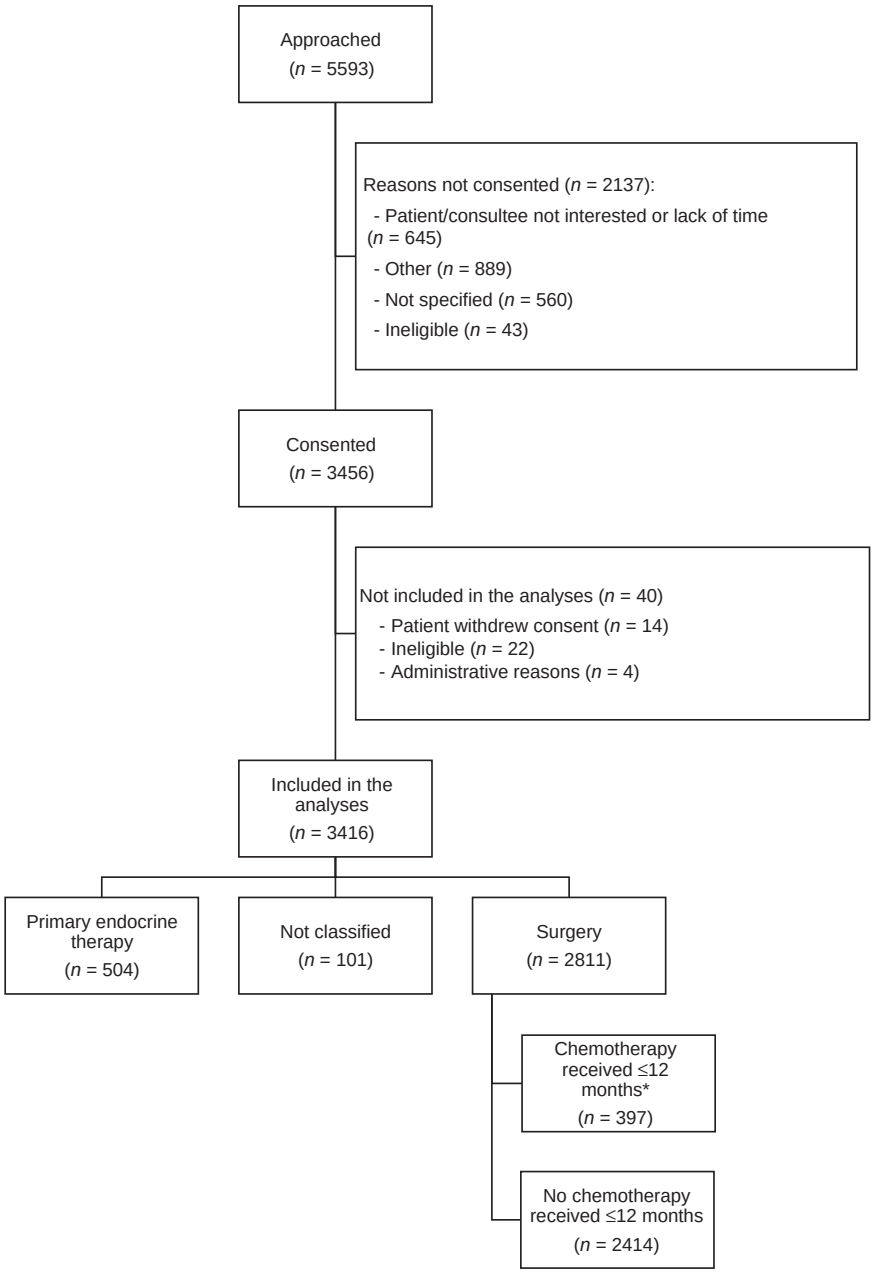


Fig. 1 STROBE diagram. STROBE flow diagram for the chemotherapy vs no chemotherapy analyses.

chemotherapy regimen received was known, 132 (34.7%) received an anthracycline-taxane combination, 124 (32.6%) a taxane (without anthracycline), 123 (32.4%) an anthracycline and 1 CMF. 332 patients (11.8%) had HER2-positive EBC. Of these patients, 150 (45.1%) received chemotherapy plus trastuzumab, 13 (3.9%) trastuzumab without chemotherapy, and 9 (2.7%) chemotherapy without trastuzumab. Overall, 1753/2811 (62.4%) patients received radiotherapy and 2239/2354 (95.1%) ER-positive patients received endocrine therapy.

Chemotherapy receipt according to tumour and patient characteristics is shown in Supplementary Tables 3 and 4. Univariate and multivariate analyses are shown in Table 2. Younger, less dependent patients with high-risk tumours and with fewer comorbidities were more likely to receive chemotherapy.

High-risk tumours were present in 1520 (54%) patients and 376/1520 (25%) received chemotherapy compared with 21/1291 (1.6%) of patients with non-high-risk tumours (Table 3a). 2059 patients (73%) were fit and 752 vulnerable or frail (27%) (Table 3b). Of those who were fit, 1100 also had high-risk EBC, and of these patients 306 (28%) received chemotherapy (Table 3c).

At a median follow-up of 52 months, mortality status was available for 98% (1495/1520) of high-risk patients (371 in the chemotherapy group, 1124 in the no chemotherapy group). Chemotherapy was associated with a longer OS, but the difference was not statistically significant when adjusted for other covariates (unadjusted HR 0.55 [95% CI 0.40–0.73, $p < 0.001$] and adjusted HR 0.87 [95% CI 0.58–1.28, $p = 0.469$] (Fig. 2a). In a propensity score-matched analysis 200 patients receiving chemotherapy were

Table 1. Baseline tumour, patient and treatment characteristics by age.

		70–74 *N* = 1173	75–79 *N* = 899	80–84 *N* = 506	≥85 *N* = 233	All *N* = 2811
Participation level	Full	926 (78.9%)	674 (75.0%)	368 (72.7%)	143 (61.4%)	2111 (75.1%)
	Partial	225 (19.2%)	209 (23.2%)	123 (24.3%)	64 (27.5%)	621 (22.1%)
	Consultee	22 (1.9%)	16 (1.8%)	15 (3.0%)	26 (11.2%)	79 (2.8%)
Main side	Right	535 (45.6%)	418 (46.5%)	247 (48.8%)	105 (45.1%)	1305 (46.4%)
	Left	638 (54.4%)	481 (53.5%)	259 (51.2%)	128 (54.9%)	1506 (53.6%)
Tumour size (mm)	≤20	649 (55.3%)	371 (41.3%)	184 (36.4%)	75 (32.2%)	1279 (45.5%)
	21–50	439 (37.4%)	439 (48.8%)	271 (53.6%)	136 (58.4%)	1285 (45.7%)
	>50	66 (5.6%)	66 (7.3%)	40 (7.9%)	16 (6.9%)	188 (6.7%)
	Unknown	19 (1.6%)	23 (2.6%)	11 (2.2%)	6 (2.6%)	59 (2.1%)
Tumour size (mm)	*n*	1154	876	495	227	2752
	Mean (SD)	23.1 (17.7)	26.5 (16.2)	27.6 (15.4)	28.8 (15.7)	25.4 (16.8)
	Median (IQR)	19.0 (12.0, 28.0)	22.0 (16.0, 32.0)	25.0 (17.0, 35.0)	25.0 (19.0, 35.0)	21.0 (15.0, 31.0)
	Min, Max	0, 210	0, 155	0, 120	7, 120	0, 210
Nodal status	pN0-1mi	867 (73.9%)	573 (63.7%)	326 (64.4%)	147 (63.1%)	1913 (68.1%)
	pN1	212 (18.1%)	223 (24.8%)	117 (23.1%)	60 (25.8%)	612 (21.8%)
	pN2	46 (3.9%)	54 (6.0%)	36 (7.1%)	11 (4.7%)	147 (5.2%)
	pN3	29 (2.5%)	25 (2.8%)	16 (3.2%)	8 (3.4%)	78 (2.8%)
	pNx	19 (1.6%)	24 (2.7%)	11 (2.2%)	7 (3.0%)	61 (2.2%)
Grade	Grade 1	199 (17.0%)	110 (12.2%)	47 (9.3%)	25 (10.7%)	381 (13.6%)
	Grade 2	635 (54.1%)	482 (53.6%)	255 (50.4%)	113 (48.5%)	1485 (52.8%)
	Grade 3	311 (26.5%)	278 (30.9%)	190 (37.5%)	86 (36.9%)	865 (30.8%)
	Unknown	28 (2.4%)	29 (3.2%)	14 (2.8%)	9 (3.9%)	80 (2.8%)
Histology	Ductal NST	761 (64.9%)	567 (63.1%)	341 (67.4%)	146 (62.7%)	1815 (64.6%)
	Lobular carcinoma	164 (14.0%)	128 (14.2%)	58 (11.5%)	25 (10.7%)	375 (13.3%)
	Tubular carcinoma	21 (1.8%)	5 (0.6%)	3 (0.6%)	0 (0.0%)	29 (1.0%)
	Mucinous carcinoma	18 (1.5%)	28 (3.1%)	12 (2.4%)	13 (5.6%)	71 (2.5%)
	Other	110 (9.4%)	83 (9.2%)	53 (10.5%)	20 (8.6%)	266 (9.5%)
	Unknown	99 (8.4%)	88 (9.8%)	39 (7.7%)	29 (12.4%)	255 (9.1%)
ER status	Negative	141 (12.0%)	117 (13.0%)	74 (14.6%)	40 (17.2%)	372 (13.2%)
	Positive	1002 (85.4%)	753 (83.8%)	414 (81.8%)	185 (79.4%)	2354 (83.7%)
	Unknown	30 (2.6%)	29 (3.2%)	18 (3.6%)	8 (3.4%)	85 (3.0%)
HER2 status	Negative	981 (83.6%)	724 (80.5%)	375 (74.1%)	192 (82.4%)	2272 (80.8%)
	Inconclusive	9 (0.8%)	7 (0.8%)	4 (0.8%)	2 (0.9%)	22 (0.8%)
	Positive	136 (11.6%)	115 (12.8%)	63 (12.5%)	18 (7.7%)	332 (11.8%)
	Unknown	47 (4.0%)	53 (5.9%)	64 (12.6%)	21 (9.0%)	185 (6.6%)
Oncotype DX test performed	No	212 (18.1%)	138 (15.4%)	76 (15.0%)	38 (16.3%)	464 (16.5%)
	Yes	26 (2.2%)	13 (1.4%)	2 (0.4%)	0 (0.0%)	41 (1.5%)
	Not Applicable	306 (26.1%)	265 (29.5%)	186 (36.8%)	75 (32.2%)	832 (29.6%)
	Unknown	629 (53.6%)	483 (53.7%)	242 (47.8%)	120 (51.5%)	1474 (52.4%)
Charlson comorbidity index (no age)	*n*	1133	869	481	224	2707
	Mean (SD)	0.90 (1.21)	1.10 (1.36)	1.19 (1.37)	1.09 (1.30)	1.03 (1.30)
	Median (IQR)	0.00 (0.00, 2.00)	1.00 (0.00, 2.00)	1.00 (0.00, 2.00)	1.00 (0.00, 2.00)	1.00 (0.00, 2.00)
	Min, Max	0, 6	0, 9	0, 9	0, 6	0, 9
Charlson calculated 10-year survival probability[a]	*n*	1133	869	481	224	2707
	Mean (SD)	0.55 (0.28)	0.51 (0.29)	0.28 (0.24)	0.26 (0.23)	0.47 (0.29)
	Median (IQR)	0.77 (0.21, 0.77)	0.53 (0.21, 0.77)	0.21 (0.02, 0.53)	0.21 (0.02, 0.53)	0.53 (0.21, 0.77)
	Min, Max	0, 0.77	0, 0.77	0, 0.77	0, 0.53	0, 0.77
Number of concurrent medications	*n*	973	801	462	210	2446
	Mean (SD)	3.85 (2.66)	4.16 (2.63)	4.26 (2.63)	4.21 (2.53)	4.06 (2.64)
	Median (IQR)	3.00 (2.00, 5.00)	4.00 (2.00, 6.00)	4.00 (2.00, 6.00)	4.00 (2.00, 6.00)	4.00 (2.00, 5.75)
	Min, Max	0, 14	0, 18	0, 14	0, 14	0, 18
ADL category	No dependency	924 (78.8%)	623 (69.3%)	331 (65.4%)	126 (54.1%)	2004 (71.3%)
	Mild dependency	89 (7.6%)	109 (12.1%)	67 (13.2%)	43 (18.5%)	308 (11.0%)
	Moderate/severe dependency	70 (6.0%)	101 (11.2%)	60 (11.9%)	47 (20.2%)	278 (9.9%)
	Unknown	90 (7.7%)	66 (7.3%)	48 (9.5%)	17 (7.3%)	221 (7.9%)
IADL category	No dependency	955 (81.4%)	679 (75.5%)	332 (65.6%)	103 (44.2%)	2069 (73.6%)
	Mild dependency	54 (4.6%)	78 (8.7%)	70 (13.8%)	47 (20.2%)	249 (8.9%)

Table 1. continued

		70–74 $N = 1173$	75–79 $N = 899$	80–84 $N = 506$	≥85 $N = 233$	All $N = 2811$
	Moderate/severe dependency	67 (5.7%)	70 (7.8%)	55 (10.9%)	66 (28.3%)	258 (9.2%)
	Unknown	97 (8.3%)	72 (8.0%)	49 (9.7%)	17 (7.3%)	235 (8.4%)
MMSE category	Normal function	1059 (90.3%)	805 (89.5%)	444 (87.7%)	186 (79.8%)	2494 (88.7%)
	Mild impairment	91 (7.8%)	74 (8.2%)	50 (9.9%)	33 (14.2%)	248 (8.8%)
	Moderate impairment	11 (0.9%)	12 (1.3%)	5 (1.0%)	8 (3.4%)	36 (1.3%)
	Severe	12 (1.0%)	8 (0.9%)	7 (1.4%)	6 (2.6%)	33 (1.2%)
APG-SGA category	Low	929 (79.2%)	709 (78.9%)	370 (73.1%)	172 (73.8%)	2180 (77.6%)
	Moderate	111 (9.5%)	88 (9.8%)	62 (12.3%)	27 (11.6%)	288 (10.2%)
	High	15 (1.3%)	13 (1.4%)	10 (2.0%)	2 (0.9%)	40 (1.4%)
	Unknown	118 (10.1%)	89 (9.9%)	64 (12.6%)	32 (13.7%)	303 (10.8%)
ECOG performance status	0	930 (79.3%)	619 (68.9%)	305 (60.3%)	90 (38.6%)	1944 (69.2%)
	1	151 (12.9%)	205 (22.8%)	142 (28.1%)	109 (46.8%)	607 (21.6%)
	2	21 (1.8%)	24 (2.7%)	23 (4.5%)	12 (5.2%)	80 (2.8%)
	3	10 (0.9%)	9 (1.0%)	8 (1.6%)	9 (3.9%)	36 (1.3%)
	4	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
	Unknown	60 (5.1%)	42 (4.7%)	28 (5.5%)	13 (5.6%)	143 (5.1%)
Breast surgery	Wide local excision (non wire localised)	769 (65.5%)	504 (56.1%)	236 (46.7%)	89 (38.2%)	1598 (56.8%)
	Therapeutic mammoplasty/ breast reshaping after WLE	35 (3.0%)	12 (1.3%)	2 (0.4%)	2 (0.9%)	51 (1.8%)
	Mastectomy	316 (26.9%)	346 (38.5%)	251 (49.6%)	136 (58.4%)	1049 (37.3%)
	Mastectomy and reconstruction	25 (2.1%)	10 (1.1%)	2 (0.4%)	0 (0.0%)	37 (1.3%)
	Other	10 (0.9%)	5 (0.6%)	5 (1.0%)	0 (0.0%)	20 (0.7%)
	Unknown	18 (1.5%)	22 (2.4%)	10 (2.0%)	6 (2.6%)	56 (2.0%)
Axillary surgery	Axillary sample	38 (3.2%)	30 (3.3%)	11 (2.2%)	9 (3.9%)	88 (3.1%)
	Axillary clearance	134 (11.4%)	134 (14.9%)	99 (19.6%)	47 (20.2%)	414 (14.7%)
	Sentinel lymph node biopsy	881 (75.1%)	633 (70.4%)	336 (66.4%)	130 (55.8%)	1980 (70.4%)
	Internal mammary node biopsy	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
	No axillary surgery	23 (2.0%)	16 (1.8%)	22 (4.3%)	19 (8.2%)	80 (2.8%)
	Unknown	97 (8.3%)	85 (9.5%)	38 (7.5%)	28 (12.0%)	248 (8.8%)

[a]Ten-year survival calculated as $0.983^{(e^{CCI \times 0.9})}$, where *CCI* Charlson Comorbidity Index.

matched to 350 who did not receive it. Supplementary Table 5 shows the characteristics of the matched dataset and the matching process and quality are summarised in Supplementary Fig. 1. Mortality status was available for 542 (99%) of the matched patients. Chemotherapy was associated with a longer OS although this was not statistically significant (HR 0.79 [95% CI 0.50–1.26, $p = 0.320$]) (Fig. 2b).

BCSS was available for 98% (1486/1520) of patients in the high-risk population. Chemotherapy was not associated with improved BCSS (unadjusted HR 0.76 [95% CI 0.53–1.10, $p = 0.147$] and adjusted HR 0.92 [95% CI 0.56–1.53, $p = 0.758$]) (Fig. 2c). In the propensity score-matched population, BCSS was available for 539 patients (98%). Chemotherapy was also not found to be associated with improved BCSS (HR 0.93 [95% CI 0.52–1.66, $p = 0.798$]) (Fig. 2d).

Metastatic recurrence data were available for 1498 high-risk patients (99%). Chemotherapy was associated with a significantly lower risk of metastatic recurrence in the unmatched population (unadjusted HR 0.67 [95% CI 0.43–1.04, $p = 0.077$] and adjusted HR 0.36 [95% CI 0.19–0.68, $p = 0.002$]) (Fig. 2e). In 541 matched patients (98%), chemotherapy was also associated with a lower metastatic recurrence risk (HR 0.53 [95% CI 0.26–1.07, $p = 0.076$]) (Fig. 2f).

Additional post-hoc exploratory analyses were performed in disease subgroups. Out of 369 patients with ER-negative EBC and known mortality status, 132 (35.8%) received chemotherapy. In a propensity score-matched analysis in 136 patients, chemotherapy was associated with better OS (HR 0.20 [0.08–0.49]) and BCSS (HR 0.12 [0.03–0.44]) (Fig. 3, Supplementary Table 6 and Supplementary Fig. 2). Three hundred twenty six patients with HER2-positive EBC and known mortality status of whom 156 (47.9%) received chemotherapy with or without trastuzumab. Fewer deaths from breast cancer and other causes occurred in those receiving chemotherapy with or without trastuzumab. However, in a matched analysis in 137 patients, the differences were not statistically significant for OS (HR 0.63 [0.27–1.48]) or BCSS (HR 0.50 ([0.16–1.63]) (Fig. 3, Supplementary Table 6 and Supplementary Fig. 2).

Supplementary Table 7 outlines chemotherapy toxicity. Among 397 patients receiving chemotherapy, there was one chemotherapy-related death (0.25%) (due to congestive heart failure) and 132 (33.2%) had an episode of infection, which was grade 3 or 4 in 50 (12.6%). Among the 163 patients who received trastuzumab, 4 (2.5%) experienced cardiac failure within the first 6 months and 12 (6.7%) within the first year.

Among 2811 patients undergoing surgery, the QoL analysis was restricted to 1520/2811 (54.1%) with high-risk EBC of whom 1315/1520 (86.5%) had an EQ-5D-5L score available at baseline. Of these patients, 376/1520 (24.7%) received chemotherapy. Health utilities were similar with estimated mean differences less than 0.02 units ($p > 0.1$), whereas the visual analogue scale (VAS) measures were significantly worse at 6 months in patients receiving chemotherapy versus not (adjusted mean difference −6.57, 95% CI −8.74 to −4.40, $p < 0.001$). Changes were no longer significant at 12 months and thereafter (Supplementary Table 8; Supplementary Fig. 3).

Table 2. Relationship between chemotherapy use and patient characteristics: univariate (Table 2a) and multi-variable (Table 2b) analyses.

(a) Results for univariate logistic regression models.

Variable	Level	OR (95% CI)	*P*-value
Age		0.84 (0.82, 0.87)	<0.001
ADL score		1.07 (1.04, 1.11)	<0.001
IADL score		1.77 (1.43, 2.25)	<0.001
CCI (no age)		0.84 (0.77, 0.93)	<0.001
APG-SGA		0.95 (0.89, 1.01)	0.127
Allred score		0.80 (0.78, 0.83)	<0.001
Tumour grade	Grade 1	–	–
	Grade 2	9.04 (3.78, 29.58)	<0.001
	Grade 3	37.67 (15.87, 122.76)	<0.001
ER positive		0.22 (0.17, 0.28)	<0.001
HER2 status[a]	Negative	–	–
	Positive	8.49 (6.57, 10.97)	<0.001
MMSE category	Normal function	–	–
	Mild impairment	0.75 (0.49, 1.11)	0.172
	Moderate impairment	1.18 (0.44, 2.67)	0.711
	Severe	0.38 (0.06, 1.27)	0.188
Nodal status[b]	pN0-1mi	–	–
	pN1	2.18 (1.69, 2.80)	<0.001
	pN2	5.05 (3.47, 7.29)	<0.001
	pN3	6.42 (3.96, 10.30)	<0.001

(b) Results from the multi-variable logistic regression model.

Variable	Level	OR (95% CI)	*P*-value
Age		0.74 (0.71, 0.78)	<0.001
IADL score		1.97 (1.53, 2.63)	<0.001
CCI (no age)		0.83 (0.73, 0.95)	0.007
Tumour grade	Grade 1	–	–
	Grade 2	8.42 (3.05, 34.90)	<0.001
	Grade 3	29.50 (10.59, 123.00)	<0.001
ER positive		0.19 (0.13, 0.28)	<0.001
HER2 status	Negative	–	–
	Positive	8.94 (6.19, 13.01)	<0.001
Nodal status	pN0-1mi		
	pN1	4.01 (2.81, 5.75)	<0.001
	pN2	11.24 (6.43, 19.74)	<0.001
	pN3	8.84 (4.31, 18.05)	<0.001

[a]Tests marked as 'Inconclusive' were removed from this analysis.
[b]Those with nodal status pNx were removed from this analysis.

A similar pattern on EQ-5D-5L usual activities score was seen in 520 propensity score-matched patients (including 118 patients receiving chemotherapy and 332 not receiving it) (Supplementary Fig. 4).

DISCUSSION

This study represents one of the largest prospective cohort studies conducted in older women with breast cancer and provides valuable data on tumour characteristics and health of older EBC patients. As expected, the majority of patients had relatively good prognosis tumours, with relatively low rates of nodal involvement and adverse biology as determined by ER and HER2 status. Nonetheless, there remained a substantial proportion of high risk, fit patients (on baseline assessments), with a high relapse risk in their expected lifetime. Ensuring that these patients receive adequate treatment is a priority for clinicians.

A key finding of this study is that 27.8% of fit high-risk EBC older patients received chemotherapy. In the ACheW study 30% of high-risk EBC patients were offered chemotherapy and 17% received it.[23] Analyses of European and US registry data report similar findings.[5,24,25] These analyses did not consider recurrence risk (as determined by histopathological variables) and patients' fitness (to not only receive treatment but also to live long enough to benefit). The current study overcame these limitations, by defining recurrence risk and fitness, and still demonstrates low

Table 3. Chemotherapy use according to risk of recurrence and fitness.

(a) Use of chemotherapy by risk status.

Risk	Chemotherapy	No Chemotherapy	Total
High risk	376 (24.7%)	1144 (75.3%)	**1520 (100.0%)**
Non-high risk	21 (1.6%)	1270 (98.4%)	**1291 (100.0%)**
Total	**397 (14.1%)**	**2414 (85.9%)**	**2811 (100.0%)**

(b) Use of chemotherapy by fitness.

Fitness	Chemotherapy	No Chemotherapy	Total
Fit	322 (15.6%)	1737 (84.4%)	**2059 (100.0%)**
Vulnerable	75 (10.0%)	675 (90.0%)	**750 (100.0%)**
Frail	0 (0.0%)	2 (100.0%)	**2 (100.0%)**
Total	**397 (14.1%)**	**2414 (85.9%)**	**2811 (100.0%)**

(c) Use of chemotherapy by risk and fitness.

Fitness	High risk		Non-high risk		Total
	Chemotherapy	No chemotherapy	Chemotherapy	No chemotherapy	
Fit	306 (14.9%)	794 (38.6%)	16 (0.8%)	943 (45.8%)	**2059 (100.0%)**
Vulnerable	70 (9.3%)	349 (46.5%)	5 (0.7%)	326 (43.5%)	**750 (100.0%)**
Frail	0 (0.0%)	1 (50%)	0 (0.0%)	1 (50%)	**2 (100%)**
Total	**376 (13.4%)**	**1144 (40.7%)**	**21 (0.7%)**	**1270 (45.2%)**	**2811 (100.0%)**

Bold values represent the total numbers for each column or row.

chemotherapy uptake. This may be due to uncertainty on chemotherapy benefit in older adults, toxicity concerns and patients' and carers' choice.

In order to investigate the survival benefits of chemotherapy for older EBC patients, we conducted survival analyses in those at high risk of recurrence. Ideally this question should be addressed by RCTs. Recruiting older patients into RCTs comparing different chemotherapy regimens is feasible,[26] but trials comparing chemotherapy with no chemotherapy have failed to recruit.[27,28] Moreover, older patients enrolled in RCTs may be fitter and not necessarily representative of a real-world population.[6] In contrast, this cohort study recruited well, and recruited patients with a broad fitness range.

Our analyses attempted to correct for confounders, specifically the fact that younger, fitter patients might be more likely to receive chemotherapy, but also are biologically more likely to survive longer irrespective of chemotherapy effect. This effect is perhaps most apparent when comparing the unmatched and matched OS analyses (Fig. 2a, b).

In the high-risk population chemotherapy reduced the risks of metastatic recurrence, which did not translate into better survival. This may be because the benefit was modest and the fact that median OS for ER-positive metastatic disease patients often exceeds 3 years with contemporary therapies.[29] Irrespective, a reduction in metastatic relapses, with their symptomatic, psychological and financial implications, may be sufficient grounds on which to offer treatment even in the absence of a survival benefit. Longer term follow-up will be required to further explore this.

Chemotherapy benefits are small for most ER-positive, HER2-negative EBC patients. Therefore, we performed exploratory analyses in patients with the more chemotherapy-sensitive subtypes, i.e. ER-negative and HER2-positive disease. In ER-negative EBC patients there was an apparent reduction of breast cancer deaths with chemotherapy. These data are consistent with an US SEER analysis suggesting that adjuvant chemotherapy benefit in older patients were restricted to those with ER-negative disease.[28,30] In HER2-positive EBC patients, fewer breast cancer deaths occurred in those who received chemotherapy with or without trastuzumab although the differences were not statistically significant in a matched analysis. This could be explained by the small numbers in this subgroup analysis. However, a retrospective study demonstrated that HER2-positive EBC older patients do not have inferior long-term outcomes compared with younger adults not receiving chemotherapy.[31] Low Ki67 and high bcl2 expression in the older cohort of HER2-positive patients might explain this better prognosis and also relative chemo-resistance.[31]

Our study found that mortality rates from chemotherapy were very low and side effects consistent with previous analyses.[32] Follow-up of the cohort is planned at 10 years and may provide data about longer term benefits, although it should be recognised that with longer follow-up competing mortality causes are likely have a greater impact.

Our analysis also demonstrates that chemotherapy has a significant negative impact at 6 months on QoL, which is a meaningful endpoint in the context of a more limited survival benefit and increased risk of toxicities in this population. However, this effect resolves at 12 months consistent with previous findings in smaller or younger cohorts of patients[33,34] and is described in a more extensive analysis performed on this patient cohort.[18]

A key strength of this study is that patients were recruited from a broad range of academic and general centres across the UK, and were likely to reflect contemporary practice and outcomes. However, despite the inclusive entry criteria and low level of intervention there was still the possibility of selection bias. In a separate analysis of this study we found that patients who did not enter the trial following screening were older and had worse functional ability.[35] Also, as patients were not randomised, unmeasured variables might have influenced our findings despite

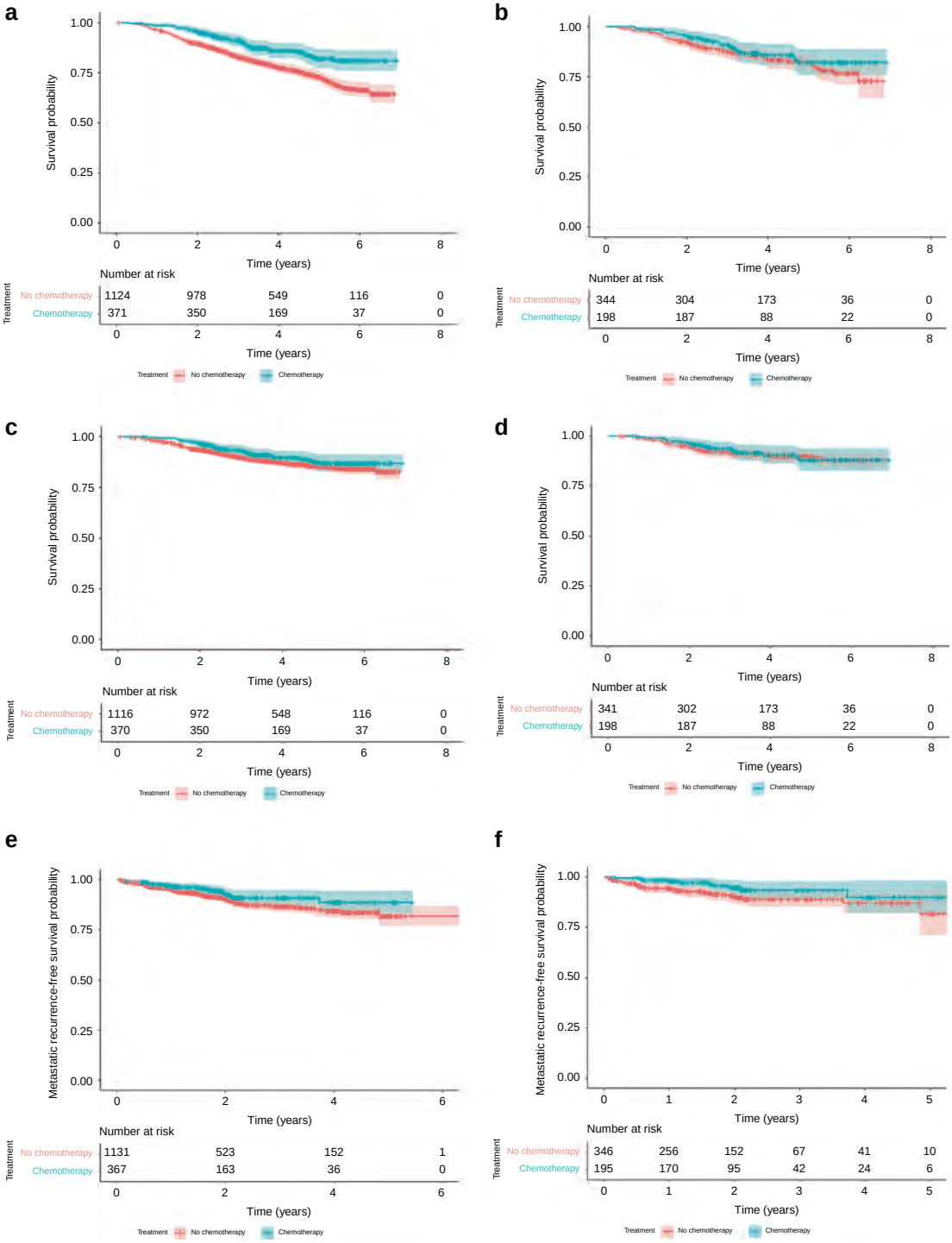


Fig. 2 Kaplan–Meier plots of survival and metastatic recurrence outcomes. a Overall Survival in unmatched high-risk patients ($n = 1495$). Adjusted HR 0.87 (95% CI 0.58–1.28, $p = 0.47$). **b** Overall survival in matched high-risk patients ($n = 542$). Adjusted HR 0.79 (95% CI: 0.50–1.26, $p = 0.32$). **c** Breast cancer-specific survival in unmatched high-risk patients ($n = 1486$). Adjusted HR 0.92 (95% CI: 0.56–1.53, $p = 0.76$). **d** Breast cancer-specific survival in matched high-risk patients ($n = 539$). Adjusted HR 0.93 (95% CI: 0.52–1.66, $p = 0.80$). **e** Metastatic recurrence in unmatched high-risk patients ($n = 1498$). Adjusted HR 0.36 (95% CI: 0.19–0.68, $p = 0.002$). **f** Metastatic recurrence in matched high-risk patients ($n = 541$). Adjusted HR 0.53 (95% CI: 0.26–1.07, $p = 0.08$).

propensity score matching. The extent to which these data reflect practice and outcomes outside of the UK is unknown, although some published data do appear comparable.[24,25]

In summary, this study demonstrates that there are a significant number of older but fit patients with high-risk EBC who are not receiving adjuvant chemotherapy. Some of these patients, particularly those with ER-negative disease, may derive benefit from chemotherapy. Clearly the benefits need to be discussed in the context of potential side effects and the transient negative impact on QoL. Nonetheless, it is important that individualised treatment decisions and discussions are made to ensure the best outcomes for older adults.

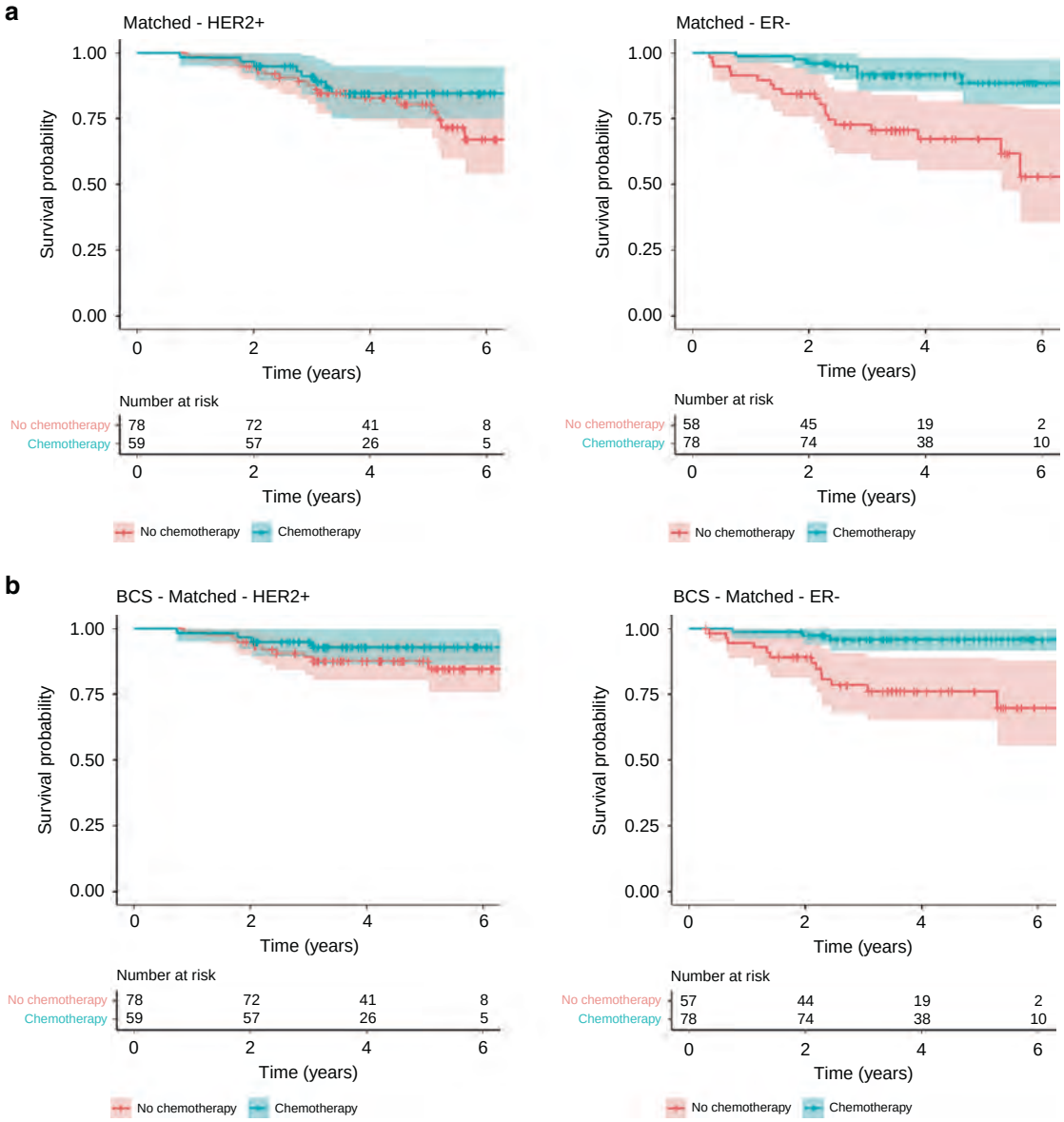


Fig. 3 Kaplan–Meier plots for survival outcomes in matched patients with HER2-positive or ER-negative breast cancer. a Overall survival in patients with HER2-positive breast cancer ($n = 137$): HR 0.63 [0.27–1.48]; and in patients with ER-negative breast cancer ($n = 136$): HR 0.20 [0.08–0.49]. **b** Breast cancer-specific survival in patients with HER2-positive breast cancer ($n = 137$): HR 0.5 [0.16–1.63]; and in patients with ER-negative breast cancer ($n = 135$): HR 0.12 [0.03–0.44].

AGE GAP TMG

Lynda Wyld[4], Malcolm WR Reed[2], Karen Collins[20], Sue Ward[6], Geoff Holmes[6], Jenna Morgan[4], Mike Bradburn[3], Stephen Walters[3], Maria Burton[20], Kate Lifford[21], Adrian Edwards[21], Kate Brain[21], Alistair Ring[22,23], Esther Herbert[3], Thomson Robinson[24], Charlene Martin[4], Tim Chater[3], Kirsty Pemberton[3], Anne Shrestha[4], Anthony Nettleship[25], Paul Richards[6], Alan Brennan[6], Kwok Leung Cheung[26], Annaliza Todd[4], Helena Harder[2], Riccardo Audisio[10], Nicolò Matteo Luca Battisti[22,23], Juliette Wright[2], Richard Simcock[2], Chris Murray[25], Alistair M Thomson[19], Margot Gosney[27], Matthew Hatton[15], Fiona Armitage[15], Julietta Patnick[28], Tracy Green[29], Deirdre Revill[29], Jacqui Gath[29], Kieran Horgan[30], Chris Holcombe[31], Matt Winter[15], Jay Naik[16], Rishi Parmeshwar[17]

[20]Faculty of Health and Wellbeing, Department of Allied Health Professions, Sheffield Hallam University, Collegiate Cresent Campus, Sheffield, UK; [21]Division of Population Medicine, Cardiff University, Heath Park, Cardiff, UK; [22]Breast Unit – Department of Medicine - The Royal Marsden NHS Foundation Trust, London, UK; [23]Breast Cancer Research Division, The Institute of Cancer Research, London, UK; [24]Department of Cardiovascular Sciences, University of Leicester, Cardiovascular Research Centre, Glenfield General Hospital, Leicester, UK; [25]EpiGenesys, University of Sheffield, Sheffield, UK; [26]University of Nottingham, Royal Derby Hospital, Derby, UK; [27]School of Psychology & Clinical Language Sciences, University of Reading, Reading, UK; [28]Cancer Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK; [29]Yorkshire and Humber Research Network Consumer Research Panel, Sheffield, UK; [30]Leeds General Infirmary, Leeds, West Yorkshire, UK and [31]Liverpool and broadgreen Hospitals NHS Foundation Trust, Thomas Drive, Liverpool, Merseyside, UK

ACKNOWLEDGEMENTS

The views expressed are those of the authors and not necessarily those of the National Health Service, the NIHR or the Department of Health.

AUTHOR CONTRIBUTIONS

Substantial contributions to the conception of the study: L.W., K.A.C., M.W.R., A.B., M.B., C.M., J.L.M., S.J.W., A.R., N.M.L.B. Design of the work: L.W., K.A.C., M.W.R., M.B., J.L.M., S.J.W., A.R., N.M.L.B., C.M., M.B., T.C., K.J.P., D.R., T.G., J.G., T.R., R.A.A., G.R.H. Acquisition of data: L.W., C.M., J.L.M., M.B., M.W.R., K.A.C., T.C., K.J.P., K.L., A.E., A.T.,

K.L.C., C.H., M.C.W., M.A.G., M.Q.H., A.M.T., J.N., R.P., D.R., A.R., N.M.L.B., T.G., J.G., T.G.R., R.A.A., K.H. Analysis of data: L.W., S.E.W., M.B., E.H., N.M.L.B., S.J.W., C.M., J.L.M., M.B. Interpretation of data for the work: L.W., S.W., M.B., E.H., J.L.M., N.M.L.B., A.R. Data monitoring and ethics committee: A.M.T., M.A.G. and M.Q.H. Drafting the work or revising it critically for important intellectual content: A.R., N.M.L.B., M.W.R.R., E.H., J.L.M., M.B., S.J.W., K.A.C., S.E.W., G.R.H., M.B., K.L., A.E., T.G.R., C.M., T.C., K.J.P., A.B., K.L.C., A.T., R.A.A., J.W., R.S., T.G., D.R., J.G., K.H., C.H., M.C.W., J.N., R.P., M.A.G., M.Q.H., A.M.T., L.W. Final approval of the version to be published: A.R., N.M.L.B., M.W.R.R., E.H., J.L.M., M.B., S.J.W., K.A.C., S.E.W., G.R.H., M.B., K.L., A.E., T.G.R., C.M., T.C., K.J.P., A.B., K.L.C., A.T., R.A.A., J.W., R.S., T.G., D.R., J.G., K.H., C.H., M.C.W., J.N., R.P., M.A.G., M.Q.H., A.M.T., L.W. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: A.R., N.M.L.B., M.W.R.R., E.H., J.L.M., M.B., S.J.W., K.A.C., S.E.W., G.R.H., M.B., K.L., A.E., T.G.R., C.M., T.C., K.J.P., A.B., K.L.C., A.T., R.A.A., J.W., R.S., T.G., D.R., J.G., K.H., C.H., M.C.W., J.N., R.P., M.A.G., M.Q.H., A.M.T., L.W.

ADDITIONAL INFORMATION

Ethics approval and consent to participate Ethics approval (NRES Committee London South East REC—IRAS: 12 LO 1808) and research governance approval were obtained. All patients (or their proxies, if cognitively impaired) gave written informed consent. The study was performed in accordance with the Declaration of Helsinki.

Consent to publish Not applicable.

Data availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests The authors declare no competing interests. Professors Stephen Walters and Thompson Robinson are National Institute for Health Research (NIHR) Senior Investigators, Jenna Morgan is a NIHR Clinical Lecturer and Kate Lifford is funded by the NIHR as part of this project. The views expressed in this article are those of the author(s) and not necessarily those of the NIHR, or the Department of Health and Social Care.

Funding information The study was sponsored by Doncaster and Bassetlaw Teaching Hospitals NHS Foundation Trust. Clinical Research Office, First Floor 'C' Block, Doncaster Royal Infirmary, Armthorpe Road, Doncaster, DN2 5LT, UK. This paper presents independent research funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research Programme (Grant Reference Number RP-PG-1209-10071). The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

The online version contains supplementary material available at https://doi.org/10.1038/s41416-021-01388-9.

REFERENCES

1. Cancer Research UK. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/incidence-invasive Accessed January 2021.
2. Statistics OfN. *Cancer survival in England: Patients diagnosed between 2010 and 2014 and followed up to 2015*. (Newport, 2016).
3. Moller, H., Flatt, G. & Moran, A. High cancer mortality rates in the elderly in the UK. *Cancer Epidemiol.* **35**, 407–412 (2011).
4. Battisti, N. M. L., Wallington, M., Ring, A., Payne, S., Birch, R., Bomb, M. et al. Is age a barrier to chemotherapy? Rates of treatment in older patients treated with breast, colon and lung cancer in England in 2014: a national registry study. *Ann. Oncol.* **29**, viii562–viii575 (2018).
5. Derks, M. G. M., Bastiaannet, E., Kiderlen, M., Hilling, D. E., Boelens, P. G., Walsh, P. M. et al. Variation in treatment and survival of older patients with non-metastatic breast cancer in five European countries: a population-based cohort study from the EURECCA Breast Cancer Group. *Br. J. Cancer* **119**, 121–129 (2018).
6. Khan, K., Seymour, M., Ring, A. & Johnson, P. in *Problem solving in older cancer patients* (eds. Ring A., Mansi J., Harari D., Kalsi T., Selby P. J.) (Clinical Publishing, 2015).
7. Ring, A., Reed, M., Leonard, R., Kunkler, I., Muss, H., Wildiers, H. et al. The treatment of early breast cancer in women over the age of 70. *Br. J. Cancer* **105**, 189–193 (2011).
8. Charlson, M. E., Pompei, P., Ales, K. L. & MacKenzie, C. R. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J. Chronic Dis.* **40**, 373–383 (1987).
9. Ottery, F. D. Definition of standardized nutritional assessment and interventional pathways in oncology. *Nutrition* **12**, S15–S19 (1996).
10. Vigano, A. L., di Tomasso, J., Kilgour, R. D., Trutschnigg, B., Lucar, E., Morais, J. A. et al. The abridged patient-generated subjective global assessment is a useful tool for early detection and characterization of cancer cachexia. *J. Acad. Nutr. Diet.* **114**, 1088–1098 (2014).
11. Mahoney, F. I. & Barthel, D. W. Functional evaluation: The Barthel Index. *Md State Med. J.* **14**, 61–65 (1965).
12. Lawton, M. P. & Brody, E. M. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist* **9**, 179–186 (1969).
13. Folstein, M. F., Folstein, S. E. & McHugh, P. R. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res.* **12**, 189–198 (1975).
14. Fayers, P. M., Aaronson, N. K., Bjordal, K., Groenvold, M., Curran, D. & Bottomley, A. *The EORTC QLQ-C30 Scoring Manual* 3rd edn. (Cancer EOfRaTo, 2001).
15. Aaronson, N. K., Ahmedzai, S., Bergman, B., Bullinger, M., Cull, A., Duez, N. J. et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J. Natl. Cancer Inst.* **85**, 365–376 (1993).
16. Sprangers, M. A., Groenvold, M., Arraras, J. I., Franklin, J., te Velde, A., Muller, M. et al. The European Organization for Research and Treatment of Cancer breast cancer-specific quality-of-life questionnaire module: first results from a three-country field study. *J. Clin. Oncol.* **14**, 2756–2768 (1996).
17. Johnson, C., Fitzsimmons, D., Gilbert, J., Arrarras, J. I., Hammerlid, E., Bredart, A. et al. Development of the European Organisation for Research and Treatment of Cancer quality of life questionnaire module for older people with cancer: The EORTC QLQ-ELD15. *Eur. J. Cancer* **46**, 2242–2252 (2010).
18. Battisti, N. M. L., Herbert, E., Bradburn, M., Morgan, J., Wyld, L. & Ring, A. *Impact of chemotherapy for early stage breast cancer on quality of life in older adults: results from 2811 women enrolled in the Bridging the Age Gap study (#2586)* (European Society for Medical Oncology, 2020).
19. R Core Team. *R: A language and environment for statistical computing*. https://www.R-project.org/. (2020).
20. Galea, M. H., Blamey, R. W., Elston, C. E. & Ellis, I. O. The Nottingham Prognostic Index in primary breast cancer. *Breast Cancer Res. Treat.* **22**, 207–219 (1992).
21. EuroQoL Research Foundation. *EQ-5D-5L User Guide: Basic information on how to use the EQ-5D-5L instrument*. (2019).
22. von Elm, E., Altman, D. G., Egger, M., Pocock, S. J., Gøtzsche, P. C. & Vandenbroucke, J. P. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J. Clin. Epidemiol.* **61**, 344–349 (2008).
23. Ring, A., Harder, H., Langridge, C., Ballinger, R. S. & Fallowfield, L. J. Adjuvant chemotherapy in elderly women with breast cancer (AChEW): an observational study identifying MDT perceptions and barriers to decision making. *Ann. Oncol.* **24**, 1211–1219 (2013).
24. Bastiaannet, E., Liefers, G. J., de Craen, A. J., Kuppen, P. J., van de Water, W., Portielje, J. E. et al. Breast cancer in elderly compared to younger patients in the Netherlands: stage at diagnosis, treatment and survival in 127,805 unselected patients. *Breast Cancer Res. Treat.* **124**, 801–807 (2010).
25. Buist, D. S., Chubak, J., Prout, M., Yood, M. U., Bosco, J. L., Thwin, S. S. et al. Referral, receipt, and completion of chemotherapy in patients with early-stage breast cancer older than 65 years and at high risk of breast cancer recurrence. *J. Clin. Oncol.* **27**, 4508–4514 (2009).
26. Muss, H. B., Berry, D. A., Cirrincione, C. T., Theodoulou, M., Mauer, A. M., Kornblith, A. B. et al. Adjuvant chemotherapy in older women with early-stage breast cancer. *N. Engl. J. Med.* **360**, 2055–2065 (2009).
27. Crivellari, D., Gray, K. P., Dellapasqua, S., Puglisi, F., Ribi, K., Price, K. N. et al. Adjuvant pegylated liposomal doxorubicin for older women with endocrine nonresponsive breast cancer who are NOT suitable for a "standard chemotherapy regimen": the CASA randomized trial. *Breast* **22**, 130–137 (2013).
28. Leonard, R., Ballinger, R., Cameron, D., Ellis, P., Fallowfield, L., Gosney, M. et al. Adjuvant chemotherapy in older women (ACTION) study—what did we learn from the pilot phase? *Br. J. Cancer* **105**, 1260–1266 (2011).
29. Im, S. A., Lu, Y. S., Bardia, A., Harbeck, N., Colleoni, M., Franke, F. et al. Overall survival with ribociclib plus endocrine therapy in breast cancer. *N. Engl. J. Med.* **381**, 307–316 (2019).
30. Giordano, S. H., Duan, Z., Kuo, Y. F., Hortobagyi, G. N. & Goodwin, J. S. Use and outcomes of adjuvant chemotherapy in older women with breast cancer. *J. Clin. Oncol.* **24**, 2750–2756 (2006).

31. Syed, B. M., Green, A. R., Ellis, I. O. & Cheung, K. L. Human epidermal growth receptor-2 overexpressing early operable primary breast cancers in older (≥70 years) women: biology and clinical outcome in comparison with younger (<70 years) patients. *Ann. Oncol.* **25**, 837–842 (2014).
32. Adjogatse, D., Thanopoulou, E., Okines, A., Thillai, K., Tasker, F., Johnston, S. R. et al. Febrile neutropaenia and chemotherapy discontinuation in women aged 70 years or older receiving adjuvant chemotherapy for early breast cancer. *Clin. Oncol. (R. Coll. Radio.)* **26**, 692–696 (2014).
33. Ferreira, A. R., Di Meglio, A., Pistilli, B., Gbenou, A. S., El-Mouhebb, M., Dauchy, S. et al. Differential impact of endocrine therapy and chemotherapy on quality of life of breast cancer survivors: a prospective patient-reported outcomes analysis. *Ann. Oncol.* **30**, 1784–1795 (2019).
34. Quinten, C., Kenis, C., Hamaker, M., Coolbrandt, A., Brouwers, B., Dal Lago, L. et al. The effect of adjuvant chemotherapy on symptom burden and quality of life over time; a preliminary prospective observational study using individual data of patients aged ≥70 with early stage invasive breast cancer. *J. Geriatr. Oncol* **9**, 152–162 (2018).
35. Todd, A., Martin, C., Morgan, J., Herbert, E., Bradburn, M., Burton, M. et al. Age specific recruitment and retention to a large multicentre observational breast cancer trial in older women: The Age Gap Trial. *J. Geriatr. Oncol*. S1879–4068(20) 30487–2. https://doi.org/10.1016/j.jgo.2020.10.015 (2020).

European Journal of Cancer 144 (2021) 269–280

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Bridging the Age Gap in breast cancer: Impact of chemotherapy on quality of life in older women with early breast cancer

Nicolò Matteo Luca Battisti [a,b], Malcolm W.R. Reed [c], Esther Herbert [d], Jenna L. Morgan [e], Karen A. Collins [f], Sue E. Ward [g], Geoffrey R. Holmes [g], Michael Bradburn [d], Stephen J. Walters [d], Maria Burton [f], Kate Lifford [h], Adrian Edwards [h], Thompson G. Robinson [i], Charlene Martin [e], Tim Chater [d], Kirsty J. Pemberton [d], Anne Shrestha [e], Alan Brennan [g], Kwok L. Cheung [j], Annaliza Todd [e], Riccardo A. Audisio [k], Juliet Wright [c], Richard Simcock [l], Tracey Green [m], Deirdre Revell [m], Jacqui Gath [m], Kieran Horgan [n], Chris Holcombe [o], Matthew C. Winter [p], Jay Naik [q], Rishi Parmeshwar [r], Margot A. Gosney [s], Matthew Q. Hatton [o], Alastair M. Thompson [t], Lynda Wyld [e,*,1], Alistair Ring [a,b,1] on behalf of the Age Gap TMG

[a] *Department of Medicine, Breast Unit the Royal Marsden Hospital NHS Foundation Trust, London, UK*
[b] *Breast Cancer Research Division, The Institute of Cancer Research, London, UK*
[c] *Brighton and Sussex Medical School, Falmer, Brighton, UK*
[d] *Clinical Trials Research Unit, School for Health and Related Research, University of Sheffield, Sheffield, UK*
[e] *Department of Oncology and Metabolism, University of Sheffield Medical School, Beech Hill Road, Sheffield, UK*
[f] *College of Health, Wellbeing and Life Sciences, Department of Allied Health Professions, Sheffield Hallam University, Collegiate Crescent Campus, Sheffield, UK*
[g] *Health Economics and Decision Science Section, School for Health and Related Research (ScHARR), University of Sheffield, UK*
[h] *Division of Population Medicine, Cardiff University, 8th Floor, Neuadd Meirionnydd, Heath Park, Cardiff, UK*
[i] *Department of Cardiovascular Sciences and NIHR Biomedical Research Centre, University of Leicester, Cardiovascular Research Centre, The Glenfield Hospital, Leicester, UK*
[j] *University of Nottingham, Royal Derby Hospital, Uttoxeter Road, Derby, UK*
[k] *University of Gothenberg, Sahlgrenska Universitetssjukhuset, Göteborg, Sweden*
[l] *Sussex Cancer Centre, Royal Sussex County Hospital, Brighton, UK*
[m] *Yorkshire and Humber Consumer Research Panel, Cottingham, UK*
[n] *Department of Breast Surgery, Bexley Cancer Centre, St James's University Hospital, Leeds, UK*

* *Corresponding author*: Department of Oncology and Metabolism, University of Sheffield Medical School, Beech Hill Road, Sheffield, S10 2RX, UK.
E-mail address: l.wyld@sheffield.ac.uk (L. Wyld).
[1] Joint senior authors.

https://doi.org/10.1016/j.ejca.2020.11.022

[o] Liverpool University Hospitals Foundation Trust, Liverpool, UK
[p] Weston Park Hospital, Sheffield, UK
[q] Pinderfields Hospital, Mid Yorkshire NHS Foundation Trust, Wakefield, UK
[r] University Hospitals of Morecambe Bay, Royal Lancashire Infirmary, Lancaster, Lancashire, UK
[s] Royal Berkshire NHS Foundation Trust, Reading, UK
[t] Department of Surgery, Baylor College of Medicine, Houston, TX, USA

Received 4 July 2020; received in revised form 9 November 2020; accepted 14 November 2020
Available online 26 December 2020

KEYWORDS
Breast cancer;
Older patients;
Adjuvant chemotherapy;
Quality of life

Abstract ***Introduction:*** Older patients with early breast cancer (EBC) derive modest survival benefit from chemotherapy but have increased toxicity risk. Data on the impact of chemotherapy for EBC on quality of life in older patients are limited, but this is a key determinant of treatment acceptance. We aimed to investigate its effect on quality of life in older patients enrolled in the Bridging the Age Gap study.
Materials and methods: A prospective, multicentre, observational study of EBC patients ≥70 years old was conducted in 2013–2018 at 56 UK hospitals. Demographics, patient, tumour characteristics, treatments and adverse events were recorded. Quality of life was assessed using the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaires (EORTC-QLQ) C30, BR23 and ELD 15 plus the Euroqol-5D (eq-5d) over 24 months and analysed at each time point using baseline adjusted linear regression analysis and propensity score-matching.
Results: Three thousand and four hundred sixteen patients were enrolled in the study; 1520 patients undergoing surgery and who had high-risk EBC were included in this analysis. 376/1520 (24.7%) received chemotherapy. At 6 months, chemotherapy had a significant negative impact in several EORTC-QLQ-C30 domains, including global health score, physical, role, social functioning, cognition, fatigue, nausea/vomiting, dyspnoea, appetite loss, diarrhoea and constipation. Similar trends were documented on other scales (EORTC-QLQ-BR23, EORTC-QLQ-ELD15 and EQ-5D-5L). Its impact was no longer significant at 18–24 months in unmatched and matched cohorts.
Conclusions: The negative impact of chemotherapy on quality-of-life is clinically and statistically significant at 6 months but resolves by 18 months, which is crucial to inform decision-making for older patients contemplating chemotherapy.
Trial registration number ISRCTN: 46099296.

1. Introduction

Almost half of all breast cancer cases are diagnosed in patients aged ≥65 years [1]. Nonetheless, older adults are under-represented in clinical trials [2]. Moreover, standard trial end-points may not be appropriate for older individuals and quality of life (QoL), functional status and cognition may be as important as chance of cure [3]. These knowledge gaps contribute to considerable variation in treatment in this age group [4].

Curative chemotherapy is associated with a survival benefit only in patients with node-positive and oestrogen receptor (ER)–negative disease [5,6]. Older adults have higher risk of treatment toxicities due to comorbidities and reduced organ function, while benefits are mitigated by competing risks [7]. The impact of chemotherapy on QoL may influence clinicians' and patients' perspectives [8].

Therefore, the effect of anticancer treatments on QoL is essential to inform treatment decisions in this cohort. The CALGB 49907 study documented better QoL for patients aged ≥65 receiving capecitabine versus standard regimens, but no QoL differences persisted at 1 year [9]. Patients receiving chemotherapy within clinical trials had better QoL improvements compared with those treated off study [10]. Nonetheless, prospective data on QoL for older patients with early breast cancer (EBC) receiving standard chemotherapy are lacking.

Comorbidities, literacy, symptoms and compliance may influence patient-reported outcomes [11], but the

European Organisation for Research and Treatment of Cancer (EORTC) questionnaires have been validated to evaluate QoL generically in cancer patients [12] and, specifically, in older individuals [13] and in those diagnosed with breast cancer [14].

We aimed to investigate the impact of chemotherapy on QoL in real-world EBC patients aged ≥70 recruited to the Bridging the Age Gap study [15]. Matching survival outcomes for the cohort are reported separately.

2. Methods

2.1. Regulatory approval

Ethics approval (IRAS: 12 LO 1808) and research governance approval were obtained. All patients (or their proxies, if cognitively impaired) gave written informed consent.

2.2. Study design

Bridging the Age Gap is a prospective multicentre, observational cohort study. Patients were recruited from 56 UK centres in England and Wales (Table S1). Eligible patients were women ≥70 years at diagnosis of operable invasive breast cancer (tumour-node-metastasis stages: T1-3, plus some operable T4b, N0-1, M0). Those unsuitable for surgery or with previous EBC within five years were not eligible.

2.3. Baseline data collection

Patients were recruited at the time of diagnosis and could participate at three levels: full, partial (no requirement to complete QoL assessments) or proxy (simple third-party data collection for those with cognitive impairment).

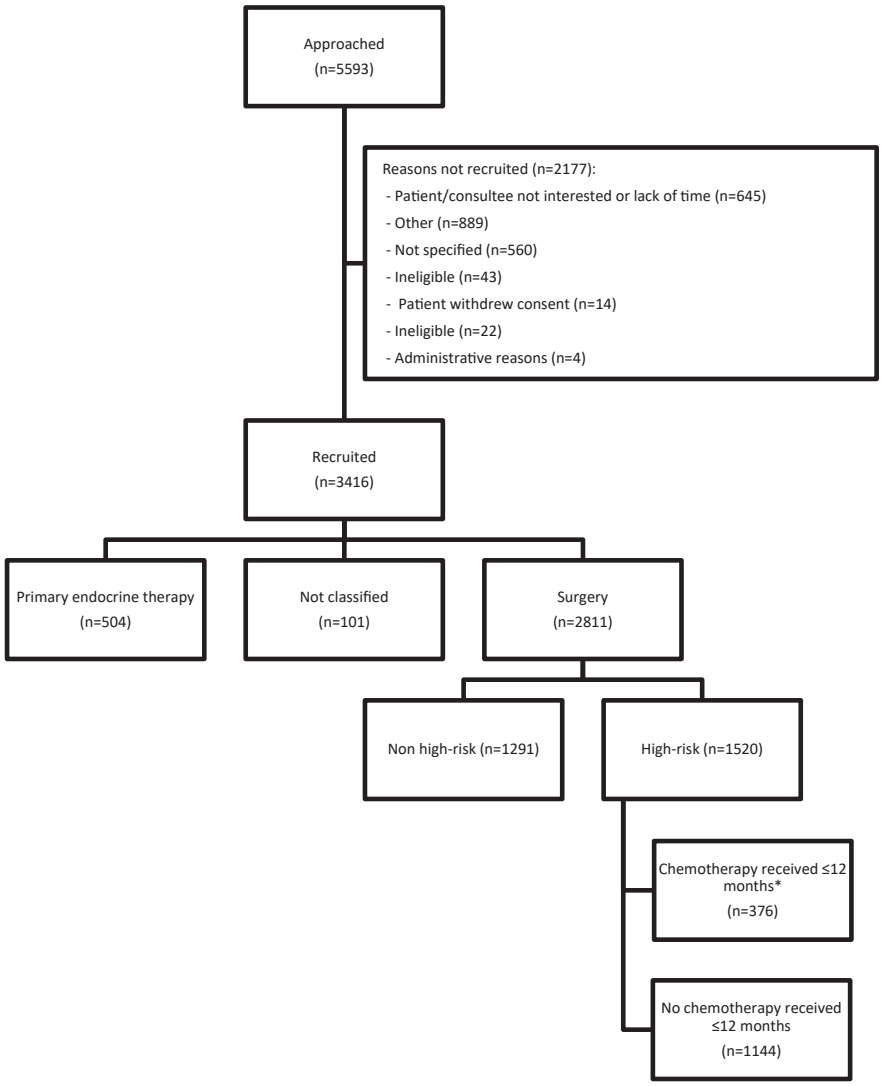


Fig. 1. The STROBE flow diagram for the chemotherapy versus no chemotherapy analyses. * Patients who only received palliative chemotherapy regimens where not counted as having received chemotherapy. STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

Primary tumour characteristics were collected at baseline. Staging was performed if indicated. Surgery, radiotherapy and systemic treatment data were also collected.

Baseline geriatric assessments included comorbidities (Charlson comorbidity index [CCI]) [16], nutrition (Abridged Patient Generated Subjective Global Assessment [aPG-SGA]) [17–19], functional status (Eastern Cooperative Oncology Group Performance status [ECOG PS], activities of daily living [ADL] [20], instrumental activities of daily living [IADL]) [21], cognition (Mini-Mental State Examination [MMSE]) [22] and medications. Patients were classified as high risk based on ≥1 of the following criteria: 1) Human epidermal growth factor receptor type 2 (HER2)-positive status; 2) ER-negative status; 3) grade III; 4) ≥1 malignant lymph node; 5) recurrence score (RS) ≥30 (Table S2).

QoL was evaluated using four questionnaires. The EORTC-QLQ-C30 includes five functional domains (physical, role, emotional, cognitive and social), nine symptoms (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties) and global health status [12]. The EORTC-QLQ-BR23 comprises 23 questions evaluating body image, sexual functioning and enjoyment, future perspective, systemic therapy side-effects, breast symptoms, arm symptoms and frustration with hair loss [14]. The EORTC-QLQ-ELD15 contains five scales (functional independence, relationships with family and friends, worries about the future, autonomy and burden of illness) [13]. The EQ-5D-5L was used in this analysis

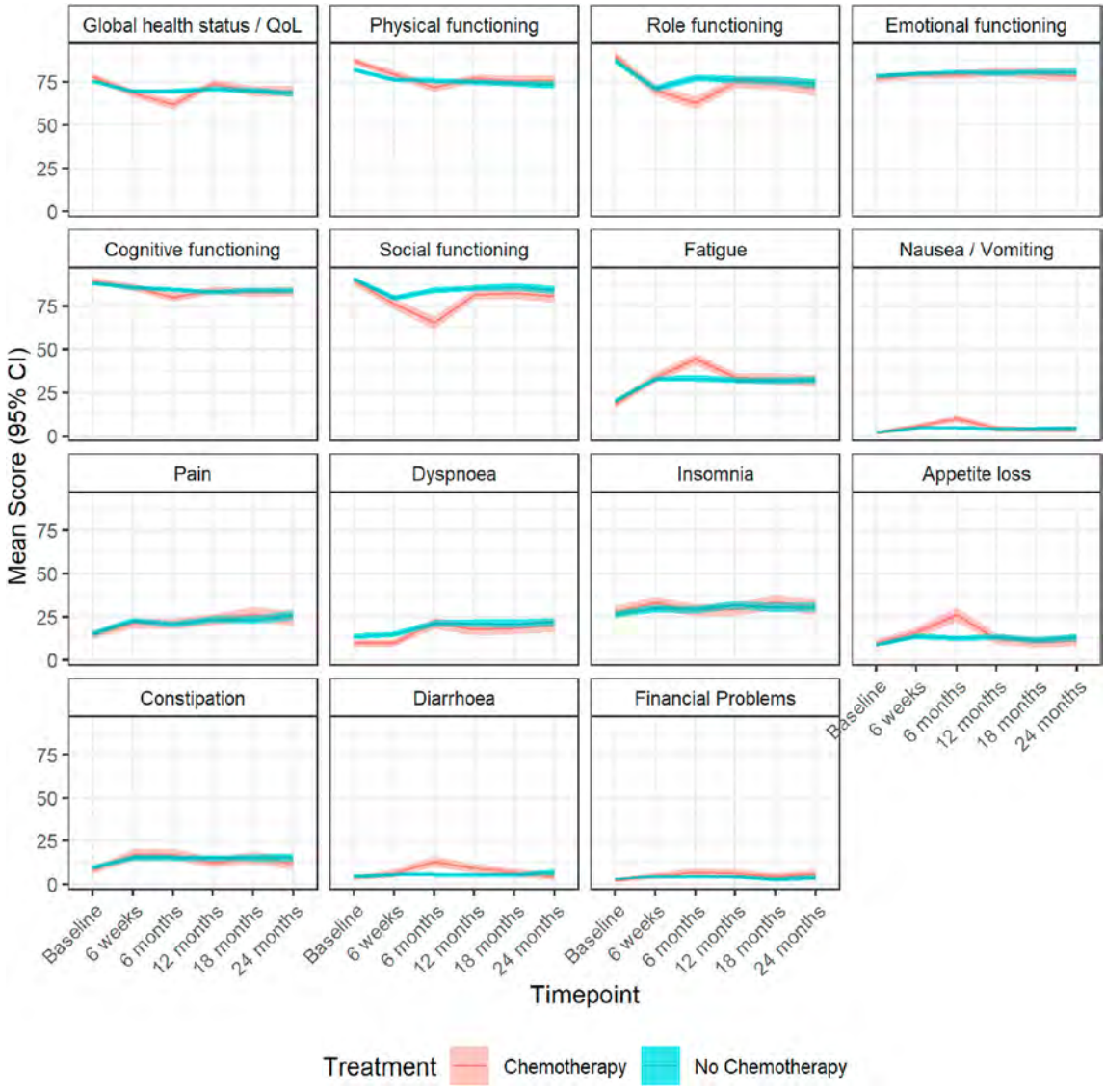


Fig. 2. Mean (95% CI) scores over time points for the chemotherapy versus no chemotherapy population measured on the EORTC-QLQ-C30 scale. CI, confidence interval; EORTC-QLQ, European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaires; QoL, quality of life.

Table 1
Baseline postoperative tumour and patient characteristics by receipt of chemotherapy.

Variable	Category	Chemotherapy	No chemotherapy	Total
		N = 376	N = 1144	N = 1520
Participation level	Full	304 (80.9%)	816 (71.3%)	1120 (73.7%)
	Partial	68 (18.1%)	284 (24.8%)	352 (23.2%)
	Consultee	4 (1.1%)	44 (3.8%)	48 (3.2%)
Main side	Right	169 (44.9%)	545 (47.6%)	714 (47.0%)
	Left	207 (55.1%)	599 (52.4%)	806 (53.0%)
Tumour size (mm)	n	375	1143	1518
	Mean (SD)	32.9 (20.7)	29.0 (17.5)	29.9 (18.4)
	Median (IQR)	29.0 (21.0, 40.0)	25.0 (18.0, 35.0)	25.0 (18.2, 36.0)
	Min, Max	0, 210	0, 155	0, 210
Tumour size (mm)	≤20	93 (24.7%)	399 (34.9%)	492 (32.4%)
	21–50	233 (62.0%)	644 (56.3%)	877 (57.7%)
	>50	49 (13.0%)	100 (8.7%)	149 (9.8%)
	Unknown	1 (0.3%)	1 (0.1%)	2 (0.1%)
Grade	Grade I	2 (0.5%)	77 (6.7%)	79 (5.2%)
	Grade II	122 (32.4%)	447 (39.1%)	569 (37.4%)
	Grade III	247 (65.7%)	617 (53.9%)	864 (56.8%)
	Unknown	5 (1.3%)	3 (0.3%)	8 (0.5%)
Histology	Ductal NST	270 (71.8%)	813 (71.1%)	1083 (71.2%)
	Lobular carcinoma	52 (13.8%)	110 (9.6%)	162 (10.7%)
	Tubular carcinoma	0 (0.0%)	5 (0.4%)	5 (0.3%)
	Mucinous carcinoma	1 (0.3%)	13 (1.1%)	14 (0.9%)
	Other	29 (7.7%)	97 (8.5%)	126 (8.3%)
	Unknown	24 (6.4%)	106 (9.3%)	130 (8.6%)
ER positive?	No	132 (35.1%)	240 (21.0%)	372 (24.5%)
	Yes	241 (64.1%)	893 (78.1%)	1134 (74.6%)
	Unknown	3 (0.8%)	11 (1.0%)	14 (0.9%)
HER2 status	Negative	210 (55.9%)	908 (79.4%)	1118 (73.6%)
	Inconclusive	3 (0.8%)	7 (0.6%)	10 (0.7%)
	Positive	159 (42.3%)	173 (15.1%)	332 (21.8%)
	Unknown	4 (1.1%)	56 (4.9%)	60 (3.9%)
Oncotype Dx test performed	No	35 (9.3%)	150 (13.1%)	185 (12.2%)
	Yes	5 (1.3%)	16 (1.4%)	21 (1.4%)
	Not Applicable	252 (67.0%)	434 (37.9%)	686 (45.1%)
	Unknown	84 (22.3%)	544 (47.6%)	628 (41.3%)
Breast surgery	Wide local excision (non wire localised)	113 (30.1%)	412 (36.0%)	525 (34.5%)
	Wire localised wide local excision	43 (11.4%)	150 (13.1%)	193 (12.7%)
	Therapeutic mammoplasty/breast reshaping after WLE	18 (4.8%)	14 (1.2%)	32 (2.1%)
	Mastectomy	186 (49.5%)	549 (48.0%)	735 (48.4%)
	Mastectomy and reconstruction	12 (3.2%)	11 (1.0%)	23 (1.5%)
	Other	4 (1.1%)	8 (0.7%)	12 (0.8%)
Axillary surgery	Axillary sample	11 (2.9%)	38 (3.3%)	49 (3.2%)
	Axillary clearance	136 (36.2%)	247 (21.6%)	383 (25.2%)
	Sentinel lymph node biopsy	200 (53.2%)	725 (63.4%)	925 (60.9%)
	Internal mammary node biopsy	0 (0.0%)	1 (0.1%)	1 (0.1%)
	No axillary surgery	7 (1.9%)	27 (2.4%)	34 (2.2%)
	Unknown	22 (5.9%)	106 (9.3%)	128 (8.4%)
Nodal status	pN0-1mi	175 (46.5%)	508 (44.4%)	683 (44.9%)
	pN1	117 (31.1%)	494 (43.2%)	611 (40.2%)
	pN2	52 (13.8%)	95 (8.3%)	147 (9.7%)
	pN3	32 (8.5%)	46 (4.0%)	78 (5.1%)
	pNx	0 (0.0%)	1 (0.1%)	1 (0.1%)
Nottingham Prognostic Index	n	371	1139	1510
	Mean (SD)	5.1 (1.0)	4.7 (0.9)	4.8 (1.0)
	Median (IQR)	4.9 (4.4, 5.7)	4.5 (4.3, 5.3)	4.6 (4.3, 5.4)
	Min, Max	2.4, 10.2	2.1, 8.1	2.1, 10.2
Age	n	376	1144	1520
	Mean (SD)	73.65 (3.33)	77.97 (5.19)	76.90 (5.14)
	Median (IQR)	73.00 (71.00, 76.00)	78.00 (74.00, 81.00)	76.00 (72.00, 80.00)
	Min, Max	69, 87	69, 95	69, 95
Charlson comorbidity index (no	n	365	1103	1468

(continued on next page)

Table 1 (*continued*)

Variable	Category	Chemotherapy	No chemotherapy	Total
		N = 376	N = 1144	N = 1520
age)	Mean (SD)	0.79 (1.08)	1.11 (1.38)	1.03 (1.32)
	Median (IQR)	0.00 (0.00, 2.00)	1.00 (0.00, 2.00)	1.00 (0.00, 2.00)
	Min, Max	0, 6	0, 9	0, 9
Charlson calculated probability	n	365	1103	1468
	Mean (SD)	0.56 (0.26)	0.43 (0.29)	0.46 (0.29)
	Median (IQR)	0.77 (0.21, 0.77)	0.53 (0.21, 0.77)	0.53 (0.21, 0.77)
	Min, Max	0, 0.77	0, 0.77	0, 0.77
Number of concurrent medications	n	314	1021	1335
	Mean (SD)	3.66 (2.51)	4.30 (2.69)	4.15 (2.66)
	Median (IQR)	3.00 (2.00, 5.00)	4.00 (2.00, 6.00)	4.00 (2.00, 6.00)
	Min, Max	0, 14	0, 18	0, 18
ADL category	No dependency	303 (80.6%)	760 (66.4%)	1063 (69.9%)
	Mild dependency	33 (8.8%)	146 (12.8%)	179 (11.8%)
	Moderate/severe dependency	16 (4.3%)	136 (11.9%)	152 (10.0%)
	Unknown	24 (6.4%)	102 (8.9%)	126 (8.3%)
IADL category	No dependency	315 (83.8%)	776 (67.8%)	1091 (71.8%)
	Mild dependency	26 (6.9%)	124 (10.8%)	150 (9.9%)
	Moderate/severe dependency	10 (2.7%)	136 (11.9%)	146 (9.6%)
	Unknown	25 (6.6%)	108 (9.4%)	133 (8.7%)
MMSE category	Normal function	342 (91.0%)	1004 (87.8%)	1346 (88.6%)
	Mild impairment	28 (7.4%)	111 (9.7%)	139 (9.1%)
	Moderate impairment	4 (1.1%)	14 (1.2%)	18 (1.2%)
	Severe	2 (0.5%)	15 (1.3%)	17 (1.1%)
APG SGA category	Low	299 (79.5%)	869 (76.0%)	1168 (76.8%)
	Moderate	38 (10.1%)	125 (10.9%)	163 (10.7%)
	High	4 (1.1%)	19 (1.7%)	23 (1.5%)
	Unknown	35 (9.3%)	131 (11.5%)	166 (10.9%)
ECOG performance status	Fully active	296 (78.7%)	740 (64.7%)	1036 (68.2%)
	Restricted in physically strenuous activity	59 (15.7%)	284 (24.8%)	343 (22.6%)
	Ambulatory and capable of all self-care	3 (0.8%)	43 (3.8%)	46 (3.0%)
	Capable of only limited self-care	2 (0.5%)	18 (1.6%)	20 (1.3%)
	Unknown	16 (4.3%)	59 (5.2%)	75 (4.9%)

SD, standard deviation; IQR, interquartile range; NST, no special type; ADL, activities of daily living; IADL, instrumental activities of daily living; MMSE, Mini–Mental State Examination; APG SGA, Abridged Patient-Generated Subjective Global Assessment; ECOG, Eastern Cooperative Oncology Group.

to assess overall QoL [23] and individual questions were scored separately from 1 to 5.

Patients were followed up at 6 weeks, 6, 12, 18 and 24 months and QoL and side-effects, based on the Common Terminology Criteria for Adverse Events (CTCAE v4.0), were assessed at each visit.

2.4. Statistical analyses

Analyses were performed in IBM SPSS statistics version 24 and R version 3.6.3 [24,25]. A $p < 0.05$ was considered statistically significant.

The questionnaires were scored according to the EORTC Scoring Manual (3rd Edition) [13]. Missing data were managed accordingly. The analysis included patients with high-risk EBC where QoL questionnaires were available. The mean difference (95% confidence interval [CI]) of the domain scores at each time point, adjusted for baseline scores, was calculated with linear regression models for high-risk participants. Effect sizes after analyses of the EORTC-QLQ-C30 were categorised as either trivial, small, medium or large according to pre-specified thresholds for each domain [26].

The chemotherapy effect on the global health score over time for high-risk patients was estimated using a mixed-effect linear model. The model allowed for time, treatment, treatment–time interaction, and baseline global health status. Differences between the chemotherapy and non-chemotherapy groups were derived at each time point using linear contrasts. The model was fitted to high-risk patients and to the propensity score–matched patients only. For the unmatched analysis the model also adjusted for age and baseline functionality scores.

Propensity score matching was performed to compare the EORTC-QLQ-C30 global health score and the EQ-5D-5L usual activities score in a matched cohort receiving chemotherapy versus patients not receiving it. Logistic regression was used to calculate propensity scores for treatment allocation in high-risk patients. These were used to match chemotherapy patients to those who did not receive chemotherapy based on ADL, IADL, MMSE, ECOG, aPG-SGA, CCI, number of medications and age. The ratio and calliper widths of the propensity scores were chosen based on examination of propensity score overlaps for several combinations of

ratios and callipers. A 1:3 ratio for chemotherapy to no chemotherapy and a calliper of 0.25 times the propensity scores standard deviation was used to optimally match quality and numbers. Participants were matched on the Nottingham prognostic index category (good: ≤3.4, moderate: 3.5–5.4, poor: >5.4) and HER2 status.

3. Results

Between January 2013 and June 2018, 3456 women were recruited from 56 hospitals in England and Wales, and 3416 included in the analysis. 2811/3416 (82.3%) underwent surgery within 6 months of diagnosis, 1520/2811 (54.1%) had high-risk EBC and 376/1520 (24.7%) received chemotherapy (Fig. 1) [27]. The time frames for treatments received in each cohort are shown in Fig. S1 wherein the slight offset in timing of endocrine therapy and radiotherapy between the chemotherapy and no chemotherapy groups can be seen and should be considered when interpreting the findings.

Patients had a median age of 76.9 years, had a median CCI of 1 (range: 0–9), and took a median of four medications (0–18); 1063 (69.9%) were independent in their ADLs and 1091 (71.8%) in their IADLs, 1346 (88.6%) had a normal MMSE, 1168 (76.8%) had a low aPG-SGA score and 1379 (90.7%) had ECOG PS of 0–1 (Table 1).

Chemotherapy data were available for 360 patients: 124 (34.4%) received anthracycline and taxanes, 119 (33.1%) a taxane alone and 116 (32.2%) an anthracycline alone; one patient received cyclophosphamide, methotrexate, fluorouracil. Three-hundred thirty-two patients (21.8%) had HER2-positive disease: 150 (45.2%) received chemotherapy plus trastuzumab, 13 (3.9%) received trastuzumab alone and 9 (2.7%) chemotherapy alone. EBC was ER-positive in 1134 patients (75.3%), with 1079 (95.1%) receiving endocrine therapy (Fig. S1).

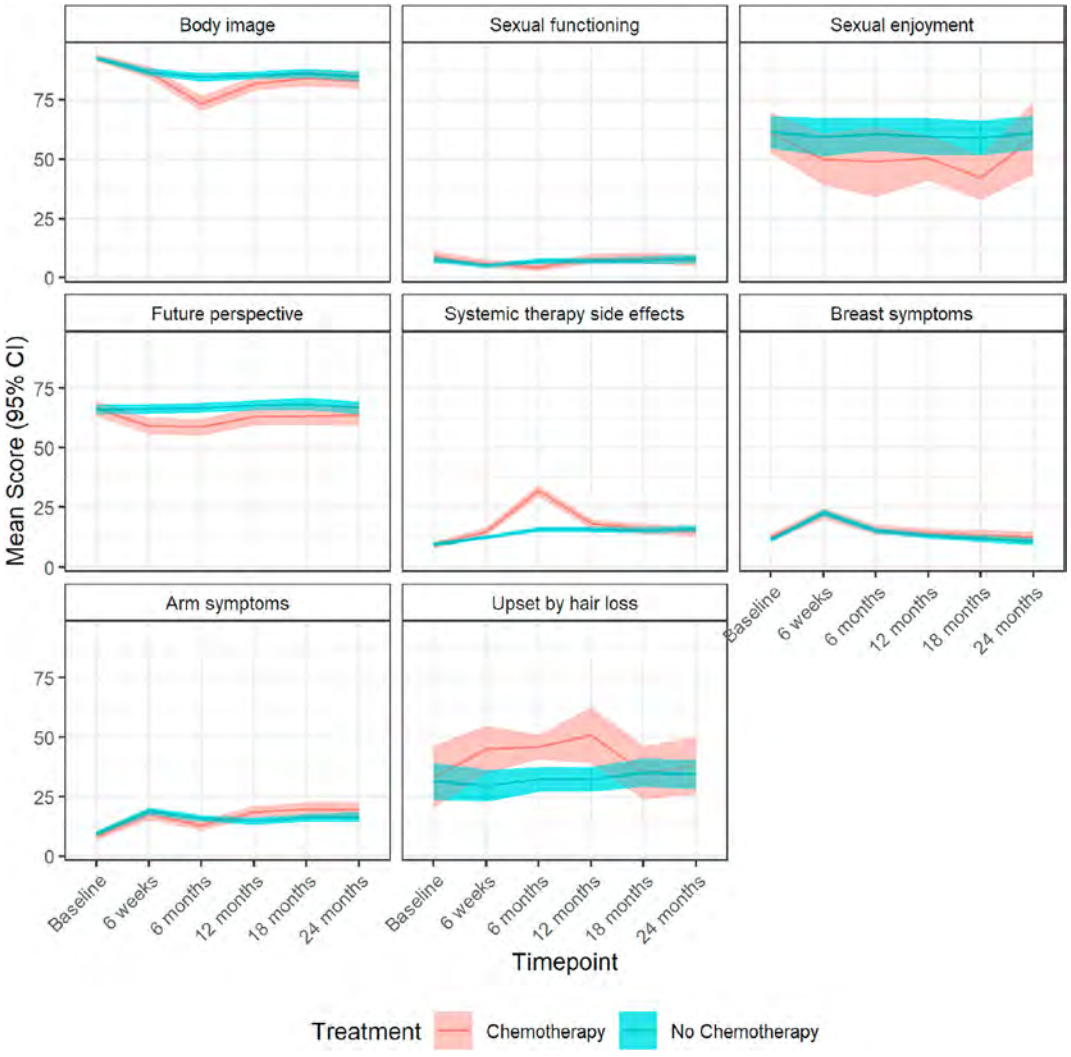


Fig. 3. Mean (95% CI) scores over time points for the chemotherapy versus no chemotherapy population measured on the EORTC-QLQ-B23 scale. CI, confidence interval; EORTC-QLQ, European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaires.

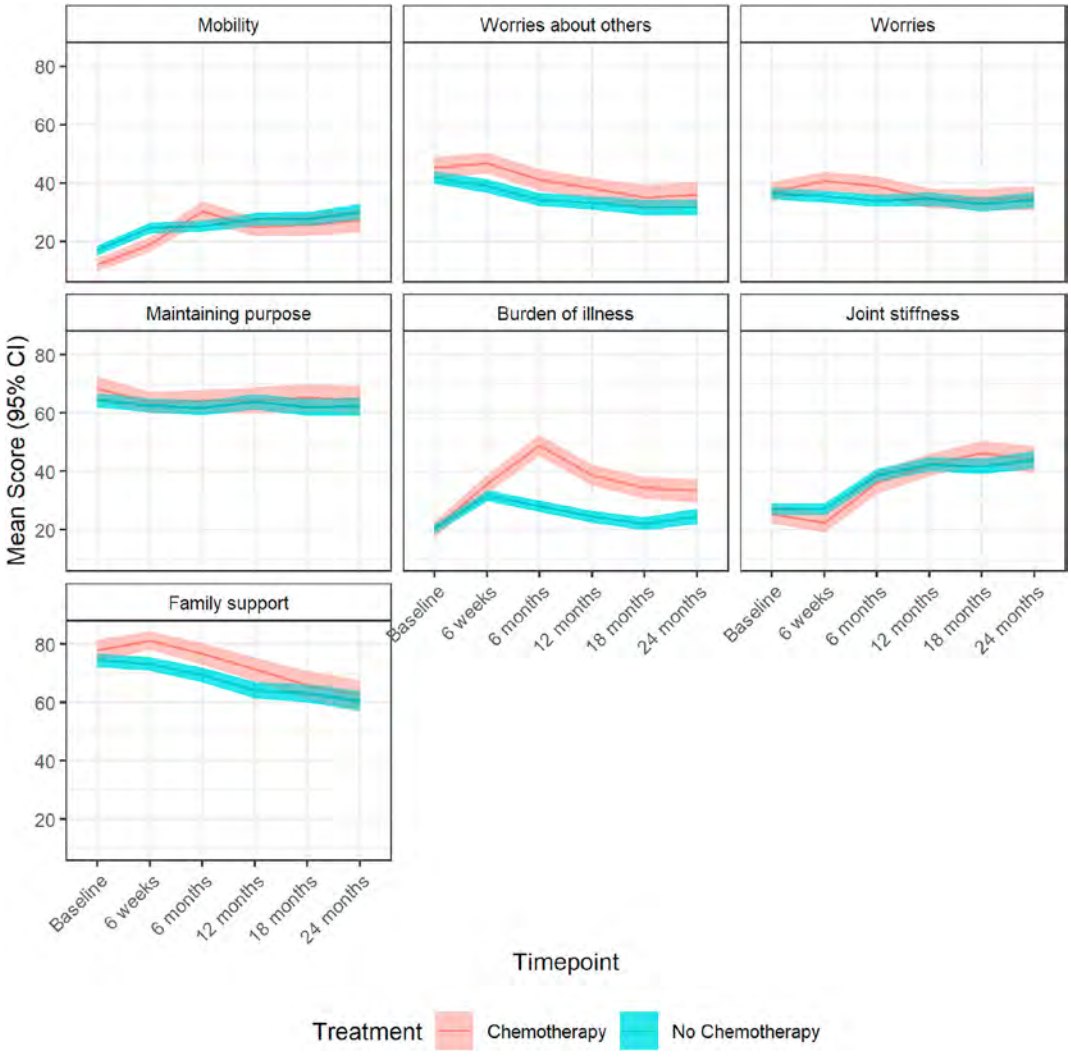


Fig. 4. Mean (95% CI) scores over time points for the chemotherapy versus no chemotherapy population measured on the EORTC-QLQ-ELD15 scale. CI, confidence interval; EORTC-QLQ, European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaires.

Of these high-risk patients, 1120 (73.7%) enrolled with full participation in the protocol (necessary for completion of QoL questionnaires) and 304/1120 (27.1%) had chemotherapy. Figs. S2–S4 and Tables S3–5 show completion rates of QoL questionnaires.

3.1. Impact on QoL domains (EORTC-QLQ-C30)

1049/1120 patients (93.7%) completed the global health-status questions included in the EORTC-QLQ-C30 questionnaire at baseline (Table S6a; Fig. 2). After adjustment for baseline scores, at 6 weeks the differences in the mean scores on some EORTC-QLQ-C30 domains were statistically significant between patients undergoing chemotherapy compared with those of patients not receiving it, including global health (adjusted mean difference: −2.81, 95% CI: −5.17 to −0.44, $p = 0.020$), social functioning (−3.57, CI: −6.71 to −0.43, $p = 0.026$) and constipation (3.43, CI: 0.23 to 6.62, $p = 0.035$). The impact of chemotherapy remained significant on most domains at 6 months, including global health which was both statistically and clinically significant but small (−9.20, CI: −11.95 to −6.44, $p < 0.001$), physical functioning (medium difference: −8.05, CI: −10.21 to −5.89, $p < 0.001$), role functioning (small difference: −17.59, CI: −21.24 to −13.95, $p < 0.001$), cognitive functioning (small difference: −5.55, CI: −7.97 to −3.13, $p < 0.001$), social functioning (large difference: −18.72, CI: −22.17 to −15.27, $p < 0.001$), and financial problems (small difference: 3.28, CI: 1.16 to 5.39, $p = 0.002$). At 12 months statistically significant differences persisted in physical

functioning (trivial difference: −2.76, CI −4.95 to −0.57, p = 0.014), role functioning (trivial difference: −4.41, CI: −8.17 to −0.64, p = 0.022), social functioning (trivial difference: −3.78, CI: −7.00 to −0.56, p = 0.022), diarrhoea (small difference: 4.15, CI: 1.62 to 6.68, p = 0.001) and financial problems (trivial difference: 2.50, CI: 0.27 to 4.73, p = 0.028). Chemotherapy was no longer impactful in any of these domains at 18 and 24 months.

The analyses were repeated on a propensity score–matched subgroup of 410 patients (150 chemotherapy, 260 no chemotherapy) with similar findings (Figs. S5–7; Table S6b).

3.2. Impact on breast cancer–specific QoL domains (EORTC-QLQ-BR23)

1054/1120 patients (94.1%) completed some or all of the EORTC-QLQ-BR23 questionnaire at baseline (Fig. 3; Table S7). After adjustment for baseline measurements patients given chemotherapy experienced a significant decline of some EORTC-QLQ-BR23 mean scores at 6 weeks compared with those not receiving it in future perspective (adjusted mean difference: −7.20, 95% CI: −10.72 to −3.68, p < 0.001) and systemic therapy side-effects (3.04, CI: 1.47 to 4.61, p < 0.001). At 6 months, mean scores were significantly different in future perspectives (−7.54, CI −11.28 to −3.80, p < 0.001) and systemic therapy side-effects (16.97, CI: 15.00 to 18.94, p < 0.001). At 12 months, the mean scores between the two groups differed in future perspectives (−4.96, CI: −8.89 to −1.03, p = 0.013), systemic therapy side-effects (3.32, CI: 1.41 to 5.22, p = 0.001) and the effect of chemotherapy became significant in arm symptoms (4.94, CI: 2.18 to 7.69, p < 0.001). At 18 months, the differences remained significant in future perspective (−4.97, CI: −9.37 to −0.57, p = 0.027) and arm symptoms (3.27, CI: 0.01 to 6.54, p = 0.049), and at 24

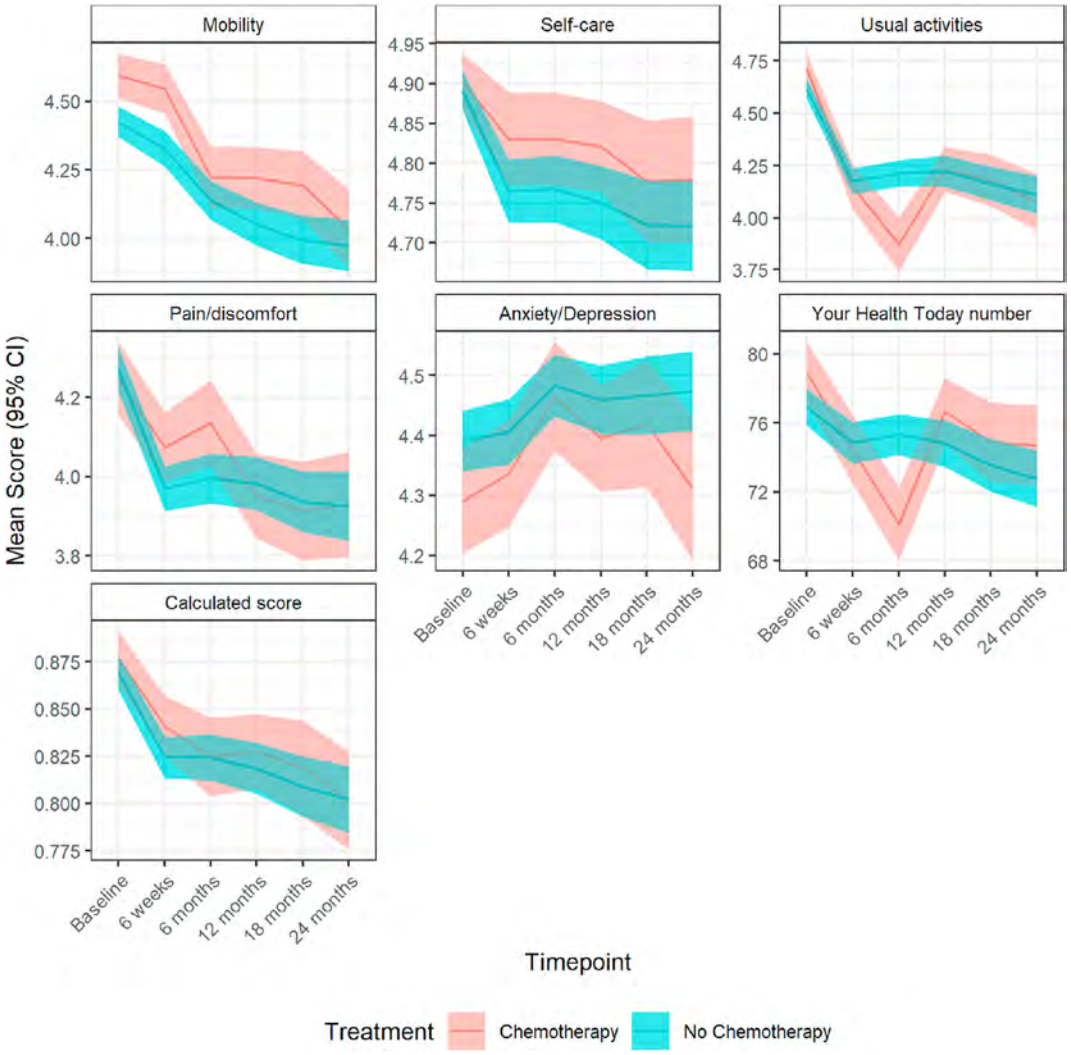


Fig. 5. Mean (95% CI) scores over time points for the chemotherapy versus no chemotherapy population measured on the EQ-5D-5L scale. The calculated score is a single summary number (index value) which reflects the health state in the context of the preferences of the general population of a country/region and is derived by applying a formula attaching weights to each of the levels in each dimension as per the EQ-5D-5L User Guide. CI, confidence interval.

months only in arm symptoms (4.02, CI: 0.13 to 7.90, p = 0.043).

3.3. Impact on older adults-specific QoL domains (EORTC-QLQ-ELD15)

Some or all of the EORTC-QLQ-ELD15 questionnaire was completed at baseline by 1048/1120 patients (Table S8; Fig. 4). At 6 weeks scores were significantly different between patients given chemotherapy and those not treated in worries about others (adjusted mean difference: 5.31, 95% CI: 1.55 to 9.07, p = 0.006), worries (4.09, CI: 0.92 to 7.27, p = 0.011) and burden of illness (4.68, CI: 1.25 to 8.11, p = 0.007). These differences persisted at 6 months (worries about others [6.19, CI: 2.44 to 9.95, p = 0.001]; worries [4.18, CI: 0.89 to 7.46, p = 0.013]; burden of illness [21.60, CI: 17.82 to 25.39, p < 0.001]); the impact on mobility also became significant (9.82, CI: 6.87 to 12.78, p < 0.001). At 12 months, changes remained significant regarding worries about others (4.47, CI: 0.42 to 8.52, p = 0.031) and burden of illness (15.21, CI: 11.30 to 19.12, p < 0.001), which was the only domain significantly influenced also at 18 months (12.99, CI: 8.81 to 17.17, p < 0.001) and 24 months (8.80, CI: 3.93 to 13.66, p < 0.001).

Maintaining purpose did not differ throughout the follow-up period, whereas chemotherapy had a positive impact on family support mean scores at 6 weeks (6.21, CI: 2.26 to 10.17, p = 0.002), at 6 months (4.91, CI: 0.26 to 9.56, p = 0.038) and at 12 months (5.43, CI: 0.39 to 10.46, p = 0.035).

3.4. Impact on EQ-5D-5L score and questions

Among the high-risk patients, an EQ-5D-5L score was calculated in 1315 patients (86.5%) at baseline. Health utilities were similar with estimated mean differences less than 0.02 units (p > 0.1), whereas the visual analogue scale measures were significantly worse at 6 months in patients receiving chemotherapy versus not (adjusted mean difference: −6.57, 95% CI: −8.74 to −4.40, p < 0.001). Changes were subsequently no longer significant (Table S9; Fig. 5).

A similar pattern on EQ-5D-5L usual activities score was seen in 520 (118 chemotherapy, 332 no chemotherapy) propensity score–matched patients (Fig. S8).

4. Discussion

This study demonstrates that chemotherapy has both a clinically and statistically significantly negative impact at 6–12 months on several QoL domains (physical, role, cognitive and social functioning, financial problems), symptom scores (fatigue, nausea, dyspnoea, appetite loss, constipation, diarrhoea), and perceived global health. These changes are clinically meaningful and involve key domains for this population [28] for whom even low-grade toxicities may be challenging [29].

Reassuringly, this effect resolves for most items over 18–24 months, which is consistent with previous QoL data reported in younger cohorts: for example, in 280 EBC patients many domains improved within 12 months after diagnosis, with the exception of cognitive function and financial problems [30], and similar improvements in role functioning were seen in a study of 817 EBC patients [31]. A registry-based analysis documented better physical functioning, role-physical, role-emotional and fatigue scales at 15 years in EBC patients including 46.9% aged ≥65 [32]. Similarly, 588 EBC patients enrolled in the Moving Beyond Cancer study had improved physical and psychosocial functioning after radical treatment regardless of chemotherapy use [31]. Neuropsychological analyses also confirmed improving cognitive function during the first four years after radical therapy for EBC [33,34], although data on financial impact are limited [30]. The CANTO study confirmed the transient nature of the impact of chemotherapy on QoL in a large population [35]. Nonetheless, these analyses have either focused on younger patients, where the risk/benefit ratio is different, or addressed the impact of breast cancer treatments (and not specifically of chemotherapy) on QoL in this age group. Our findings are consistent with a previous study in 109 patients aged 70 or older, of whom 57 received adjuvant docetaxel/cyclophosphamide chemotherapy [36].

To our knowledge, this is the largest study to evaluate the impact of contemporary chemotherapy regimens in older adults with EBC in real-world patients. QoL is a meaningful end-point for older patients, who typically derive less survival benefit and increased toxicities on systemic anticancer treatments [37,38]. These benefits need to be carefully balanced with the detrimental impact on QoL and treatment side-effects [39].

Our analysis included baseline geriatric assessments characterising patients in relevant health domains for this age group, such as functional status, comorbidity, cognition, nutrition and concurrent medications which may impact QoL. A comprehensive geriatric assessment can help achieve the required balance between treatment benefits and side-effects and is recommended by guidelines from the American Society of Clinical Oncology, the National Comprehensive Cancer Network, and the International Society for Geriatric Oncology [28,40]. In a randomised study, integrated oncogeriatric care has recently been shown to improve QoL in older patients with cancer being considered for systemic anticancer therapy [41]. Of particular interest was our finding that in patients ≥80 the negative impact on QoL does not resolve, which suggests a lack of resilience in this cohort.

The study has several limitations. Selection bias may have influenced our findings despite its inclusive entry criteria and the different levels of participation. The recruited population was slightly skewed

toward younger individuals compared with the general UK EBC patient population [42]. Moreover, we did not include socio-economic factors that might influence frailty nor the effect of endocrine therapy or radiotherapy on QoL, owing to multiple confounders to such an analysis. We did not capture the impact of chemotherapy on QoL outcomes beyond 24 months, and missing data on longitudinal QoL assessments may have influenced findings. Other factors not measured by our analysis may also impact on chemotherapy decisions; therefore, the propensity score matching does not adjust for all differences between the groups. Furthermore, some effects of chemotherapy on QoL documented in our analysis might be statistically significant but not clinically relevant, although for the majority of domains clinically meaningful changes are seen at the six-month time point, which represents the time when most women would have been on chemotherapy. Finally, it was not possible to categorise chemotherapy effects on QoL measured on BR23, ELD15 and EQ-5D-5L domains as thresholds have not been established for these specific tools, and the latter is a utility scale.

In conclusion, our analysis shows that chemotherapy has an impact on several QoL domains in older EBC patients compared with a matched cohort who did not receive cytotoxics. Nonetheless, these effects are temporary and largely resolve within two years. This is essential information for older women to use in decision-making because individualised decisions on treatment options should be based on their values.

Sponsorship

The study was sponsored by Doncaster and Bassetlaw Teaching Hospitals NHS Foundation Trust. Clinical Research Office, First Floor 'C' Block, Doncaster Royal Infirmary, Armthorpe Road, Doncaster, DN2 5LT, UK.

Conflict of interest statement

The authors declare no conflict of interest. Professors Stephen Walters and Thompson Robinson are National Institute for Health Research (NIHR) Senior Investigators; Jenna Morgan is a NIHR Clinical Lecturer; and Kate Lifford is funded by the NIHR as part of this project. The views expressed in this article are those of the author(s) and not necessarily those of the NIHR, or the Department of Health and Social Care.

Acknowledgements

This paper presents independent research funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research Programme (grant reference number RP-PG-1209-10071). In addition, NB and AR would like to acknowledge the support of the Cridlan Ross Smith Charitable Trust and the NIHR Biomedical Research Centre at The Royal Marsden NHS Foundation Trust and the Institute of Cancer Research, London.

The views expressed are those of the authors and not necessarily those of the National Health Service, the NIHR or the Department of Health.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2020.11.022.

References

[1] Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, et al. Global cancer observatory: cancer today. 2018. Lyon, France; Available from: https://gco.iarc.fr/today.

[2] Hurria A, Levit LA, Dale W, Mohile SG, Muss HB, Fehrenbacher L, et al. Improving the evidence base for treating older adults with cancer: American Society of clinical oncology statement. J Clin Oncol 2015;33(32):3826–33.

[3] Wildiers H, Mauer M, Pallis A, Hurria A, Mohile SG, Luciani A, et al. End points and trial design in geriatric oncology research: a joint European organisation for research and treatment of cancer–Alliance for Clinical Trials in Oncology–International Society of Geriatric Oncology position article. J Clin Oncol 2013;31(29):3711–8.

[4] Battisti NML, Wallington M, Ring A, Payne S, Birch R, Bomb M, et al. Is age a barrier to chemotherapy? Rates of treatment in older patients treated with breast, colon and lung cancer in England in 2014: a national registry study. Ann Oncol 2018;29. p. viii562–viii575.

[5] Giordano SH, Duan Z, Kuo YF, Hortobagyi GN, Goodwin JS. Use and outcomes of adjuvant chemotherapy in older women with breast cancer. J Clin Oncol 2006;24(18):2750–6.

[6] Biganzoli L, Wildiers H, Oakman C, Marotti L, Loibl S, Kunkler I, et al. Management of elderly patients with breast cancer: updated recommendations of the international society of geriatric oncology (SIOG) and European society of breast cancer specialists (EUSOMA). Lancet Oncol 2012;13(4):e148–60.

[7] Kim J, Hurria A. Determining chemotherapy tolerance in older patients with cancer. J Natl Compr Canc Netw 2013;11(12):1494–502.

[8] Ring A, Harder H, Langridge C, Ballinger RS, Fallowfield LJ. Adjuvant chemotherapy in elderly women with breast cancer (AChEW): an observational study identifying MDT perceptions and barriers to decision making. Ann Oncol 2013;24(5):1211–9.

[9] Kornblith AB, Lan L, Archer L, Partridge A, Kimmick G, Hudis C, et al. Quality of life of older patients with early-stage breast cancer receiving adjuvant chemotherapy: a companion study to cancer and leukemia group B 49907. J Clin Oncol 2011;29(8):1022–8.

[10] Mandelblatt JS, Makgoeng SB, Luta G, Hurria A, Kimmick G, Isaacs C, et al. A planned, prospective comparison of short-term quality of life outcomes among older patients with breast cancer treated with standard chemotherapy in a randomized clinical trial vs. an observational study: CALGB #49907 and #369901. J Geriatr Oncol 2013;4(4):353–61.

[11] Scotté F, Bossi P, Carola E, Cudennec T, Dielenseger P, Gomes F, et al. Addressing the quality of life needs of older patients with cancer: a SIOG consensus paper and practical guide. Ann Oncol 2018;29(8):1718–26.

[12] Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85(5):365–76.
[13] Johnson C, Fitzsimmons D, Gilbert J, Arrarras JI, Hammerlid E, Bredart A, et al. Development of the European Organisation for Research and Treatment of Cancer quality of life questionnaire module for older people with cancer: the EORTC QLQ-ELD15. Eur J Canc 2010;46(12):2242–52.
[14] Sprangers MA, Groenvold M, Arraras JI, Franklin J, te Velde A, Muller M, et al. The European Organization for Research and Treatment of Cancer breast cancer-specific quality-of-life questionnaire module: first results from a three-country field study. J Clin Oncol 1996;14(10):2756–68.
[15] Collins K, Reed M, Lifford K, Burton M, Edwards A, Ring A, et al. Bridging the age gap in breast cancer: evaluation of decision support interventions for older women with operable breast cancer: protocol for a cluster randomised controlled trial. BMJ Open 2017;7(7):e015133.
[16] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chron Dis 1987;40(5):373–83.
[17] Ottery FD. Definition of standardized nutritional assessment and interventional pathways in oncology. Nutrition 1996;12(1 Suppl):S15–9.
[18] Read JA, Crockett N, Volker DH, MacLennan P, Choy ST, Beale P, et al. Nutritional assessment in cancer: comparing the mini-nutritional assessment (MNA) with the scored patient-generated subjective global assessment (PGSGA). Nutr Canc 2005;53(1):51–6.
[19] Vigano AL, di Tomasso J, Kilgour RD, Trutschnigg B, Lucar E, Morais JA, et al. The abridged patient-generated subjective global assessment is a useful tool for early detection and characterization of cancer cachexia. J Acad Nutr Diet 2014;114(7):1088–98.
[20] Mahoney FI, Barthel DW. Functional evaluation: the barthel index. Md State Med J 1965;14:61–5.
[21] Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 1969;9(3):179–86.
[22] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12(3):189–98.
[23] Devlin NJ, Shah KK, Feng Y, Mulhern B, van Hout B. Valuing health-related quality of life: an EQ-5D-5L value set for England. Health Econ 2018;27(1):7–22.
[24] Team RC. *R*: A language and environment for statistical computing. 2020. Vienna, Austria; Available from: https://www.R-project.org/.
[25] Corp I. IBM SPSS statistics for windows. Armonk, NY: IBM Corp.; 2016. Version 24.0 ed.
[26] Cocks K, King MT, Velikova G, Martyn St-James M, Fayers PM, Brown JM, et al. Evidence-based guidelines for determination of sample size and interpretation of the European organisation for the research and treatment of cancer quality of life questionnaire core 30. J Clin Oncol 2011;29(1):89–96.
[27] von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol 2008;61(4):344–9.
[28] Mohile SG, Dale W, Somerfield MR, Hurria A. Practical assessment and management of vulnerabilities in older patients receiving chemotherapy: ASCO guideline for geriatric oncology summary. J Oncol Pract 2018;14(7):442–6.
[29] Kalsi T, Babic-Illman G, Fields P, Hughes S, Maisey N, Ross P, et al. The impact of low-grade toxicity in older people with cancer undergoing chemotherapy. Br J Canc 2014;111(12):2224–8.
[30] Hsu T, Ennis M, Hood N, Graham M, Goodwin PJ, et al. Quality of life in long-term breast cancer survivors. J Clin Oncol 2013;31(28):3540–8.
[31] Ganz PA, Kwan L, Stanton AL, Bower JE, Belin TR, et al. Physical and psychosocial recovery in the year after primary treatment of breast cancer. J Clin Oncol 2011;29(9):1101–9.
[32] Klein D, Mercier M, Abeilard E, Puyraveau M, Danzon A, Dalstein V, et al. Long-term quality of life after breast cancer: a French registry-based controlled study. Breast Canc Res Treat 2011;129(1):125–34.
[33] Schagen SB, Muller MJ, Boogerd W, Rosenbrand RM, van Rhijn D, Rodenhuis S, et al. Late effects of adjuvant chemotherapy on cognitive function: a follow-up study in breast cancer patients. Ann Oncol 2002;13(9):1387–97.
[34] Ahles TA, Saykin AJ, McDonald BC, Li Y, Furstenberg CT, Hanscom BS, et al. Longitudinal assessment of cognitive changes associated with adjuvant treatment for breast cancer: impact of age and cognitive reserve. J Clin Oncol 2010;28(29):4434–40.
[35] Ferreira AR, Di Meglio A, Pistilli B, Gbenou AS, El-Mouhebb M, Dauchy S, et al. Differential impact of endocrine therapy and chemotherapy on quality of life of breast cancer survivors: a prospective patient-reported outcomes analysis. Ann Oncol 2019;30(11):1784–95.
[36] Quinten C, Kenis C, Hamaker M, Coolbrandt A, Brouwers B, Dal Lago L, et al. The effect of adjuvant chemotherapy on symptom burden and quality of life over time; a preliminary prospective observational study using individual data of patients aged ≥70 with early stage invasive breast cancer. J Geriatr Oncol 2018;9(2):152–62.
[37] Extermann M, Boler I, Reich RR, Lyman GH, Brown RH, DeFelice J, et al. Predicting the risk of chemotherapy toxicity in older patients: the chemotherapy risk assessment scale for high-age patients (CRASH) score. Cancer 2012;118(13):3377–86.
[38] Hurria A, Togawa K, Mohile SG, Owusu C, Klepin HD, Gross CP, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. J Clin Oncol 2011;29(25):3457–65.
[39] Wu HS, Harden JK. Symptom burden and quality of life in survivorship: a review of the literature. Canc Nurs 2015;38(1):E29–54.
[40] Wildiers H, Heeren P, Puts M, Topinkova E, Janssen-Heijnen ML, Extermann M, et al. International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. J Clin Oncol 2014;32(24):2595–603.
[41] Soo W-K, King M, Pope A, Parente P, Darzins P, Davis ID. Integrated geriatric assessment and treatment (INTEGERATE) in older people with cancer planned for systemic anticancer therapy. J Clin Oncol 2020;38(15_suppl):12011.
[42] Todd A, Martin C, Morgan J, Herbert E, Bradburn M, Burton M, et al. Age specific recruitment and retention to a large multicentre observational breast cancer trial in older women: the Age Gap Trial. J Geriatr Oncol 2020. https://doi.org/10.1016/j.jgo.2020.10.015.

Radiotherapy and Oncology 161 (2021) 166–176

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Observational cohort study in older women with early breast cancer: Use of radiation therapy and impact on health-related quality of life and mortality

Nicolò Matteo Luca Battisti [a], Matthew Q. Hatton [b], Malcolm W.R. Reed [c], Esther Herbert [d], Jenna L. Morgan [e], Michael Bradburn [d], Richard Simcock [f], Stephen J. Walters [d], Karen A. Collins [g], Sue E. Ward [h], Geoffrey R. Holmes [h], Maria Burton [g], Kate J. Lifford [i], Adrian Edwards [i], Thompson G. Robinson [j], Charlene Martin [e], Tim Chater [d], Kirsty J. Pemberton [d], Alan Brennan [h], Kwok Leung Cheung [k], Annaliza Todd [e], Riccardo A. Audisio [l], Juliet Wright [c], Tracy Green [m], Deirdre Revell [m], Jacqui Gath [m], Kieran Horgan [n], Chris Holcombe [o], Matthew C. Winter [p], Jay Naik [q], Rishi Parmeshwar [r], Margot A. Gosney [s], Alastair M. Thompson [t], Lynda Wyld [e,*,1], Alistair Ring [a,*,1], on behalf of theBridging the Age Gap TMG

[a] *Department of Medicine, Breast Unit, The Royal Marsden Hospital NHS Foundation Trust, London, UK & Breast Cancer Research Division, The Institute of Cancer Research, London;* [b] *Weston Park Hospital, Sheffield Teaching Hospitals NHS Foundation Trust;* [c] *Brighton and Sussex Medical School, Brighton;* [d] *Clinical Trials Research Unit, School for Health and Related Research, University of Sheffield;* [e] *Department of Oncology and Metabolism, University of Sheffield Medical School, Sheffield;* [f] *Brighton and Sussex University Hospitals NHS Trust, Brighton;* [g] *College of Health, Wellbeing and Life Sciences, Department of Allied Health Professions, Sheffield Hallam University;* [h] *Department of Health Economics and Decision Science, School for Health and Related Research (ScHARR), University of Sheffield;* [i] *Division of Population Medicine, Cardiff University, Cardiff;* [j] *Department of Cardiovascular Sciences and NIHR Biomedical Research Centre, University of Leicester, Cardiovascular Research Centre, Leicester;* [k] *School of Medicine, University of Nottingham, Royal Derby Hospital, Derby;* [l] *University of Gothenberg, Sahlgrenska Universitetssjukhuset, Göteborg, Sweden;* [m] *Yorkshire and Humber Consumer Research Panel, Sheffield;* [n] *Department of Breast Surgery, Bexley Cancer Centre, St James's University Hospital, Leeds;* [o] *Liverpool University Hospitals Foundation Trust, Liverpool;* [p] *Weston Park Hospital, Sheffield Teaching Hospitals NHS Foundation Trust;* [q] *Pinderfields Hospital, Mid Yorkshire NHS Foundation Trust, Wakefield;* [r] *University Hospitals of Morecambe Bay, Royal Lancashire Infirmary, Lancaster;* [s] *Royal Berkshire NHS Foundation Trust, Reading; and* [t] *Department of Surgery, Baylor College of Medicine, Houston, USA*

ARTICLE INFO

Article history:
Received 21 February 2021
Received in revised form 7 June 2021
Accepted 9 June 2021
Available online 17 June 2021

Keywords:
Breast cancer
Older
Frailty
Comorbidity
Health-related quality of life
Adjuvant radiotherapy

ABSTRACT

Background: Radiotherapy reduces in-breast recurrence risk in early breast cancer (EBC) in older women. This benefit may be small and should be balanced against treatment effect and holistic patient assessment. This study described treatment patterns according to fitness and impact on health-related quality-of-life (HRQoL).

Methods: A multicentre, observational study of EBC patients aged ≥ 70 years, undergoing breast-conserving surgery (BCS) or mastectomy, was undertaken. Associations between radiotherapy use, surgery, clinico-pathological parameters, fitness based on geriatric parameters and treatment centre were determined. HRQoL was measured using the European Organisation for the Research and Treatment of Cancer (EORTC) questionnaires.

Results: In 2013–2018 2811 women in 56 UK study centres underwent surgery with a median follow-up of 52 months. On multivariable analysis, age and tumour risk predicted radiotherapy use. Among healthier patients (based on geriatric assessments) with high-risk tumours, 534/613 (87.1%) having BCS and 185/341 (54.2%) having mastectomy received radiotherapy. In less fit individuals with low-risk tumours undergoing BCS, 149/207 (72.0%) received radiotherapy. Radiotherapy effects on HRQoL domains, including breast symptoms and fatigue were seen, resolving by 18 months.

Conclusion: Radiotherapy use in EBC patients ≥ 70 years is affected by age and recurrence risk, whereas geriatric parameters have limited impact regardless of type of surgery. There was geographical variation in treatment, with some fit older women with high-risk tumours not receiving radiotherapy, and some older, low-risk, EBC patients receiving radiotherapy after BCS despite evidence of limited benefit. The impact on HRQoL is transient.

* Corresponding authors at: Department of Oncology and Metabolism, University of Sheffield Medical School, Beech Hill Road, Sheffield S10 2RX, UK (L. Wyld). Department of Medicine, Breast Unit, The Royal Marsden Hospital NHS Foundation Trust, London, UK & Breast Cancer Research Division, The Institute of Cancer Research, London, UK (A. Ring).
E-mail address: l.wyld@sheffield.ac.uk (L. Wyld).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.radonc.2021.06.021
0167-8140/

Table 1
Postoperative tumour, patient and treatment characteristics by surgery type.

		BCS *N* = 1669	Mastectomy *N* = 1087	Unknown *N* = 55	Total *N* = 2811
Age (years)	70–74	813 (48.7%)	342 (31.5%)	18 (32.7%)	1173 (41.7%)
	75–79	521 (31.2%)	356 (32.7%)	22 (40.0%)	899 (32.0%)
	80–84	243 (14.5%)	253 (23.3%)	10 (18.2%)	506 (18.0%)
	≥85	92 (5.6%)	136 (12.5%)	5 (9.1%)	233 (8.3%)
Participation level	Full	1277 (76.5%)	792 (72.9%)	42 (76.4%)	2111 (75.1%)
	Partial	356 (21.3%)	253 (23.3%)	12 (21.8%)	621 (22.1%)
	Consultee	36 (2.2%)	42 (3.9%)	1 (1.8%)	79 (2.8%)
Laterality	Right	776 (46.5%)	501 (46.1%)	28 (50.9%)	1305 (46.4%)
	Left	893 (53.5%)	586 (53.9%)	27 (49.1%)	1506 (53.6%)
Tumour size (mm)	≤20	1001 (60.0%)	278 (25.6%)	0 (0.0%)	1279 (45.5%)
	21–50	641 (38.4%)	644 (59.2%)	0 (0.0%)	1285 (45.7%)
	>50	24 (1.4%)	163 (15.0%)	1 (1.8%)	188 (6.7%)
	Unknown	3 (0.2%)	2 (0.2%)	54 (98.2%)	59 (2.1%)
Nodal status	pN0	1302 (78.0%)	610 (56.1%)	1 (1.8%)	1913 (68.1%)
	pN1	302 (18.1%)	310 (28.5%)	0 (0.0%)	612 (21.8%)
	pN2	48 (2.9%)	99 (9.1%)	0 (0.0%)	147 (5.2%)
	pN3	13 (0.8%)	64 (5.9%)	0 (0.0%)	77 (2.7%)
	Unknown	4 (0.2%)	4 (0.4%)	54 (98.2%)	62 (2.2%)
Grade	1	306 (18.3%)	75 (6.9%)	0 (0.0%)	381 (13.6%)
	2	920 (55.1%)	565 (52.0%)	0 (0.0%)	1485 (52.8%)
	3	427 (25.6%)	437 (40.2%)	1 (1.8%)	865 (30.8%)
	Unknown	16 (1.0%)	10 (0.9%)	54 (98.2%)	80 (2.8%)
Histology	Ductal carcinoma	1133 (67.9%)	658 (60.5%)	24 (43.6%)	1815 (64.6%)
	Lobular carcinoma	163 (9.8%)	202 (18.6%)	10 (18.2%)	375 (13.3%)
	Tubular carcinoma	27 (1.6%)	2 (0.2%)	0 (0.0%)	29 (1.0%)
	Mucinous carcinoma	47 (2.8%)	23 (2.1%)	1 (1.8%)	71 (2.5%)
	Other	162 (9.7%)	103 (9.5%)	1 (1.8%)	266 (9.5%)
	Unknown	137 (8.2%)	99 (9.1%)	19 (34.5%)	255 (9.1%)
ER status	Negative	167 (10.0%)	205 (18.9%)	0 (0.0%)	372 (13.2%)
	Positive	1487 (89.1%)	866 (79.7%)	1 (1.8%)	2354 (83.7%)
	Unknown	15 (0.9%)	16 (1.5%)	54 (98.2%)	85 (3.0%)
HER2 status	Negative	1424 (85.3%)	847 (77.9%)	1 (1.8%)	2272 (80.8%)
	Positive	146 (8.7%)	186 (17.1%)	0 (0.0%)	332 (11.8%)
	Inconclusive	16 (1.0%)	6 (0.6%)	0 (0.0%)	22 (0.8%)
	Unknown	83 (5.0%)	48 (4.4%)	54 (98.2%)	185 (6.6%)
ADL category	No dependency	1203 (72.1%)	759 (69.8%)	42 (76.4%)	2004 (71.3%)
	Mild dependency	184 (11.0%)	122 (11.2%)	2 (3.6%)	308 (11.0%)
	Moderate/severe dependency	152 (9.1%)	123 (11.3%)	3 (5.5%)	278 (9.9%)
	Unknown	130 (7.8%)	83 (7.6%)	8 (14.5%)	221 (7.9%)
IADL category	No dependency	1269 (76.0%)	767 (70.6%)	33 (60.0%)	2069 (73.6%)
	Mild dependency	134 (8.0%)	108 (9.9%)	7 (12.7%)	249 (8.9%)
	Moderate/severe dependency	128 (7.7%)	122 (11.2%)	8 (14.5%)	258 (9.2%)
	Unknown	138 (8.3%)	90 (8.3%)	7 (12.7%)	235 (8.4%)
MMSE category	Normal function	1498 (89.8%)	945 (86.9%)	51 (92.7%)	2494 (88.7%)
	Mild impairment	135 (8.1%)	111 (10.2%)	2 (3.6%)	248 (8.8%)
	Moderate impairment	19 (1.1%)	16 (1.5%)	1 (1.8%)	36 (1.3%)
	Severe impairment	17 (1.0%)	15 (1.4%)	1 (1.8%)	33 (1.2%)
AGP SGA category	Low	1310 (78.5%)	834 (76.7%)	36 (65.5%)	2180 (77.6%)
	Moderate	159 (9.5%)	122 (11.2%)	7 (12.7%)	288 (10.2%)
	High	27 (1.6%)	13 (1.2%)	0 (0.0%)	40 (1.4%)
	Unknown	173 (10.4%)	118 (10.9%)	12 (21.8%)	303 (10.8%)
ECOG performance status	0	1197 (71.7%)	717 (66.0%)	30 (54.5%)	1944 (69.2%)
	1	332 (19.9%)	259 (23.8%)	16 (29.1%)	607 (21.6%)
	2	39 (2.3%)	38 (3.5%)	3 (5.5%)	80 (2.8%)
	3	15 (0.9%)	21 (1.9%)	0 (0.0%)	36 (1.3%)
	4	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)
	Unknown	86 (5.2%)	51 (4.7%)	6 (10.9%)	143 (5.1%)
Charlson comorbidity index (no age)	N	1607	1052	48	2707
	Mean (SD)	1.00 (1.26)	1.05 (1.36)	1.58 (1.32)	1.03 (1.30)
	Median (IQR)	1.00 (0.00, 2.00)	0.00 (0.00, 2.00)	2.00 (1.00, 2.00)	1.00 (0.00, 2.00)
	Min, Max	0, 9	0, 9	0, 6	0, 9
Number of concurrent medications	n	1447	961	38	2446
	Mean (SD)	4.02 (2.63)	4.11 (2.66)	4.37 (2.55)	4.06 (2.64)
	Median (IQR)	4.00 (2.00, 6.00)	4.00 (2.00, 5.00)	4.00 (3.00, 5.75)	4.00 (2.00, 5.75)
	Min, Max	0, 15	0, 18	1, 13	0, 18
Axillary surgery	Axillary sampling	49 (2.9%)	37 (3.4%)	2 (3.6%)	88 (3.1%)
	Axillary clearance	113 (6.8%)	292 (26.9%)	9 (16.4%)	414 (14.7%)
	Sentinel lymph node biopsy	1329 (79.6%)	628 (57.8%)	23 (41.8%)	1980 (70.4%)
	Internal mammary node biopsy	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)
	No axillary surgery	44 (2.6%)	34 (3.1%)	2 (3.6%)	80 (2.8%)
	Unknown	134 (8.0%)	95 (8.7%)	19 (34.5%)	248 (8.8%)
Chemotherapy use	Yes	186 (11.1%)	202 (18.6%)	9 (16.4%)	397 (14.1%)
	No	1483 (88.9%)	885 (81.4%)	46 (83.6%)	2414 (85.9%)
Radiotherapy use	Yes	1385 (83.0%)	341 (31.4%)	27 (49.1%)	1753 (62.4%)
	No	284 (17.0%)	746 (68.6%)	28 (50.9%)	1058 (37.6%)

Half of breast cancer (BC) cases are diagnosed ≥ 65 years [1]. Nonetheless, outcomes are worse in older individuals [2,3] who are underrepresented in trials [4–6]. In older patients outcomes may be influenced by competing risks, late presentation, and treatment variation [7,8]: frailty data are crucial to aid decision-making.

Radiation therapy (RT) is generally well tolerated in older women after breast-conserving surgery (BCS) or mastectomy, although it may cause inconvenience [9]. Local recurrence rates after BCS are lower in older patients although RT benefits decline with age [10,11].

After BCS, the Cancer and Leukaemia Group B (CALGB) 9343 and PRIME-II trials showed that omitting RT in older women with small, node-negative, oestrogen receptor (ER)-positive tumours is associated with high loco-regional recurrence risk but no survival disadvantage [12–14]. An Early Breast Cancer Trialist's Collaborative Group (EBCTCG) meta-analysis found that whole breast RT reduced the 10-year absolute local recurrence risk and 15-year mortality, although the annual recurrence probability without RT inversely correlated with age [15]. However, survival effects may be less pronounced in older frail patients. RT omission may be appropriate in frail older women. Conversely, there is a risk of undertreating fit older patients at higher risk of recurrence and longer life expectancy.

Our study recruited older women with BC and included baseline geriatric assessments [16–19]. This analysis describes patients' characteristics undergoing RT and investigates the factors associated with RT use and impacts on health-related quality of life (HRQoL).

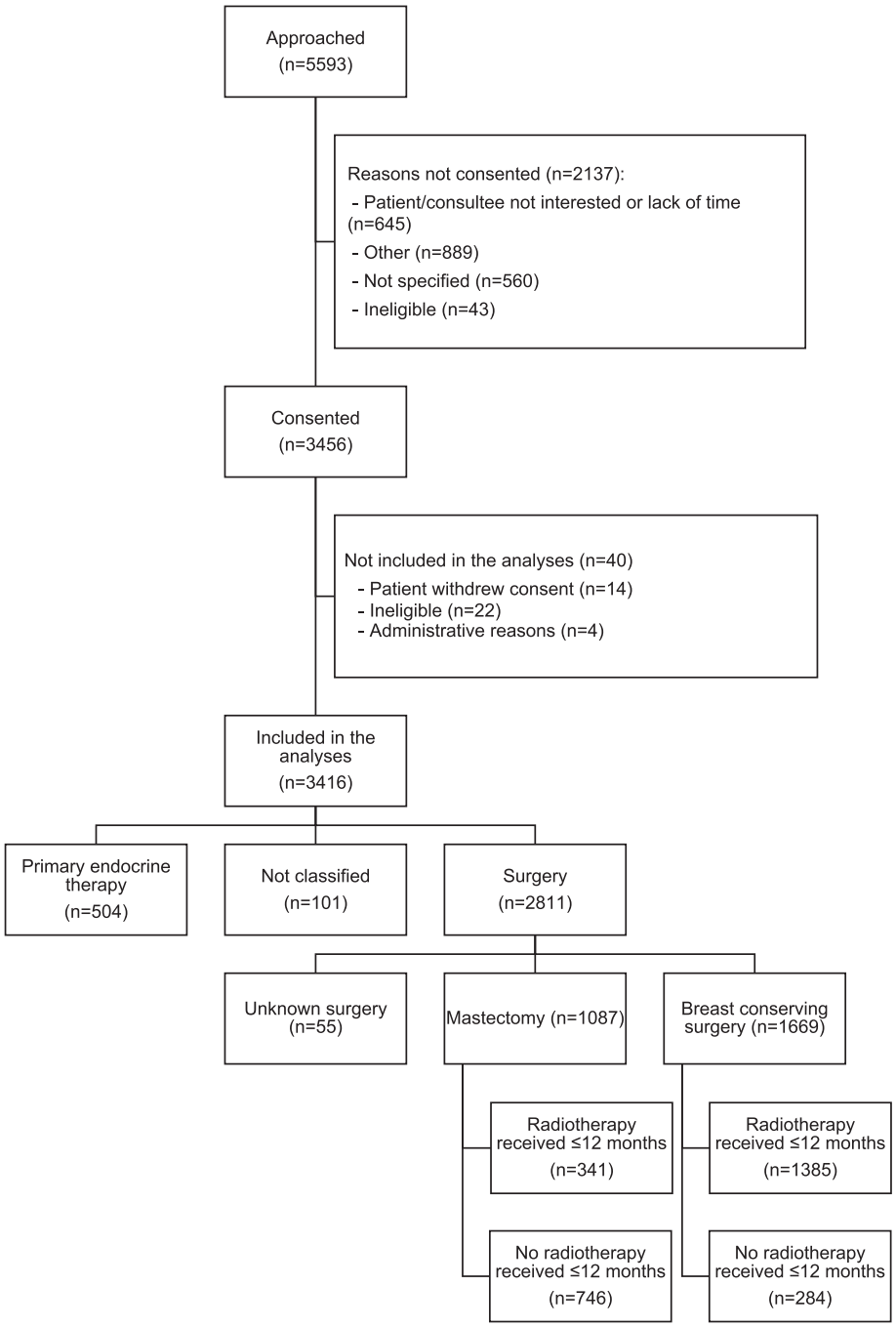


Fig. 1. STROBE flow diagram for the radiotherapy vs no radiotherapy analyses.

Materials and methods

Study design

The Bridging the Age Gap study was a multicentre, observational cohort study funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research Programme (grant reference number RP-PG-1209-10071). Ethics approval (IRAS: 12 LO 1808) and research governance approval were obtained. Patients were recruited from 56 centres in England and Wales (Supplementary Table 1). Women $\geq$ 70 years with operable invasive BC (TNM stages: T1-3 and operable T4b, N0-1, M0) were eligible. Staging investigations were performed if clinically indicated. Those unsuitable for surgery or with previous EBC within 5 years were not eligible.

Baseline data collection

Consenting patients were recruited at EBC diagnosis and could participate at three levels: full, partial (no requirement to complete HRQoL questionnaires) or by proxy (third-party data collection for those with significant cognitive impairment). Baseline tumour, surgical, RT and systemic therapy data were collected.

At baseline, patients underwent geriatric assessments: comorbidities (Charlson Comorbidity Index) [20], nutrition (abridged Patient Generated Subjective Global Assessment) [21,22], functional status (Activities of Daily Living) [23], advanced functional status (Instrumental Activities of Daily Living) [24], cognitive capacity (Mini Mental State Examination) [25], Eastern Cooperative Oncology Group Performance (ECOG) Status and medications.

HRQoL was assessed using the European Organisation for the Research and Treatment of Cancer (EORTC) HRQoL Questionnaires: EORTC-QLQ-C30 [26]; EORTC-QLQ-BR23 [27]; EORTC-QLQ-ELD15 [28]; EuroQol-5D-5L (EQ-5D-5L) [29] (Supplementary Table 2).

Follow-up and outcomes

Patients were followed up at 6 weeks, 6, 12, 18 and 24 months after enrolment (at the time of diagnosis) and assessed for recurrence and HRQoL. Complications were categorised using the Common Terminology Criteria for Adverse Events (CTCAE v4.0).

Table 2
Relationship between radiotherapy use and patient characteristics: univariate (Table 2a) and multivariable (Table 2b) analyses.

Table 2a - Results for univariate logistic regression models

Variable	Level	OR (95% CI)	*P*-value
Breast conserving surgery cohort			
Increasing age		0.94 (0.92, 0.97)	<0.001
Increasing ADL score		1.02 (1.00, 1.05)	0.070
Increasing IADL score		1.34 (1.17, 1.53)	<0.001
Increasing CCI (not age-adjusted)		0.93 (0.84, 1.03)	0.163
Increasing APG SGA score		0.94 (0.89, 1.00)	0.051
MMSE category	Normal function	–	–
	Mild impairment	0.64 (0.42, 0.99)	0.039
	Moderate impairment	0.72 (0.26, 2.53)	0.555
	Severe impairment	0.17 (0.06, 0.45)	<0.001
Tumour grade	Grade 1	–	–
	Grade 2	1.97 (1.44, 2.69)	<0.001
	Grade 3	2.49 (1.70, 3.66)	<0.001
ER-positive status		1.10 (0.71, 1.65)	0.657
HER2 status*	Negative	–	–
	Positive	0.87 (0.57, 1.38)	0.539
Nodal status**	pN0	–	–
	pN1	2.50 (1.66, 3.95)	<0.001
	pN2	0.86 (0.44, 1.84)	0.674
	pN3	0.26 (0.09, 0.83)	0.017
Mastectomy cohort			
Increasing age		0.99 (0.97, 1.02)	0.519
Increasing ADL score		1.00 (0.98, 1.02)	0.906
Increasing IADL score		1.01 (0.90, 1.15)	0.831
Increasing CCI (not age-adjusted)		1.07 (0.97, 1.17)	0.184
Increasing APG SGA score		1.01 (0.93, 1.09)	0.800
MMSE category	Normal function	–	–
	Mild impairment	0.82 (0.52, 1.25)	0.364
	Moderate impairment	0.96 (0.30, 2.66)	0.938
	Severe	0.15 (0.01, 0.75)	0.068
Tumour grade	Grade 1	–	–
	Grade 2	3.08 (1.58, 6.75)	0.002
	Grade 3	4.24 (2.16, 9.33)	<0.001
ER-positive status		0.89 (0.64, 1.23)	0.472
HER2 status*	Negative	–	–
	Positive	1.04 (0.74, 1.46)	0.821
T stage	T1	–	–
	T2	3.38 (2.30, 5.08)	<0.001
	T3	11.39 (7.14, 18.58)	<0.001
Nodal status**	pN0	–	–
	pN1	4.46 (3.24, 6.16)	<0.001
	pN2	17.11 (10.48, 28.71)	<0.001
	pN3	19.90 (10.94, 38.21)	<0.001

* Tests marked as 'Inconclusive' were removed from this analysis.
** Those with nodal status pNx were removed from this analysis

Deaths were categorised as BC-related or other causes. Deaths were reviewed by the chief investigator blind to treatment decisions. Patients for whom the cause could not be established were excluded from cause-specific analyses.

Statistical methods

Analyses were performed in IBM SPSS version 24, R version 3.6.3 [30] and Stata version 16 [31]. A two-sided $p < 0.05$ was considered statistically significant.

The relationships between RT use, tumour and patient characteristics were evaluated using univariate and multivariable logistic regression for patients undergoing BCS or mastectomy.

Patients undergoing BCS were considered at high risk of recurrence if the tumour was $\geq$ 3 cm, ER-negative, human epidermal growth factor receptor 2 (HER2)-positive, node-positive, or grade 3 (Supplementary Table 3a) [13]. Those undergoing mastectomy where considered high-risk if the tumour was T3, T4, or if $\geq$ 4 lymph nodes were involved (Supplementary Table3a) [32,33]. Fitness was defined based on geriatric assessments in order to categorize women as fit, vulnerable or frail (Supplementary Table 3b). RT use was reported by recurrence risk and fitness

Quality-of-life

The EORTC-QLQ questionnaires were scored according to the EORTC Scoring Manual (3rd Edition) [29]. The pre-planned analysis was conducted separately for patients undergoing BCS or mastectomy. We also pre-planned to exclude from this analysis patients who received chemotherapy due to its significant effect on HRQoL [18]. The mean differences of the domain scores at each time point, adjusted for baseline, were calculated using linear regression models. The paper reports statistical significance. Clinically meaningful differences in global health status of 1, 7 and 13 for trivial, small and medium impacts respectively were inferred from the data [34].

Results

Between January 2013 and June 2018, 3456 women were recruited (Supplementary Table 1). This analysis included 2811 women undergoing surgery within 6 months of diagnosis (Fig. 1) [35]. Of these, 397 (14.1%) received chemotherapy. Overall, 2239/2354 (95.1%) ER-positive patients received endocrine therapy. Surgery was BCS in 1669 patients and mastectomy in 1087 patients (Table 1; Supplementary Tables 4–5).

Of the 1669 patients undergoing BCS, 1385 (83.0%) received RT within 12 months of surgery. Of 1383 patients undergoing BCS where the RT volume was known, 1372 (99.2%) received breast RT and 154 (11.2%) nodal RT (62 [4.5%] to axilla, 92 [6.7%] to supraclavicular fossa [SCF]). Internal mammary chain RT was not recorded. Of the 1087 patients undergoing a mastectomy, 341 (31.4%) received RT within 12 months. Of those 338 patients undergoing a mastectomy where the RT volume was known, 247 (73.1%) received chest wall RT and 221 (65.4%) nodal RT (68 [20.1%] to axilla, 153 [45.3%] to SCF) (Supplementary Table 4–6).

In the BCS cohort, younger patients with higher risk tumours (high grade, node positive) were more likely to receive RT (Table 2).

Table 3
Radiotherapy use according to risk of recurrence and fitness.* Table 3a - Use of radiotherapy after breast-conserving surgery by risk of recurrence and fitness.

Risk	Radiotherapy	No radiotherapy	Total
Risk of recurrence			
Higher risk	709 (86.5%)	111 (13.5%)	**820 (100.0%)**
Lower risk	676 (79.6%)	173 (20.4%)	**849 (100.0%)**
Total	**1385 (14.1%)**	**284 (85.9%)**	**1669 (100.0%)**
Fitness			
Fit	**1061 (84.5%)**	**194 (15.4%)**	**1255 (100.0%)**
Vulnerable	**323 (78.2%)**	**90 (21.8%)**	**413 (100.0%)**
Frail	**1 (100.0%)**	**0 (0.0%)**	**1 (100.0%)**
Total	**1385 (83.0%)**	**284 (17.0%)**	**1669 (100.0%)**

Table 2b
Results from the multivariable logistic regression model.

Variable	Level	OR (95% CI)	*P*-value
Breast conserving surgery cohort			
Increasing age		0.95 (0.92, 0.99)	0.008
Increasing IADL score		1.14 (0.93, 1.38)	0.208
Increasing APG SGA score		0.96 (0.90, 1.03)	0.212
Tumour grade	Grade 1	–	–
	Grade 2	1.87 (1.23, 2.83)	0.003
	Grade 3	3.68 (2.14, 6.46)	<0.001
MMSE category	Normal function	–	–
	Mild impairment	0.64 (0.37, 1.11)	0.103
	Moderate/severe impairment*	1.14 (0.34, 5.30)	0.851
Nodal status**	pN0	–	–
	pN1	2.55 (1.45, 4.87)	0.002
	pN2	0.90 (0.38, 2.50)	0.825
	pN3	1.03 (0.16, 20.43)	0.976
Mastectomy cohort			
Tumour grade	Grade 1	–	–
	Grade 2	1.55 (0.74, 3.58)	0.269
	Grade 3	1.73 (0.82, 4.02)	0.172
T stage	T1	–	–
	T2	2.27 (1.47, 3.58)	<0.001
	T3	7.52 (4.42, 13.06)	<0.001
Nodal status*	pN0	–	–
	pN1	4.37 (3.12, 6.16)	<0.001
	pN2	14.19 (8.48, 24.38)	<0.001
	pN3	14.22 (7.59, 27.98)	<0.001

* Moderate and severe categories have been combined due to small numbers in the severe category.
** Those with nodal status pNx were removed from this analysis

Table 3b
Use of radiotherapy after breast-conserving surgery by combined risk of recurrence and fitness.

Fitness	Higher risk		Lower risk		Total
	Radiotherapy	No radiotherapy	Radiotherapy	No radiotherapy	
Fit	534 (42.55%)	79 (6.29%)	527 (41.99%)	115 (9.16%)	**1255 (100.00%)**
Vulnerable	174 (42.1%)	32 (7.7%)	149 (36.1%)	58 (14.0%)	**413 (100.0%)**
Frail	1 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	**1 (100%)**
Total	**709 (42.5%)**	**111 (6.7%)**	**676 (40.5%)**	**173 (10.4%)**	**1669 (100.0%)**

Table 3c
Use of radiotherapy after mastectomy by risk of recurrence and fitness.

Risk	Radiotherapy	No radiotherapy	Total
Risk of recurrence			
Higher risk	255 (53.2%)	224 (46.8%)	**479 (100.0%)**
Lower risk	86 (14.1%)	522 (85.9%)	**608 (100.0%)**
Total	**341 (31.4%)**	**746 (68.6%)**	**1087 (100.0%)**
Fitness			
Fit	**242 (31.6%)**	**524 (68.4%)**	**766 (100.0%)**
Vulnerable	**98 (30.6%)**	**222 (69.4%)**	**320 (100.0%)**
Frail	**1 (100.0%)**	**0 (0.0%)**	**1 (100.0%)**
Total	**341 (31.4%)**	**746 (68.6%)**	**1087 (100.0%)**

In the mastectomy cohort, patients with larger tumours and higher nodal involvement were more likely to receive it.

In the BCS cohort, high-risk tumours were present in 820/1669 patients (49.1%); of these, 709/820 (86.5%) received RT compared with 676/849 (79.6%) of patients with low-risk tumours (Table 3). Of those who were fit, 613 had high-risk tumours, and of these patients, 534/613 (87.1%) received RT (Table 3b). Of those 207 vulnerable individuals with low-risk tumours, 149/207 (72.0%) received RT.

In the mastectomy group, high-risk tumours were present in 479/1087 patients (44.1%) and 255/479 (53.2%) received RT compared with 86/608 (14.1%) of patients with non-high-risk tumours (Table 3c). Of those who were fit, 341 had high-risk tumours, and of these patients 185/341 (54.2%) received RT (Table 3d).

RT use varied from 17.6% to 90.9% between sites, although the number of patients recruited varied widely (Fig. 3; Supplementary Table 7).

Among 2811 patients undergoing surgery, the HRQoL analysis was restricted to 1789/2811 (63.6%) who did not receive chemotherapy and who consented to full participation. Of the patients included, 1125/1789 (62.9%) underwent BCS and 628/1789 (35.1%) underwent a mastectomy. Out of those undergoing BCS, 927/1125 (82.4%) received RT; out of those undergoing a mastectomy, 177/628 (28.2%) received RT. Supplementary table 8 and Figs. 1-3 show HRQoL questionnaires completion rates.

Among those undergoing BCS, 1042/1125 patients (92.6%) completed some or all of the EORTC QLQ-BR23 questionnaire at baseline (Supplementary Table 8). No significant effects were observed at 6 weeks (after surgery but before RT). Patients undergoing RT reported worse breast symptoms at 6 months compared with those not receiving it (mean difference 6.27, 95% CI 3.34 to 9.19, $p < 0.001$) which persisted at 12 months (mean difference 3.89, 95% CI 1.13 to 6.64, $p = 0.006$) but not at 18 months or thereafter (Supplementary Table 9; Fig. 2).

Among those undergoing a mastectomy, 588/628 patients (93.6%) completed some or all of the EORTC QLQ-BR23 questionnaire at baseline (Supplementary Table 8). No significant effects were seen at 6 weeks. At 6 months, a significant difference was observed in breast symptoms (5.52, 95% CI 2.67 to 8.37, $p < 0.001$). At 12 months, the effect persisted in breast symptoms (7.12, 95% CI 4.07 to 10.17, $p < 0.001$) and arm symptoms (6.34, 95% CI 2.99 to 9.70, $p < 0.001$). No differences were found at 18 months; at 24 months these were observed in arm symptoms (6.19, 95% CI 1.21 to 11.17, $p = 0.015$) (Supplementary Table 9; Fig. 2).

1004/1125 patients (89.2%) undergoing BCS and 567/628 patients (90.3%) undergoing a mastectomy completed all questions included in the EORTC QLQ-C30 questionnaire at baseline (Supplementary Table 8). In the BCS cohort the RT effect on global health status was statistically (but not clinically) significant at 12 months (adjusted mean difference 3.19, 95% CI −0.08 to −6.29, $p = 0.044$) but not afterwards (Supplementary Tables 10–11; Supplementary Fig. 4).

Patients undergoing mastectomy and given RT experienced global health decline at 6 weeks (−3.18, 95% CI −6.32 to −0.04, $p = 0.047$) which resolved subsequently (Supplementary Tables 10–11; Supplementary Fig. 5). RT impacted fatigue at 6 months (adjusted mean difference 4.45, 95% CI 0.77 to 8.14, $p = 0.018$), 12 months (7.26, 95% CI 3.07 to 11.46, $p = 0.001$), 18 months (5.44, 95% CI 0.64 to 10.23, $p = 0.026$) and 24 months (6.56, 95% CI 1.76 to 11.37, $p = 0.008$), although this effect was clinically significant only at 12 months. No other effects were observed.

1002/1125 patients (89.1%) undergoing BCS and 559/628 patients (89.0%) undergoing a mastectomy completed all EORTC QLQ-ELD15 questions at baseline (Supplementary Table 8). In the BCS cohort, no significant impact was observed at 6 weeks in patients receiving RT compared with those not receiving it (usually predating RT). At 6 months, RT impacted on illness burden (5.49, 95% CI 1.33 to 9.64, $p = 0.010$). At 12–18 months, no significant differences were observed; at 24 months, only on worries about others (−6.21, 95% CI −11.70 to −0.71, $p = 0.027$) (Supplementary Table 12; Supplementary Fig. 4).

In the mastectomy cohort, illness burden was impacted in patients receiving RT versus not at 6 weeks (5.54, 95% CI 0.84 to 10.24, $p = 0.021$), 6 months (9.66, 95% CI 4.67 to 14.66, $p < 0.001$), 12 months (5.70, 95% CI 0.34 to 11.06, $p = 0.037$),

Table 3d
Use of radiotherapy after mastectomy by combined risk of recurrence and fitness.

Fitness	Higher risk		Lower risk		Total
	Radiotherapy	No Radiotherapy	Radiotherapy	No Radiotherapy	
Fit	185 (24.2%)	156 (20.4%)	57 (7.4%)	368 (48.0%)	766 (100.0%)
Vulnerable	70 (21.88%)	68 (21.25%)	28 (8.75%)	154 (48.12%)	320 (100.00%)
Frail	0 (0.0%)	0 (0.0%)	1 (100%)	0 (0.0%)	1 (100%)
Total	255 (23.5%)	224 (20.6%)	86 (7.9%)	522 (48.0%)	1087 (100.0%)

*Risk of recurrence and fitness defined as shown in Supplementary Table 3.

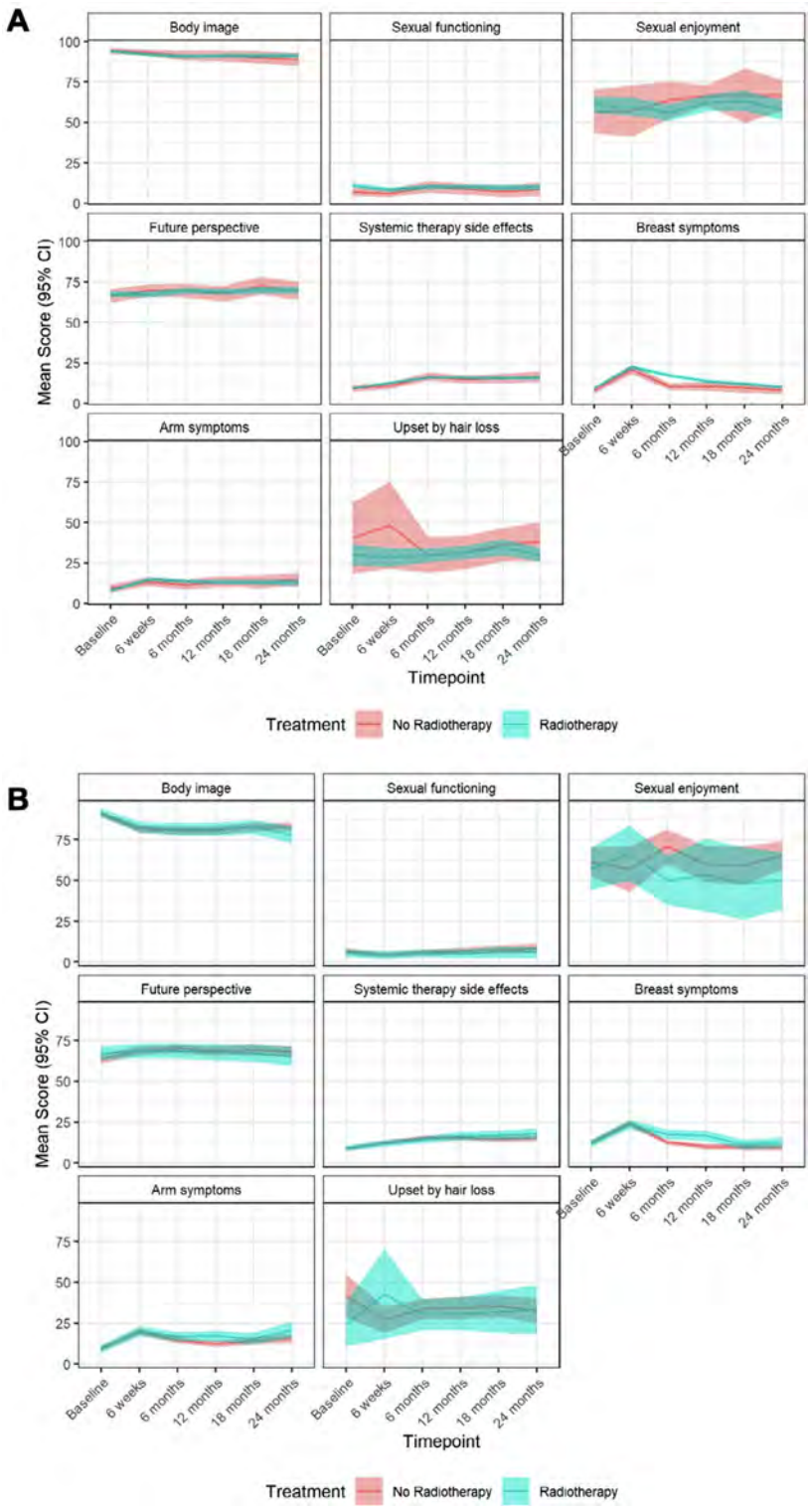


Fig. 2. Mean (95% CI) scores over time points for the radiotherapy versus no radiotherapy population measured on the EORTC-QLQ-BR23 in patients undergoing breast-conserving surgery (A) and a mastectomy (B).

18 months (8.19, 95% CI 2.64 to 13.74, p = 0.004) and 24 months (8.34, 95% CI 1.25 to 15.43, p = 0.021) (Supplementary Table 12; Supplementary Fig. 5).

Baseline EQ-5D-5L score was calculated in 1060/1125 patients undergoing BCS (94.2%) and in 593/628 patients (94.4%) undergoing mastectomy. No significant differences were observed in the BCS cohort (Supplementary Table 12; Supplementary Fig. 4).

In the mastectomy cohort, RT impacted the visual analogue scale at 18 months (adjusted mean difference −0.04, 95% CI −0.07 to −0.01, p = 0.029) and 24 months (−0.05, 95% CI −0.08 to −0.02, p = 0.004) (Supplementary Table 13; Supplementary Fig. 5).

Supplementary Table 15 reports adverse events.

At a median of 52 months of follow-up, mortality data were available for 2757/2811 patients (98.1% of cohort) and cause of

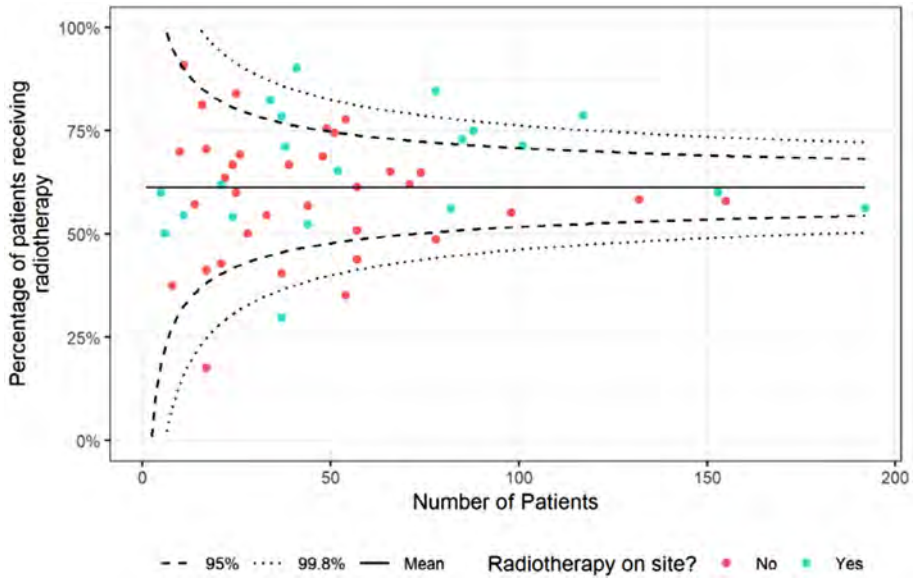


Fig. 3. Funnel plot of radiotherapy use by site (N = 56). Proportion of patients enrolled in cohort study receiving radiotherapy against number of patients enrolled.

death for 2738/2811 (97.4% of cohort). Of 464/2757 (16.8%) deaths due to all causes, 193/464 (41.6%) were due to BC (Supplementary Table 16).

In patients undergoing BCS, mortality data were available for 1631/1669 (97.7%) and death cause data for 1624/1669 (97.3%). Of those receiving RT with mortality data available, 149/1354 (11.0%) died from any cause; among those receiving RT for whom a death cause was known, 51/1348 (3.8%) died from BC. For those not receiving RT with mortality data available, 48/277 (17.3%) died from any cause; among those receiving RT for whom a death cause was known, 9/276 (3.3%) died from BC.

In patients undergoing a mastectomy, mortality data were available for 1073/1087 (98.7%) and cause of death data for 1062/1087 (97.7%). Of those receiving RT with mortality data available, 93/336 (27.7%) died from any cause; among those receiving RT for whom a death cause was known, 63/332 (19.0%) died from BC. For those not receiving RT with mortality data available, 163/737 (22.1%) died from any cause; among those receiving RT for whom a death cause was known, 65/730 (8.9%) died from BC.

Discussion

This analysis is the largest prospective cohort study describing RT use patterns and its impact on HRQoL, adverse events and mortality in older EBC patients, which integrates tumour characteristics and geriatric assessments data.

Life expectancy is increasing in Western countries [36] and older patients may experience disease relapse within their lifetime. Recurrence has symptomatic, adverse psychological and cost implications even without influencing survival [11]. Therefore, ensuring that older patients are adequately treated is a priority.

RT following BCS is standard-of-care for all EBC patients not at low risk. However, the definition of recurrence risk differs among national [32] and international guidelines [37,38] and might explain RT uptake variations. Guidelines support omitting RT in low-risk patients $\geq$ 70 years assuming that they remain on endocrine therapy. However, compliance cannot be guaranteed when RT is omitted [39]. A meta-analysis did not document any differential benefit of post-mastectomy RT (PMRT) on locoregional recurrence in patients $\geq$ 60 years [40]. The SUPREMO study excluded patients defined as high-risk in this analysis [41]. RT use after BCS or mastectomy declines with age [42] although it might relate to age, comorbidities, frailty, patient reluctance, or HRQoL impact.

In our analysis almost 13% of fit, high-risk patients undergoing BCS and more than 45% of fit, high-risk patients undergoing mastectomy did not receive RT. This may relate to patient, clinician and geographical factors. Recently 5 RT fractions over one week were found non-inferior to the previous standard for local control in patients with pT1-3N0-1 tumours after BCS or mastectomy [43]. This may facilitate compliance with RT scehdules.

In low-risk older patients, there is a low additional ipsilateral recurrence risk and no survival or breast preservation benefits without RT [12,13,44,45]. In the PRIME II study, at 10 years 93.4% of mortality was not due to BC [14], despite the rate of ipsilateral breast recurrence (1.3% with RT versus 4.1% with no RT) observed also in this specific age group. In our analysis, in the BCS cohort only one third of mortality was due to BC and RT might be safely omitted in low-risk older patients with a shorter life expectancy [46]. In our study, despite 849/1669 patients (50.9%) having a low risk of recurrence after BCS (some of whom were vulnerable/frail), 82.1% received RT. This suggests a degree of over-treatment which reflects the lack of concordance between national and international guidelines for the omission of RT after BCS and underlines the importance of considering risk profile and health status in decision-making.

Previous trials did not include fitness data which may impact life expectancy and mitigate local recurrence benefits. This study overcomes these limitations, by defining risk of recurrence and fitness, and still demonstrates a low impact of fitness considerations on RT uptake. Some clinicians overestimate the benefits of RT [47] although this does not always correspond with patients' perceived risks, lack of benefit and inconvenience [48]. Geriatric assessments are standard-of-care to evaluate fitness and guide anticancer treatment decisions in older adults with cancer based on international consensus [49–51]. This may also prove valuable for to radiotherapy decision-making and reduce treatment variation. Our findings demonstrate significant RT use variation as previously confirmed [42,52,53], although caution is required in view of case-mix and geography bias.

This analysis demonstrates that RT has limited and temporary impact on toxicities and HRQoL, a meaningful endpoint due to

the lack of survival benefits and increased toxicity risk on standard treatments in this population. The most significant impact occurred on breast symptoms, although this resolved by 18 months. Our findings are consistent with the PRIME study documenting no effect of RT on overall HRQoL in patients $\geq$ 65 years at low risk of recurrence after BCS [54] and with the SUPREMO trial showing an effect of PMRT on chest wall symptoms up to 2 years in patients undergoing a mastectomy [34]. The recent UK IMPORT LOW study demonstrated that partial breast RT could be employed with a reduction in breast effects and a non-inferior impact on local recurrence [55]. Trials investigating the role of biomarkers to select patients at low recurrence risk who may be spared RT, such as PRIMETIME (ISRCTN41579286), PRECISION (NCT02653755), LUMINA (NCT01791829), NATURAL (NCT03646955) and EUROPA (NCT04134598) will be highly relevant to older BC patients.

This analysis also has some limitations. The study criteria to define high-risk EBC did not include data on lymphovascular invasion, which is considered for radiotherapy decision-making after a mastectomy and an eligibility criterion for the adjuvant RT trials [56,57]. The definitions of recurrence risk, whilst based on published data and justifiable, would no doubt be debated between clinicians. Similarly, the definitions of fitness could be challenged. Nonetheless, there are no universally agreed definitions in the published literature, these definitions were predefined and have been used consistently across our analyses [17,18]. Despite broad eligibility criteria and a pragmatic design selection bias was possible due to clinician issues, staffing resources, patients' lack of interest and trial burden [58]. Missing data on longitudinal HRQoL assessments may have influenced our findings. The impact of endocrine therapy was not factored in the HRQoL analysis although this can be prolonged [59]. We could not investigate the impact of RT dose and nodal RT on HRQoL as those data were not routinely collected within the study and only 13.7% of patients received it to the regional nodes. Our findings may not be applicable to other countries, although previous data appear comparable [60]. Some statistically significant effects of RT on HRQoL might not be clinically relevant, whereas small effects may still substantially influence patients' perceived well-being. Finally, we have not evaluated the impact of RT on ipsilateral recurrence risk as data on relapse laterality were not captured.

In summary, this study demonstrates that fitness is not a major determinant of RT decisions for older EBC patients undergoing BCS or mastectomy and a significant number of vulnerable older women with both high-risk and low-risk EBC receive adjuvant RT. Some may derive little benefit from RT. There was also a low PMRT rate of in women at high-risk suggesting some undertreatment. Potential risks and benefits require discussion in view of the toxicity risk and the transient negative impact on breast symptoms. Nonetheless, individualised treatment decisions and discussions should be made to ensure the best outcomes. These findings argue for the routine measurement of fitness in older patients to be included in radiotherapy practice guidelines for older patients with operable breast cancer.

Disclaimer

This paper presents independent research funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research Programme (Grant Reference Number RP-PG-1209-10071). The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

Clinical Trial Registration: ISRCTN 46099296

Acknowledgements

This paper presents independent research funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research Programme (grant reference number RP-PG-1209-10071). In addition, NB and AR would like to acknowledge the support of the Cridlan Ross Smith Charitable Trust and the NIHR Biomedical Research Centre at The Royal Marsden NHS Foundation Trust and the Institute of Cancer Research, London.

The views expressed are those of the authors and not necessarily those of the National Health Service, the NIHR or the Department of Health.

Authors' contributions

All the authors conceived and designed the work that led to the submission, drafted and revised the manuscript and approved the final version.

Ethics approval and consent to participate

Ethics approval (IRAS: 12 LO 1808) and research governance approval were obtained. All patients (or their proxies, if cognitively impaired) gave written informed consent.

Consent for publication

Not applicable.

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no conflict of interest. Professors Stephen Walters and Thompson Robinson are National Institute for Health Research (NIHR) Senior Investigators, Jenna Morgan is a NIHR Clinical Lecturer and Kate Lifford was funded by the NIHR as part of this project. The views expressed in this article are those of the author(s) and not necessarily those of the NIHR, or the Department of Health and Social Care.

Funding information

The study was sponsored by Doncaster and Bassetlaw Teaching Hospitals NHS Foundation Trust. Clinical Research Office, First Floor 'C' Block, Doncaster Royal Infirmary, Armthorpe Road, Doncaster, DN2 5LT, UK.

This paper presents independent research funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research Programme (Grant Reference Number RP-PG-1209-10071). The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2021.06.021.

References

[1] Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, et al. Global cancer observatory: cancer today. France: Lyon; 2018.
[2] Statistics OfN. Cancer survival in England: Patients diagnosed between 2010 and 2014 and followed up to 2015. Newport, UK2016.
[3] Moller H, Flatt G, Moran A. High cancer mortality rates in the elderly in the UK. Cancer Epidemiol 2011;35:407–12.
[4] Hutchins LF, Unger JM, Crowley JJ, Coltman CA, Albain KS. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. N Engl J Med 1999;341:2061–7.
[5] Al-Refaie WB, Vickers SM, Zhong W, Parsons H, Rothenberger D, Habermann EB. Cancer trials versus the real world in the United States. Ann Surg 2011;254:438–42. discussion 42-3.
[6] Sedrak MS, Freedman RA, Cohen HJ, Muss HB, Jatoi A, Klepin HD, et al. Older adult participation in cancer clinical trials: A systematic review of barriers and interventions. CA: A Cancer Journal for Clinicians. n/a.
[7] Battisti NML, Wallington M, Ring A, Payne S, Birch R, Bomb M, et al. Is age a barrier to chemotherapy? Rates of treatment in older patients treated with breast, colon and lung cancer in England in 2014: a national registry study. Ann Oncol 2018;29:viii562–i575.
[8] Derks MGM, Bastiaannet E, Kiderlen M, Hilling DE, Boelens PG, Walsh PM, et al. Variation in treatment and survival of older patients with non-metastatic breast cancer in five European countries: a population-based cohort study from the EURECCA Breast Cancer Group. Br J Cancer 2018;119:121–9.
[9] Cree A, O'Donovan A, O'Hanlon S. New horizons in radiotherapy for older people. Age Ageing 2019;48:605–12.
[10] Veronesi U, Luini A, Del Vecchio M, Greco M, Galimberti V, Merson M, et al. Radiotherapy after breast-preserving surgery in women with localized cancer of the breast. N Engl J Med 1993;328:1587–91.
[11] Smith BD, Gross CP, Smith GL, Galusha DH, Bekelman JE, Haffty BG. Effectiveness of radiation therapy for older women with early breast cancer. J Natl Cancer Inst 2006;98:681–90.
[12] Hughes KS, Schnaper LA, Bellon JR, Cirrincione CT, Berry DA, McCormick B, et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. J Clin Oncol 2013;31:2382–7.
[13] Kunkler IH, Williams LJ, Jack WJL, Cameron DA, Dixon JM. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. Lancet Oncol 2015;16:266–73.
[14] Kunkler IH, Williams LJ, Jack WJL, Cameron D, Dixon JM. PRIME 2 randomized trial (Postoperative Radiotherapy in Minimum-Risk Elderly): wide local excision and adjuvant hormonal therapy +/- whole breast irradiation in women ≥65 years with early invasive breast cancer: 10 year results [GS2-03]. 2020 San Antonio Breast Cancer Symposium. Virtual2020.
[15] Darby S, McGale P, Correa C, Taylor C, Arriagada R, Clarke M, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet 2011;378:1707–16.
[16] Wyld L, Reed MWR, Morgan J, Collins K, Ward S, Holmes GR, et al. Bridging the age gap in breast cancer. Impacts of omission of breast cancer surgery in older women with oestrogen receptor positive early breast cancer. A risk stratified analysis of survival outcomes and quality of life. Eur J Cancer 2021;142:48–62.
[17] Battisti NML, Ring A, Bradburn M, Wyld L. Abstract P2–14-08: Use of systemic therapy for early stage breast cancer in older adults: Results from the Bridging the Age Gap study. Cancer Res 2020;80. P2–14-08-P2-14-08.
[18] Battisti NML, Herbert E, Bradburn M, Morgan J, Wyld L, Ring A. Impact of chemotherapy for early stage breast cancer on quality of life in older adults: results from 2811 women enrolled in the Bridging the Age Gap study (#2586). European Society for Medical Oncology (ESMO) Virtual Congress2020.
[19] Morgan JL, Holmes G, Ward S, Martin C, Burton M, Walters SJ, et al. Observational cohort study to determine the degree and causes of variation in the rate of surgery or primary endocrine therapy in older women with operable breast cancer. Eur J Surg Oncol 2020.
[20] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–83.
[21] Ottery F. Definition of standardized nutritional assessment and interventional pathways in oncology. Nutrition 1996;12:S15–9.
[22] Vigano AL, di Tomasso J, Kilgour RD, Trutschnigg B, Lucar E, Morais JA, et al. The abridged patient-generated subjective global assessment is a useful tool for early detection and characterization of cancer cachexia. J Acad Nutr Diet 2014;114:1088–98.
[23] Mahoney FI, Barthel DW. Functional evaluation: the barthel index. Md State Med J 1965;14:61–5.
[24] Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 1969;9:179–86.
[25] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–98.
[26] Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365–76.
[27] Sprangers MA, Groenvold M, Arraras JI, Franklin J, te Velde A, Muller M, et al. The European Organization for Research and Treatment of Cancer breast cancer-specific quality-of-life questionnaire module: first results from a three-country field study. J Clin Oncol 1996;14:2756–68.
[28] Johnson C, Fitzsimmons D, Gilbert J, Arrarras J-I, Hammerlid E, Bredart A, et al. Development of the European Organisation for Research and Treatment of Cancer quality of life questionnaire module for older people with cancer: The EORTC QLQ-ELD15. Eur J Cancer 2010;46:2242–52.
[29] Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A. The EORTC QLQ-C30 Scoring Manual (3rd Edition) 2001.
[30] R: A language and environment for statistical computing. R Foundation for Statistical Computing. Vienna, Austria: R Core Team 2020.
[31] Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC; 2019.
[32] (NICE) NIfHaCE. Early and locally advanced breast cancer: diagnosis and management. 2018.
[33] Mukesh MB, Duke S, Parashar D, Wishart G, Coles CE, Wilson C. The Cambridge post-mastectomy radiotherapy (C-PMRT) index: a practical tool for patient selection. Radiother Oncol 2014;110:461–6.
[34] Velikova G, Williams LJ, Willis S, Dixon JM, Loncaster J, Hatton M, et al. Quality of life after postmastectomy radiotherapy in patients with intermediate-risk breast cancer (SUPREMO): 2-year follow-up results of a randomised controlled trial. Lancet Oncol 2018;19:1516–29.
[35] von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol 2008;61:344–9.
[36] World Population Aging. United Nations: Department of Economic and Social Affairs; 2019.
[37] Breast Cancer. Version 2.2021 (12/03/2021). NCCN Clinical Practice Guidelines in Oncology: National Comprehensive Cancer Network; 2021.
[38] Burstein HJ, Curigliano G, Loibl S, Dubsky P, Gnant M, Poortmans P, et al. Estimating the benefits of therapy for early-stage breast cancer: the St. Gallen International Consensus Guidelines for the primary therapy of early breast cancer 2019. Ann Oncol 2019;30:1541–57.
[39] Postoperative radiotherapy for breast cancer: UK consensus statements. The Royal College of Radiologists: Faculty of Clinical Oncology; 2016.
[40] McGale P, Taylor C, Correa C, Cutter D, Duane F, Ewertz M, et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet 2014;383:2127–35.
[41] Kunkler IH, Canney P, van Tienhoven G, Russell NS. Elucidating the role of chest wall irradiation in 'intermediate-risk' breast cancer: the MRC/EORTC SUPREMO Trial. Clin Oncol 2008;20:31–4.
[42] National Audit of Breast Cancer in Older Patients. 2020 Annual Report: Results of the prospective audit in England and Wales for women diagnosed between January 2014 and December 2018.: NABCOP project team; 2020.
[43] Murray Brunt A, Haviland JS, Wheatley DA, Sydenham MA, Alhasso A, Bloomfield DJ, et al. Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial. Lancet 2020;395:1613–26.
[44] de Boer AZ, Bastiaannet E, de Glas NA, Marang-van de Mheen PJ, Dekkers OM, Siesling S, et al. Effectiveness of radiotherapy after breast-conserving surgery in older patients with T1–2N0 breast cancer. Breast Cancer Res Treat 2019;178:637–45.
[45] Hughes KS, Schnapper LA, Berry D, Cirrincione C, McCormick B, Shank B. Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer. 2004;351:971-7.
[46] van de Water W, Bastiaannet E, Scholten AN, Kiderlen M, de Craen AJ, Westendorp RG, et al. Breast-conserving surgery with or without radiotherapy in older breast patients with early stage breast cancer: a systematic review and meta-analysis. Ann Surg Oncol. 2014;21:786-94.
[47] Shumway DA, Griffith KA, Sabel MS, Jones RD, Forstner JM, Bott-Kothari TL, et al. Surgeon and radiation oncologist views on omission of adjuvant radiotherapy for older women with early-stage breast cancer. Ann Surg Oncol 2017;24:3518–26.
[48] Wang T, Mott N, Miller J, Berlin NL, Hawley S, Jagsi R, et al. Patient perspectives on treatment options for older women with hormone receptor-positive breast cancer: a qualitative study. JAMA Netw Open 2020;3:e2017129. https://doi.org/10.1001/jamanetworkopen.2020.17129.
[49] Older Adult Oncology. Version 1.2020 (07/02/2020). NCCN Clinical Practice Guidelines in Oncology: National Comprehensive Cancer Network; 2020.
[50] Decoster L, Van Puyvelde K, Mohile S, Wedding U, Basso U, Colloca G, et al. Screening tools for multidimensional health problems warranting a geriatric assessment in older cancer patients: an update on SIOG recommendations†. Ann Oncol 2015;26:288–300.
[51] Wildiers H, Heeren P, Puts M, Topinkova E, Janssen-Heijnen ML, Extermann M, et al. International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. J Clin Oncol 2014;32:2595–603.
[52] McCormick B, Ottesen RA, Hughes ME, Javid SH, Khan SA, Mortimer J, et al. Impact of guideline changes on use or omission of radiation in the elderly with early breast cancer: practice patterns at National Comprehensive Cancer Network Institutions. J Am Coll Surg 2014;219:796–802.
[53] Chu QD, Zhou M, Medeiros KL, Peddi P, Wu XC. Impact of CALGB 9343 trial and sociodemographic variation on patterns of adjuvant radiation therapy practice

for elderly women (≥70 Years) with stage i, estrogen receptor-positive breast cancer: analysis of the national cancer data base. Anticancer Res 2017;37:5585–94.

[54] Williams LJ, Kunkler IH, King CC, Jack W, van der Pol M. A randomised controlled trial of post-operative radiotherapy following breast-conserving surgery in a minimum-risk population. Quality of life at 5 years in the PRIME trial. 2011;15:12.

[55] Coles CE, Griffin CL, Kirby AM, Titley J, Agrawal RK, Alhasso A, et al. Partial-breast radiotherapy after breast conservation surgery for patients with early breast cancer (UK IMPORT LOW trial): 5-year results from a multicentre, randomised, controlled, phase 3, non-inferiority trial. Lancet 2017;390:1048–60.

[56] Truong PT, Olivotto IA, Speers CH, Wai ES, Berthelet E, Kader HA. A positive margin is not always an indication for radiotherapy after mastectomy in early breast cancer. Int J Radiat Oncol Biol Phys 2004;58:797–804.

[57] Smitt MC, Nowels KW, Zdeblick MJ, Jeffrey S, Carlson RW, Stockdale FE, et al. The importance of the lumpectomy surgical margin status in long-term results of breast conservation. Cancer 1995;76:259–67.

[58] Todd A, Martin C, Morgan J, Herbert E, Bradburn M, Burton M, et al. Age specific recruitment and retention to a large multicentre observational breast cancer trial in older women: The Age Gap Trial. J Geriatric Oncol 2021;12:714–23.

[59] Ferreira AR, Di Meglio A, Pistilli B, Gbenou AS, El-Mouhebb M, Dauchy S, et al. Differential impact of endocrine therapy and chemotherapy on quality of life of breast cancer survivors: a prospective patient-reported outcomes analysis. Ann Oncol 2019;30:1784–95.

[60] Bastiaannet E, Liefers GJ, de Craen AJ, Kuppen PJ, van de Water W, Portielje JE, et al. Breast cancer in elderly compared to younger patients in the Netherlands: stage at diagnosis, treatment and survival in 127,805 unselected patients. Breast Cancer Res Treat. 2010;124:801-7.

JACC: CARDIOONCOLOGY VOL. 4, NO. 2, 2022

ORIGINAL RESEARCH

Prevalence of Cardiovascular Disease in Patients With Potentially Curable Malignancies

A National Registry Dataset Analysis

Nicolò Matteo Luca Battisti, MD,[a,b,*] Catherine A. Welch, BSc, MSc, PhD,[c,d,*] Michael Sweeting, PhD,[c,d] Mark de Belder, MA, MD,[e,f] John Deanfield, BA,[g] Clive Weston, MD,[h,i,j] Michael D. Peake, MD,[d,k] David Adlam, BA, BM BCh, DPhil,[l,m,†] Alistair Ring, MA, MD[a,b,†]

ABSTRACT

BACKGROUND Although a common challenge for patients and clinicians, there is little population-level evidence on the prevalence of cardiovascular disease (CVD) in individuals diagnosed with potentially curable cancer.

OBJECTIVES We investigated CVD rates in patients with common potentially curable malignancies and evaluated the associations between patient and disease characteristics and CVD prevalence.

METHODS The study included cancer registry patients diagnosed in England with stage I to III breast cancer, stage I to III colon or rectal cancer, stage I to III prostate cancer, stage I to IIIA non-small-cell lung cancer, stage I to IV diffuse large B-cell lymphoma, and stage I to IV Hodgkin lymphoma from 2013 to 2018. Linked hospital records and national CVD databases were used to identify CVD. The rates of CVD were investigated according to tumor type, and associations between patient and disease characteristics and CVD prevalence were determined.

RESULTS Among the 634,240 patients included, 102,834 (16.2%) had prior CVD. Men, older patients, and those living in deprived areas had higher CVD rates. Prevalence was highest for non-small-cell lung cancer (36.1%) and lowest for breast cancer (7.7%). After adjustment for age, sex, the income domain of the Index of Multiple Deprivation, and Charlson comorbidity index, CVD remained higher in other tumor types compared to breast cancer patients.

CONCLUSIONS There is a significant overlap between cancer and CVD burden. It is essential to consider CVD when evaluating national and international treatment patterns and cancer outcomes. (J Am Coll Cardiol CardioOnc 2022;4:238–253) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

From the [a]Breast Unit, Department of Medicine, The Royal Marsden NHS Foundation Trust, London, United Kingdom; [b]Breast Cancer Research Division, The Institute of Cancer Research, London, United Kingdom; [c]Biostatistics Research Team, Department of Health Sciences, University of Leicester, Leicester, United Kingdom; [d]Public Health England, London, United Kingdom; [e]National Institute for Cardiovascular Outcomes Research, London, United Kingdom; [f]Barts Health NHS Trust, London, United Kingdom; [g]Institute of Cardiovascular Sciences, University College London, London, United Kingdom; [h]Myocardial Ischaemia National Audit Project; [i]School of Medicine, Swansea University, Swansea, United Kingdom; [j]Glangwili General Hospital, Carmarthen, United Kingdom; [k]University of Leicester, Leicester, United Kingdom; [l]Department of Cardiovascular Sciences, University of Leicester and Leicester National Institute of Health Research Biomedical Research Centre, Glenfield Hospital, Leicester, United Kingdom; and the [m]University Hospitals of Leicester NHS Trust, Leicester, United Kingdom. *Drs Battisti and Welch contributed equally to this work. †Drs Adlam and Ring are joint senior and corresponding authors.

ISSN 2666-0873 https://doi.org/10.1016/j.jaccao.2022.03.004

Cancer is associated with significant morbidity and mortality in England.[1] Cancer and cardiovascular disease (CVD) survival is improving.[2,3] However, they share risk factors and pathophysiological processes[4] and may coexist.[5] Furthermore, cancer and its treatment may result in cardiac complications.[6] CVD may influence cancer management and contribute to disparities[7] in the UK,[8-12] in older adults,[13,14] and internationally.[2,15]

Pre-existing CVD in individuals with potentially curable cancer has been described in various countries.[16-19] However, this has not been widely reported in England. The impact of cancer-related factors and social deprivation on cancer and CVD has also not been previously assessed. Investigating the intersection of cancer and CVD is central to understanding outcomes, informing cancer policy, and service provision.

We analyzed the prevalence of pre-existing CVD in a cohort of individuals with potentially curable tumors in England, as differences in cancer management due to comorbidities may affect survival. We also assessed the associations between CVD prevalence and patient and tumor characteristics.

METHODS

As part of the Virtual Cardio-Oncology Research Initiative program,[20] we linked Public Health England National Cancer Registration Dataset (NCRD),[21] Hospital Episode Statistics (HES),[22] and National Institute for Cardiovascular Outcomes Research (NICOR)[23] data to identify CVD recorded in hospital records and registry datasets. We linked English cancer registry data (NCRD) and 6 CVD-specific audits managed by NICOR (Supplemental Table 1). Four NICOR databases were included in this study: the Myocardial Ischaemia National Audit Project,[24] National Adult Cardiac Surgery Audit,[25] National Adult Percutaneous Coronary Intervention,[26] and National Heart Failure Audit.[27] While the Myocardial Ischaemia National Audit Project and National Heart Failure Audit are audit programs including data on patients with suspected acute coronary syndromes and with heart failure, respectively, the National Adult Cardiac Surgery Audit and National Adult Percutaneous Coronary Intervention collect data on those undergoing cardiac surgery and those undergoing percutaneous coronary procedures, respectively. Patients are included in the audits if they have certain diagnoses or procedures, but they may have other CVD diagnoses that were not the reason they were included in the specific audit. The NICOR audit datasets do not report International Statistical Classification of Diseases and Related Health Problems-10th Revision (ICD-10) codes. To include a wider range of CVD compared with those included in the 4 NICOR audits, we included HES administrative data collected during hospital admissions for remuneration purposes. HES records a wide range of patient information, and diagnoses can be recorded as primary diagnoses or comorbidities. We chose a permissive approach to include CVD in any position to identify all patients with relevant comorbidities. NICOR data are derived from specialist audits restricted to recording information about specific CVD: they include codes related to cardiovascular admissions in a specialist unit. NICOR and HES include diagnoses captured in the inpatient setting. Robust quality assurance checks are in place for the NICOR and HES datasets.[28,29] Therefore, CVD prevalence was defined according to either presence of an inpatient hospitalization CVD diagnosis code and/or a NICOR CVD audit record.

NCRD has existing linkages with the National Radiotherapy Dataset and Systemic Anti-Cancer Therapy database. The National Radiotherapy Dataset standard (SCCI0111)[30] requires all National Health Service radiotherapy providers in England to collect standardized data. National Health Service Trusts providing systemic anticancer therapy submit data to the Systemic Anti-Cancer Therapy database. Data quality is considered sufficient for data analysis from 2013.

This study was reviewed and approved by the Virtual Cardio-Oncology Research Initiative Consortium Project Review Panel. The Virtual Cardio-Oncology Research Initiative research program has received favorable ethical opinion from the Northeast-Newcastle & North Tyneside 2 Research Ethics Committee (reference 18/NE/0123). The study was performed in accordance with the Declaration of Helsinki.

ABBREVIATIONS AND ACRONYMS

CVD = cardiovascular disease

DLBCL = diffuse large B-cell lymphoma

HES = Hospital Episode Statistics

ICD-10 = International Statistical Classification of Diseases and Related Health Problems-10th Revision

NCRD = National Cancer Registration Dataset

NICOR = National Institute for Cardiovascular Outcomes Research

NSCLC = non-small-cell lung cancer

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received September 23, 2021; revised manuscript received March 8, 2022, accepted March 10, 2022.

IDENTIFICATION OF THE PATIENT COHORT. We analyzed NCRD data to identify patients from England with potentially curable cancers. Specifically, we included individuals diagnosed with malignancy (breast cancer, non-small-cell-lung cancer [NSCLC], colon cancer, rectal cancer, prostate cancer, diffuse large B-cell lymphoma [DLBCL], and Hodgkin lymphoma) and with potentially curable cancer stages. We used the ICD-10 codes[31] to identify the first record of breast cancer (code C50), colon cancer (codes C18 and C19), rectal cancer (code C20), prostate cancer (code C61) and NSCLC (code C34 excluding small-cell morphology codes 8041, 8042, 8043, 8044, or 8045), DLBCL (code C83.3), and Hodgkin lymphoma (code C81) from January 1, 2013, to December 31, 2018.

If patients had >1 tumor diagnosed at different sites, we included the first tumor diagnosed in the analysis. If patients had synchronous diagnoses, we included the tumor with the worst prognosis on the basis of stage, grade, receptor status (for breast cancer), and Gleason group (for prostate cancer) (Supplemental Table 2). We excluded patients with synchronous tumors diagnosed in the same site with similar prognostic features and those with synchronous tumors diagnosed in different sites.

We included patients 25 to 100 years of age at cancer diagnosis, those with residency in England, and those with complete data on vital status, sex, and National Health Service number (to allow linkage). We restricted the analysis to potentially curable tumors (stage I-III breast cancer, stage I-III colon or rectal cancer, stage I-III prostate cancer, stage I-IIIA NSCLC, stage I-IV DLBCL, and stage I-IV Hodgkin lymphoma) (Supplemental Table 3). Patients with missing data on age, sex, National Health Service number, mortality status, or cancer stage were excluded. Data on age, sex, ethnicity, histology, grade, and tumor-node-metastasis stage were extracted at cancer diagnosis. Cancer-specific characteristics were retrieved.

The Index of Multiple Deprivation is the official measure of deprivation in England.[32] An established methodological framework is followed to derive 7 distinct domains of deprivation, which are weighted and then combined to calculate the Index of Multiple Deprivation at the lower layer super output area (a government-defined geographic region). We extracted the income domain of the Index of Multiple Deprivation for analysis, which was already divided into quintiles of deprivation. Nonincome components of the Index of Multiple Deprivation were not included, as only the income domain was available for analysis.

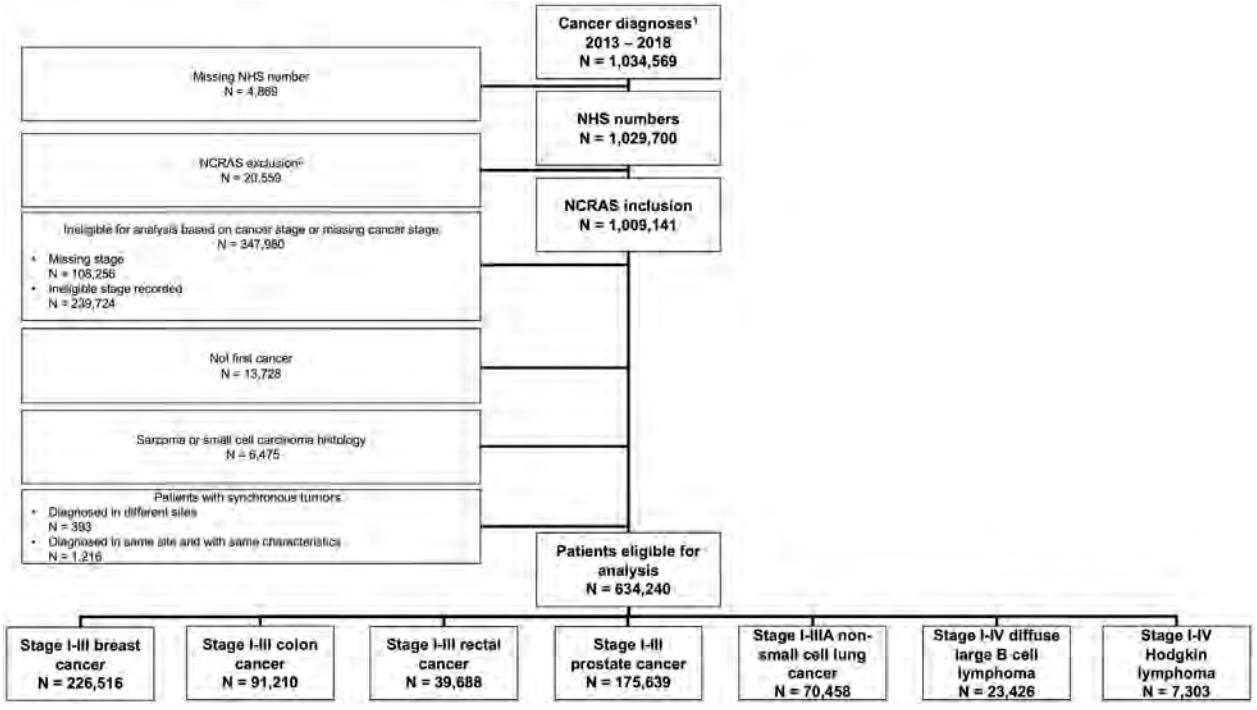
Using linkages with the National Radiotherapy Dataset, Systemic Anti-Cancer Therapy dataset, and HES,[22] a database of hospital admissions, surgical procedures, radiation therapy, and systemic anticancer treatments performed in England was extracted. We identified curative treatments (surgery, radiotherapy, and chemotherapy) using previously agreed-upon algorithms.[33]

COMORBIDITIES. We extracted comorbidities defined within the Charlson comorbidity index,[34] identified using HES admitted patient care diagnoses recorded within 5 years before cancer diagnosis, and derived a Charlson comorbidity index excluding CVD to avoid counting them in both the CVD exposure and the index (Supplemental Table 4).

We identified CVD comorbidities using the ICD-10 code list (Supplemental Table 5) from diagnoses recorded in any diagnostic position in HES admitted patient care (inpatient) data or if the patient had a record in a NICOR database[23] within 5 years before cancer diagnosis.[35] ICD-10 CVD codes were obtained from a Virtual Cardio-Oncology Research Initiative study[36] and divided into cerebrovascular, stroke (cerebrovascular subgroup), congestive cardiac failure, ischemic heart disease, acute myocardial infarction, peripheral artery disease, and valvular heart disease (Supplemental Table 6).

STATISTICAL ANALYSIS. Patient and tumor characteristics for each cancer were summarized. CVD prevalence (identified using HES and NICOR CVD diagnosis code list) by patient and tumor characteristics was also explored. We report the mean ± SD for continuous variable and count (percentage) for categorical variables. Because of the large sample size, even trivial differences are likely to have small P values. Thus, we focused on presenting point estimates and 95% CIs. The point estimates reported estimate the true proportion in the population, so we also report CIs as a measure of uncertainty in the point estimates. We fit logistic regression models to determine the unadjusted associations between patient and tumor characteristics and CVD hospitalization prior to cancer diagnosis, in the full cohort and by cancer site, and report ORs with 95% CIs. We also fit fully adjusted logistic regression analysis to understand the association between each variable and CVD after adjusting for the potential confounders age, sex, race, Index of Multiple Deprivation (income domain), Charlson comorbidity index, tumor-node-metastasis stage, laterality (for breast and lung), and treatment modality.

FIGURE 1 **Consolidated Standards of Reporting Trials Diagram**



The diagram shows the selection of cancer diagnoses included in the analysis. NCRAS = National Cancer Registration and Analysis Service; NHS = National Health Service.

We analyzed observed CVD prevalence overall, by patient characteristics, and by cancer site. The observed prevalence is influenced by the age distribution, which varies by cancer site. We also calculated CVD prevalence directly standardized to the age and sex distribution of the 2016 English population obtained from the Office of National Statistics. This allows a fairer comparison of the impact of CVD across cancer sites and provides estimates of CVD prevalence in a cancer population with the same age and sex distribution as the general English population. Uncertainty in the prevalence estimates was displayed in the figures with 95% CIs obtained assuming a binomial distribution. To assess the CVD burden, we plotted absolute numbers of patients with CVD by cancer site and age. We also investigated the association between cancer site and CVD using logistic regression analysis adjusting for age, sex, the income domain of the Index of Multiple Deprivation, and Charlson comorbidity index. We produced an unadjusted logistic regression analysis to investigate the association between the income domain of the Index of Multiple Deprivation and CVD, cancer stage, surgery, chemotherapy, and radiotherapy with interactions between each covariate and the income domain of the Index of Multiple Deprivation.

All analyses were performed in Stata MP version 16 (StataCorp) and R version 4.0.2 (R Foundation for Statistical Computing).

RESULTS

We extracted data from 1,034,569 cancer diagnoses in England between 2013 and 2018. After exclusions (Supplemental Table 3), 1,009,141 records remained. We excluded 347,960 tumor records on the basis of stage or missing stage, 13,728 metachronous tumor records, and 6,475 records of tumors with sarcomatous or small-cell histology (**Figure 1**). To analyze data at the patient level, we excluded 393 patients with 798 synchronous tumors diagnosed at ≥2 different sites and 1,216 patients with 2,454 synchronous tumors diagnosed at the same site with the same prognosis (Supplemental Table 2).

Overall, the analysis included 634,240 patients (226,516 with stage I-III breast cancer, 91,210 with stage I-III colon cancer, 39,688 with stage I-III rectal cancer, 175,639 with stage I-III prostate cancer, 70,458

with stage I-IIIA NSCLC, 23,426 with stage I-IV DLBCL, and 7,303 with stage I-IV Hodgkin lymphoma) (**Figure 1**).

The mean age was 67.2 ± 12.7 years, ranging from 62.5 ± 13.7) years in the breast cancer cohort to 72.9 ± 10.3) years in the NSCLC cohort. Men represented 303,021 diagnoses (47.8%), 564,687 (89.0%) had White race, 417,407 (65.8%) had the income domain of the Index of Multiple Deprivation score 1 to 3, and 295,961 (46.7%) had no Charlson comorbidity index comorbidities (excluding CVDs) recorded within 5 years before cancer diagnosis (**Table 1,** Supplemental Tables 7 to 13).

CARDIOVASCULAR DISEASE. Prior CVD was identified in 102,834 (16.2%) of the overall cohort (**Table 2,** Supplemental Table 14). Although 0.2% of CVD records were identified in NICOR only, 18,182 (17.7%) were found in both HES and NICOR datasets, with most records (84,424 [82.1%]) identified from HES only (Supplemental Figure 1). Although ischemic heart disease was the most common, many HES CVD codes were cerebrovascular, which would not feature in NICOR audits unless accompanied by other CVD diagnostic codes. Similarly, most tumors with CVD records included in an individual NICOR audit dataset were also featured in HES with a cardiovascular diagnostic code within 5 years before cancer diagnosis (**Table 2,** Supplemental Figure 1). Most tumors with specific CVD records were retrieved from HES.

The odds of prior CVD hospitalization increased with age, the income domain of the Index of Multiple Deprivation, and Charlson comorbidity index and were higher in men (**Table 2**). In the individual cancer cohorts, prevalent CVD was identified in 17,453 of 226,5162 patients in the breast cancer cohort (7.7%; 95% CI: 7.6%-7.8%), 20,161 of 91,210 in the colon cancer cohort (22.1%; 95% CI: 21.8%-22.3%), 6,699 of 39,688 in the rectal cancer cohort (16.8%; 95% CI: 16.5%-17.2%), 27,123 of 175,639 in the prostate cancer cohort (15.4%; 95% CI: 15.3%-15.6%), 25,459 of 70,458 in the NSCLC cohort (36.1%; 95% CI: 35.7%-36.4%), 5,091 of 23,426 in the DLBCL cohort (21.7%; 95% CI: 21.2%-22.2%), and 850 of 7,303 in the Hodgkin lymphoma cohort (11.6%; 95% CI: 10.8%-12.3%) (Supplemental Table 14). In the rectal cancer and NSCLC cohorts, the percentages of patients with CVD were more than 4% higher in those with stage I vs stage III disease (5.3% [95% CI: 4.4%-6.2%] and 4.3% [95% CI: 3.5%-5.1%], respectively); in Hodgkin lymphoma, CVD prevalence was 4.2% lower (95% CI: 1.6%-6.7%) (Supplemental Table 14). Prior CVD rates showed no laterality differences in the breast cancer and NSCLC cohorts.

We present the unadjusted logistic regression analysis (Supplemental Table 15) and the adjusted logistic regression analysis (**Table 2**) for the associations between CVD prevalence and patient- and treatment-specific characteristics in the overall and tumor-specific cohorts. We observed a significant association between increasing age, male sex, increasing income domain of the Index of Multiple Deprivation, not having surgery, radiotherapy, or chemotherapy and increasing CVD odds in the adjusted and unadjusted logistic regression analyses. In the unadjusted logistic regression analysis (Supplemental Table 15), all races had lower or similar CVD odds compared with White race. After fitting the adjusted logistic regression analysis (**Table 2**), Asian race had significantly higher CVD odds compared with White race in the overall cohort and in each tumor cohort, except NSCLC. In the overall cohort, the CVD odds decreased for stage II compared with stage I and increased for stages III and IV compared with stage I in both unadjusted and adjusted analyses. For rectal cancer and NSCLC, the CVD odds in stages II and III compared with stage I were lower. For breast cancer, prostate cancer, DLBCL, and Hodgkin lymphoma, we observed a significant but nonlinear association between stage and CVD odds in unadjusted logistic regression analysis, but this was no longer significant in the adjusted analysis. Charlson comorbidity index was not associated with CVD odds in the adjusted and unadjusted analysis.

An increasing income domain of the Index of Multiple Deprivation was associated with more advanced stage in the individual tumor cohorts (Supplemental Table 16). Increasing income domain of the Index of Multiple Deprivation score was associated with higher CVD rates in all tumor groups except the Hodgkin lymphoma cohort (Supplemental Tables 7 to 13). In the overall cohort, the CVD rates ranged from 13.3% for patients living in areas with income domain of the Index of Multiple Deprivation of 1 (least deprived) to 20.7% in those with an income domain of the Index of Multiple Deprivation of 5 (most deprived). CVD prevalence ranged from 6.1% to 10.1% in the breast cancer cohort, from 19.7% to 25.9% in the colon cancer cohort, from 14.9% to 20.4% in the rectal cancer cohort, from 13.5% to 18.9% in the prostate cancer cohort, from 32.6% to 38.4% in the NSCLC cohort, from 19.6% to 23.4% in the DLBCL cohort, and from 11.3% to 12.7% in the Hodgkin lymphoma cohort.

Supplemental Table 14 also outlines the absolute number of individuals with CVD hospitalization before cancer diagnosis across the tumor cohorts and

TABLE 1 Patient, Disease, and Tumor Characteristics in the Overall and Individual Tumor Cohorts

	Full Cohort (N = 634,240)	Breast (n = 226,516)	Colon (n = 91,210)	Rectal (n = 39,688)	Prostate (n = 175,639)	NSCLC (n = 70,458)	DLBCL (n = 23,426)	Hodgkin Lymphoma (n = 7,303)
Age at cancer diagnosis, y	67.2 ± 12.7	62.5 ± 13.9	71.2 ± 12.3	68.6 ± 12.2	69.1 ± 8.6	72.9 ± 10.3	52.5 ± 18.3	68.0 ± 13.9
Age at cancer diagnosis, y								
25-34	7,802 (1.2)	17,286 (7.6)	912 (1.0)	371 (0.9)	4 (0.0)	155 (0.2)	652 (2.8)	1,686 (23.1)
35-44	23,295 (3.7)	50,203 (22.2)	2,036 (2.2)	999 (2.5)	366 (0.2)	444 (0.6)	994 (4.2)	1,170 (16.0)
45-54	73,968 (11.7)	51,844 (22.9)	5,710 (6.3)	3,527 (8.9)	8,534 (4.9)	2,655 (3.8)	2,214 (9.5)	1,125 (15.4)
55-64	131,394 (20.7)	55,876 (24.7)	15,385 (16.9)	8,860 (22.3)	39,927 (22.7)	10,327 (14.7)	3,975 (17.0)	1,076 (14.7)
65-74	207,512 (32.7)	32,983 (14.6)	27,277 (29.9)	12,630 (31.8)	79,141 (45.1)	24,292 (34.5)	7,138 (30.5)	1,158 (15.9)
75-84	144,670 (22.8)	14,302 (6.3)	28,583 (31.3)	9,995 (25.2)	41,980 (23.9)	23,882 (33.9)	6,364 (27.2)	883 (12.1)
≥85	45,599 (7.2)	17,286 (7.6)	11,307 (12.4)	3,306 (8.3)	5,687 (3.2)	8,703 (12.4)	2,089 (8.9)	205 (2.8)
Sex								
Male	303,021 (47.8)	0 (0.0)	48,431 (53.1)	25,420 (64.0)	175,639 (100)	36,229 (51.4)	12,981 (55.4)	4,321 (59.2)
Female	331,219 (52.2)	226,516 (100)	42,779 (46.9)	14,268 (36.0)	0 (0.0)	34,229 (48.6)	10,445 (44.6)	2,982 (40.8)
Ethnicity								
White	564,687 (89.0)	198,738 (87.7)	83,317 (91.3)	36,153 (91.1)	153,282 (87.3)	66,312 (94.1)	20,921 (89.3)	5,964 (81.7)
Mixed	2,694 (0.4)	1,184 (0.5)	274 (0.3)	131 (0.3)	762 (0.4)	163 (0.2)	99 (0.4)	81 (1.1)
Asian	16,923 (2.7)	8,044 (3.6)	1,883 (2.1)	1,066 (2.7)	3,309 (1.9)	1,183 (1.7)	952 (4.1)	486 (6.7)
Black	13,579 (2.1)	4,522 (2.0)	1,339 (1.5)	418 (1.1)	6,093 (3.5)	625 (0.9)	351 (1.5)	231 (3.2)
Other	7,124 (1.1)	3,118 (1.4)	911 (1.0)	388 (1.0)	1,723 (1.0)	518 (0.7)	311 (1.3)	155 (2.1)
Missing	29,233 (4.6)	10,910 (4.8)	3,486 (3.8)	1,532 (3.9)	10,470 (6.0)	1,657 (2.4)	792 (3.4)	386 (5.3)
Income domain of the Index of Multiple Deprivation[a]								
1 (least)	140,873 (22.2)	51,814 (22.9)	20,257 (22.2)	8,776 (22.1)	43,793 (24.9)	9,891 (14.0)	5,020 (21.4)	1,322 (18.1)
2	144,911 (22.8)	52,228 (23.1)	21,337 (23.4)	9,039 (22.8)	43,060 (24.5)	12,467 (17.7)	5,317 (22.7)	1,463 (20.0)
3	131,623 (20.8)	47,406 (20.9)	18,932 (20.8)	8,361 (21.1)	36,888 (21.0)	13,612 (19.3)	4,880 (20.8)	1,544 (21.1)
4	114,231 (18.0)	40,605 (17.9)	16,392 (18.0)	7,171 (18.1)	28,899 (16.5)	15,262 (21.7)	4,371 (18.7)	1,531 (21.0)
5 (most)	102,602 (16.2)	34,463 (15.2)	14,292 (15.7)	6,341 (16.0)	22,999 (13.1)	19,226 (27.3)	3,838 (16.4)	1,443 (19.8)
Charlson comorbidity index[b]								
0	295,961 (46.7)	106,251 (46.9)	43,371 (47.6)	18,900 (47.6)	79,618 (45.3)	33,258 (47.2)	11,051 (47.2)	3,512 (48.1)
1	53,655 (8.5)	19,325 (8.5)	7,641 (8.4)	3,364 (8.5)	14,857 (8.5)	6,020 (8.5)	1,840 (7.9)	608 (8.3)
2	155,699 (24.5)	55,420 (24.5)	22,466 (24.6)	9,708 (24.5)	43,368 (24.7)	17,203 (24.4)	5,805 (24.8)	1,729 (23.7)
3	65,527 (10.3)	23,372 (10.3)	9,293 (10.2)	4,078 (10.3)	18,266 (10.4)	7,278 (10.3)	2,504 (10.7)	736 (10.1)
≥4	56,561 (8.9)	20,238 (8.9)	8,193 (9.0)	3,533 (8.9)	15,547 (8.9)	6,283 (8.9)	2,126 (9.1)	641 (8.8)
Missing[c]	6,837 (1.1)	1,910 (0.8)	246 (0.3)	105 (0.3)	3,983 (2.3)	416 (0.6)	100 (0.4)	77 (1.1)
Screen-detected								
Yes	–	99,072 (43.7)	–	–	–	–	–	–
No	–	75,931 (33.5)	–	–	–	–	–	–
Missing	–	51,513 (22.7)	–	–	–	–	–	–
TNM stage								
I	255,320 (40.3)	104,899 (46.3)	19,213 (21.1)	12,357 (31.1)	79,477 (45.3)	33,890 (48.1)	4,478 (19.1)	1,006 (13.8)
II	211,316 (33.3)	98,987 (43.7)	36,820 (40.4)	9,365 (23.6)	44,469 (25.3)	15,322 (21.7)	3,973 (17.0)	2,380 (32.6)
III	154,349 (24.3)	22,630 (10.0)	35,177 (38.6)	17,966 (45.3)	51,693 (29.4)	21,246 (30.2)	4,066 (17.4)	1,571 (21.5)
IV	13,255 (2.1)	–	–	–	–	–	10,909 (46.6)	2,346 (32.1)
Laterality								
Left		115,340 (50.9)	–	–	–	29,043 (41.2)	–	–
Right		108,849 (48.1)	–	–	–	40,480 (57.5)	–	–
Bilateral		2,219 (1.0)	–	–	–	122 (0.2)	–	–
Missing		108 (0.0)	–	–	–	813 (1.2)	–	–

Values are mean ± SD or n (% of total). [a]Income domain of the Index of Multiple Deprivation derived in 2015 was used for patients diagnosed with cancer in 2013, and income domain of the Index of Multiple Deprivation derived in 2019 was used for patients diagnosed with cancer after 2013. [b]5 years before diagnosis and excluding cardiovascular disease. [c]Missing if not linked to Hospital Episode Statistics.

DLBCL = diffuse large B-cell lymphoma; NSCLC = non-small-cell lung cancer; TNM = tumor-node-metastasis.

age groups. The prostate cancer cohort had the largest burden of CVD hospitalization (n = 27,123), followed by the NSCLC cohort (n = 25,459), colon cancer cohort (n = 20,161), breast cancer cohort (n = 17,453), and rectal cancer cohort (n = 6,699). The DLBCL cohort and the Hodgkin lymphoma cohort had the lowest burden of CVD (n = 5,091 and n = 850, respectively). The highest absolute number of individuals with prior

TABLE 2 Case Ascertainment of CVD Hospitalizations Identified Using ICD-10 Code List[a] in HES or NICOR[b]

	HES Only	HES and MINAP	HES and NACSA	HES and PCI	HES and NHFA	HES and NICOR	NICOR Only[c]	Total
Hospitalized CVD[d]	84,424	8,359	4,020	9,250	3,108	18,182	230	102,834
CVD category								
Cerebrovascular	18,584	775	473	633	479	1,782	–	20,366
Stroke	7,948	273	158	240	184	654	–	8,602
Congestive cardiac failure	15,393	2,325	1,044	1,722	3,024	6,069	–	21,462
Ischemic heart disease	48,138	8,290	3,475	9,240	1,995	16,482	–	64,620
Acute myocardial infarction	2,122	7,099	955	5,251	555	8,279	–	10,401
Peripheral artery disease	18,090	1,214	866	1,187	560	2,821	–	20,911
Valvular heart disease	12,376	1,944	2,235	1,545	1,381	5,398	–	17,775

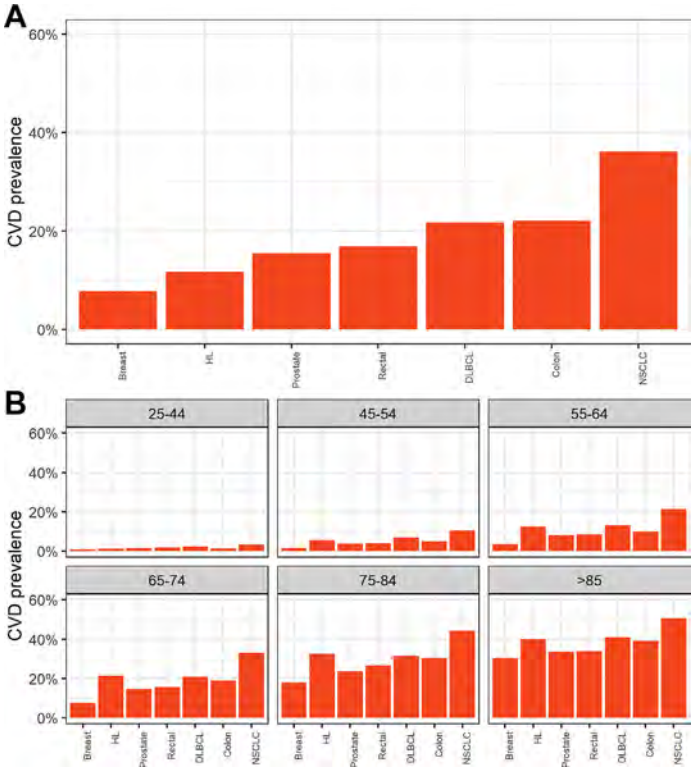
[a]ICD-10 codes for each CVD category can be found in Supplemental Table 7. [b]Occurrences are reported, so rows and columns do not add up to the totals. [c]CVD categories are not reported, because ICD-10 codes are not recorded in NICOR datasets. [d]CVD categories are retrieved from HES ICD-10 codes and not from a NICOR dataset (ICD-10 codes are not reported in NICOR datasets).

CVD = cardiovascular disease; HES = Hospital Episode Statistics; ICD-10 = International Statistical Classification of Diseases and Related Health Problems-10th Revision; NICOR = National Initiative for Cardiovascular Outcomes Research; MINAP = Myocardial Ischaemia National Audit Project; NACSA = National Adult Cardiac Surgery Audit; PCI = percutaneous coronary intervention audit; NHFA = National Heart Failure Audit.

hospitalization for CVD occurred between 65 and 84 years of age in all cancer cohorts. The overall proportion of patients with CVD is shown in **Figures 2A and 2B**.

The observed CVD prevalence across tumor groups is shown in **Figure 3**. Age- and sex-standardized CVD prevalence was much lower than the observed prevalence, as patients with cancer were older than the

FIGURE 2 Patients With Prevalent Cardiovascular Disease According to Tumor Type and Age



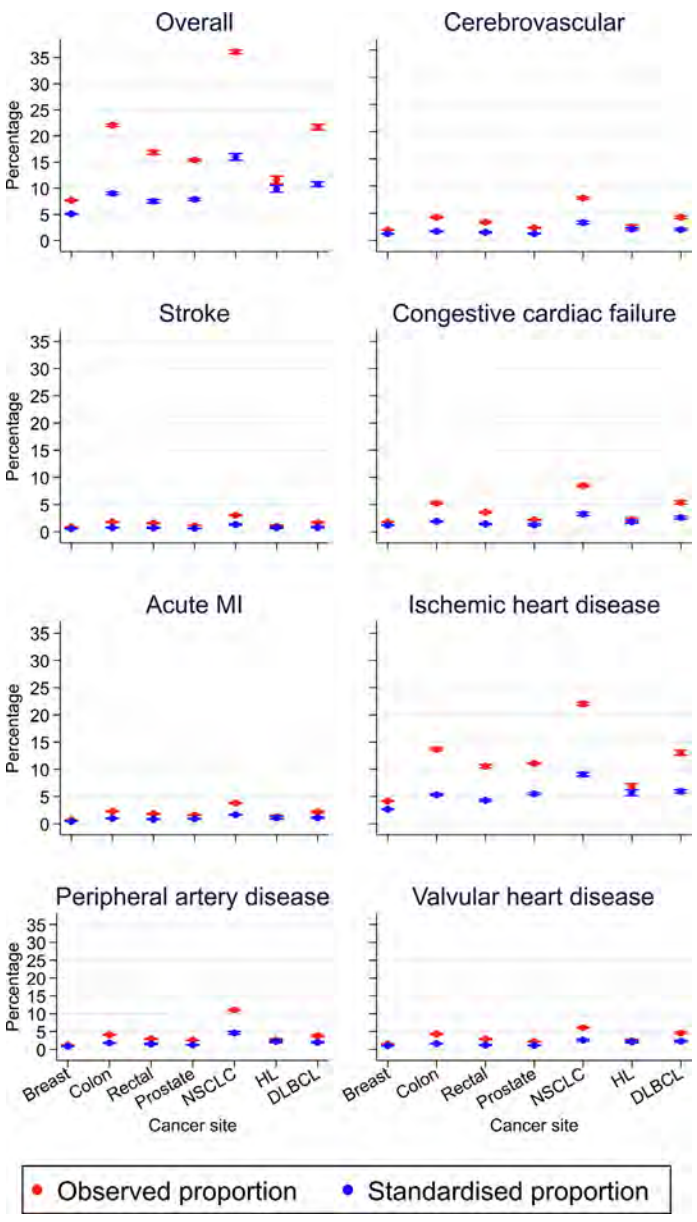
Patients with prevalent cardiovascular disease according to tumor type **(A)** and age **(B)**. The figure shows the proportion of patients with diagnoses of cardiovascular disease in each tumor cohort and according to age group. CVD = cardiovascular disease; DLBCL, diffuse large B-cell lymphoma; HL = Hodgkin lymphoma; NSCLC = non-small-cell lung cancer.

general population. The NSCLC cohort had a higher standardized prevalence compared with other cancer sites. The NSCLC cohort also had the highest observed prevalence of cerebrovascular disease (7.8%; 95% CI: 7.6%-8.0%), stroke (3.0%; 95% CI: 2.9%-3.2%), congestive cardiac failure (8.5%; 95% CI: 8.3%-8.6%), acute myocardial infarction (3.8%; 95% CI: 3.6%-3.9%), ischemic heart disease (22.0%; 95% CI: 21.7%-22.3%), peripheral vascular disease (11.1%; 95% CI: 10.8%-11.3%), and valvular heart disease (6.1%; 95% CI: 5.9%-6.2%). The prevalence of CVD subtypes was lowest in patients with breast cancer (cerebrovascular disease [1.9%; 95% CI: 1.9%-2.0%], stroke [0.8%; 95% CI: 0.8%-0.9%], congestive cardiac failure [1.8%; 95% CI: 1.7%-1.8%], acute myocardial infarction [0.7%; 95% CI: 0.6%-0.7%], ischemic heart disease [4.2%; 95% CI: 4.1%-4.2%], peripheral vascular disease [1.2%; 95% CI: 1.1%-1.2%], and valvular heart disease [1.5%; 95% CI: 1.5%-1.6%]).

Compared with breast cancer, other cancer cohorts had significantly higher CVD prevalence, with the unadjusted OR for each cancer site compared with breast cancer >1.5 and for NSCLC an OR of 6.75 (95% CI: 6.60-6.89) (Figure 4). After adjustment for age, sex, the income domain of the Index of Multiple Deprivation, and Charlson comorbidity index, all cancer sites apart from Hodgkin lymphoma were significantly different from breast cancer but with attenuated ORs. Also, Hodgkin lymphoma was no longer significantly different compared with breast cancer after adjusting only for age and sex. CVD odds in patients with NSCLC were significantly higher than in those with breast cancer after adjustment (OR 3.06; 95% CI: 2.98-3.14).

In the overall population, compared with patients not undergoing any anticancer treatment, those receiving surgery, radiotherapy, or chemotherapy had lower odds of CVD (surgery: OR: 0.41 [95% CI: 0.41-0.42]; radiotherapy: OR: 0.50 [95% CI: 0.50-0.51]; chemotherapy: OR: 0.43 [95% CI: 0.42-0.44]) (Table 3). Patients receiving surgery, radiotherapy, or chemotherapy had lower odds of CVD compared with those not treated in most individual tumor cohorts (breast, colon, rectal, DLBCL, and Hodgkin lymphoma), but not in the prostate and NSCLC cohorts.

FIGURE 3 Prevalence of Cardiovascular Disease Before Cancer Diagnosis by Cancer Site



The figure shows the observed and standardized prevalence of cardiovascular disease in Hospital Episode Statistics by cancer site. Prevalence is standardized by the age- and sex stratum-specific 2016 Office for National Statistics population estimates. MI = myocardial infarction; other abbreviations as in Figure 2.

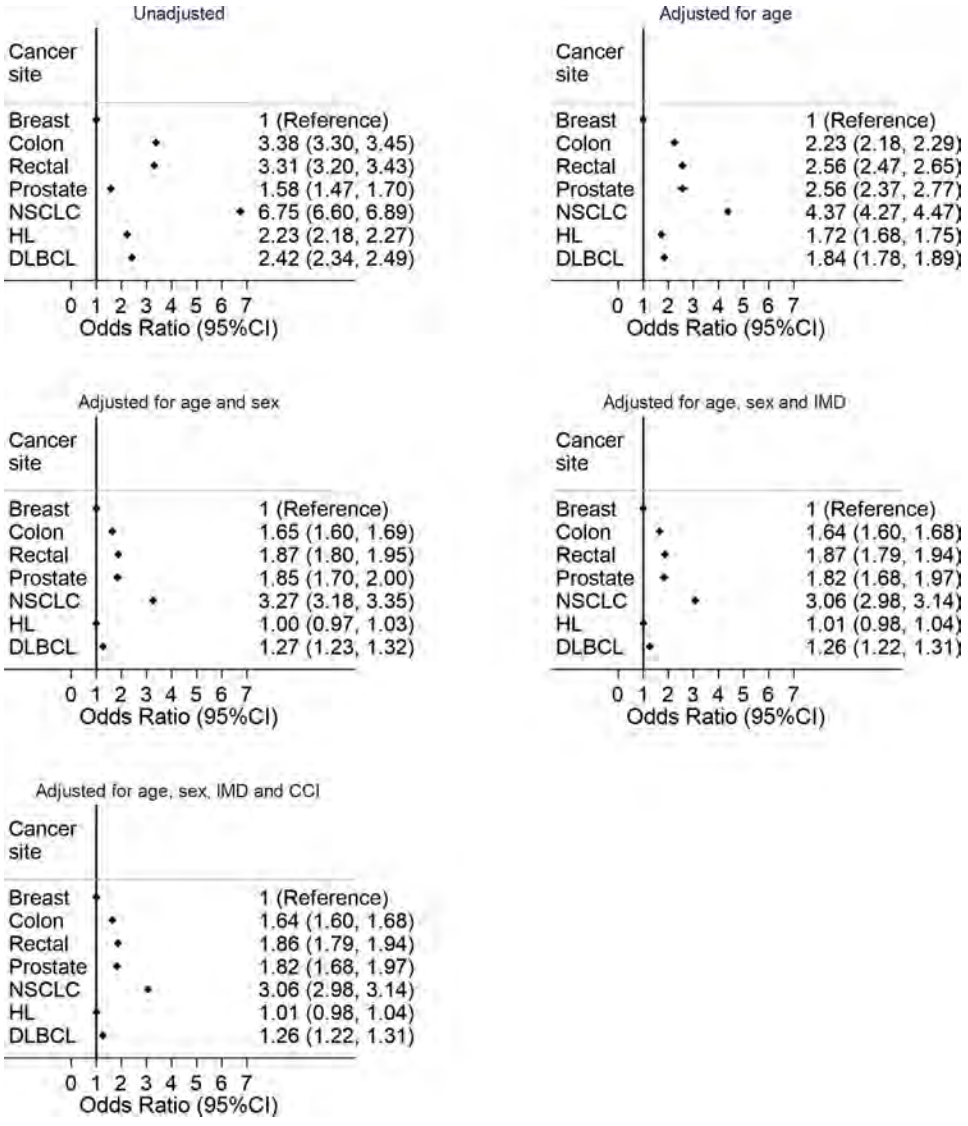
DISCUSSION

Our study was a large-scale, population-based analysis describing CVD prevalence in individuals with potentially curable cancers. Understanding the intersection between cancer and CVD is key to informing anticancer treatment decisions, interpreting outcomes, and planning health care provision.[37] We used linked national registry datasets of patients diagnosed with potentially curable malignancies over 6 years in England and found an overlap between cancer and CVD in 16.2% of individuals.

An analysis of English National Cancer Diagnosis Audit data linked to primary care records showed that

JACC: CARDIOONCOLOGY, VOL. 4, NO. 2, 2022
JUNE 2022:238–253

FIGURE 4 Associations Between Prevalent Cardiovascular Disease and Cancer Site



The figure shows the progressively adjusted logistic regression analysis reporting odds ratios of associations between cardiovascular disease recorded in Hospital Episode Statistics and/or National Institute for Cardiovascular Outcomes Research and cancer site. The reference is the breast cancer cohort. CCI = Charlson comorbidity index; IMD = Index of Multiple Deprivation; other abbreviations as in Figure 2.

more than three-quarters of patients with cancer had ≥1 comorbidity,[38] with comparable standardized CVD prevalence across tumor types. Our study revealed a much higher standardized prevalence in patients with NSCLC, reflecting the high observed prevalence in this cohort and suggesting that age and sex can only partially explain the high CVD burden in this group. This difference is likely to be driven not only by the older age of individuals with NSCLC but also by risk factors shared by CVD and lung malignancies.[4] Lifestyle factors may explain the difference in CVD prevalence among the various tumor groups, including the higher CVD rate in the NSCLC cohort. The difference between the Hodgkin lymphoma and the breast cancer cohort was no longer significant after adjusting for age and sex, which are key drivers of the CVD prevalence in this cohort. Nonetheless, these findings are relevant to better inform the provision of cardio-oncology services and allocate resources to improve outcomes for patients with cancer and a higher CVD prevalence.

Comorbidities are more common among lung cancer survivors and less frequent among breast and prostate cancer survivors.[39] One study documented that 43.6% of patients diagnosed with potentially curable NSCLC in England from 2012 to 2016 had CVD,[36] which affected resection and mortality rates.[21] In the general population, older age is associated with a higher prevalence of CVD,[40] and CVD contributes to an increasing burden of morbidity and disability in community-dwelling older individuals. Prospective trials and cancer registry analyses have documented higher risk for heart failure in patients with potentially curable malignancies and CVD and cardiovascular risk factors receiving cytotoxic or targeted therapies.[41-45] Similar concerns exist for patients potentially suitable for locoregional treatments.[36,46] Pre-existing CVD may represent a contraindication for pursuing specific anticancer treatment options or require adjustments, possibly hindering the chances of cure in individuals with potentially curable cancer. In future analyses, we plan to examine the geographic variation of CVD rates and its impact on anticancer treatments.

CVD is also an increasingly prevalent exclusion criterion for studies investigating novel anticancer treatments.[47] This has substantial implications on limiting not only the access of patients with cancer to experimental treatments but also trial results applicability,[48] trial design, drug development, and drug labeling.[49]

Our study confirms that men, older individuals, and those living in socioeconomically deprived areas had a higher CVD burden. These factors have important impact on the prevalence of CVD in patients with potentially curable malignancies (**Figure 4**). Male sex is a risk factor for higher coronary artery disease rates and mortality.[50] Patients undergoing surgery, radiotherapy, or chemotherapy have lower odds of CVD compared with those not treated in the overall cohort and in most individual tumor cohorts. The burden of comorbidities increases with age[39,51] and may influence overall and non-cancer-related mortality[52-54] but also affect anticancer treatment tolerance.[55] For patients with breast cancer, CVD may also influence tumor-specific mortality.[56]

We demonstrated an increasing prevalence of CVD associated with worse deprivation in all tumor cohorts except Hodgkin lymphoma. In this analysis, a higher score of the income domain of the Index of Multiple Deprivation, which corresponds to lower income and higher levels of deprivation, was also associated with more advanced tumor stage. Socioeconomic inequalities have a significant impact on cancer presentation, diagnosis, and treatment.[57] Despite efforts aiming to reduce them in England, their impact on cancer survival has not substantially changed.[58] An accurate review of care pathways for patients with cancer and comorbidities may mitigate their detrimental effect on outcomes.[59]

Our analysis suggests that CVD can be ascertained in HES, although the sensitivity and specificity of diagnostic codes from this source still need to be defined. A significant number of CVD codes were retrieved from HES, while fewer were included also in the various NICOR datasets. Despite having both NICOR and HES data focus on hospital-based diagnoses captured in the inpatient setting, NICOR includes data on procedures and HES data are derived from admission codes. As a result, these datasets include different populations. As HES was the primary source of CVD records, HES is a sensitive source of data to ascertain the CVD burden in this population. Although NICOR databases may be more specific and have better diagnostic accuracy to determine specific CVD categories and its severity, HES is a valuable source of data to elucidate the coexistence of cancer and CVD.

Our findings have relevant clinical implications. We found that pre-existing CVD is common in individuals with potentially curable cancers. Although the decreased CVD odds in patients undergoing specific anticancer treatments may be confounded by multiple factors and causality cannot be determined, CVD may influence cancer treatment decision making. Importantly, our analysis showed that CVD is not evenly distributed among cohorts of individuals with different cancers. Specifically, we have identified categories in which CVD is particularly common: older adults, those with NSCLC, and those living in deprived areas. These factors have important implications on the provision of cardio-oncology services across England, to ensure service distribution matches need. We plan to investigate the geographic CVD distribution in this population and how this relates to the availability of specialized cardio-oncology services across England.

STUDY LIMITATIONS. First, we did not incorporate confounders such as smoking, diet, physical activity, obesity, alcohol, and concurrent medications because they were not recorded in cancer registry datasets, although social deprivation might represent a proxy for these lifestyle confounders. Cardiovascular risk factors are captured only by the NICOR datasets; therefore, these are available only for a subset of the individuals included in this study.

Second, our analysis was focused on hospitalizations, and we did not investigate events recorded only in primary care. This increases diagnostic

TABLE 3 Adjusted Odds Ratios of Cardiovascular Disease Hospitalization According to Cancer Type and Patient Characteristics[a,b]

	Full Cohort (N = 600,057)	Breast (n = 214,285)	Colon (n = 87,546)
Total with prevalent CVD	101,014	17,183	19,810
Age at cancer diagnosis,[c] y			
25-54	0.18 (0.17-0.19)	0.20 (0.19-0.22)	0.19 (0.16-0.21)
55-64	0.50 (0.48-0.51)	0.49 (0.46-0.52)	0.49 (0.46-0.52)
65-74	1.00 (reference)	1.00 (reference)	1.00 (reference)
75-84	1.90 (1.86-1.93)	1.95 (1.87-2.04)	1.71 (1.64-1.79)
≥85	2.78 (2.71-2.85)	2.41 (2.27-2.55)	2.31 (2.19-2.44)
Sex			
Male	1.00 (reference)	–	1.00 (reference)
Female	0.71 (0.69-0.72)	–	0.56 (0.54-0.58)
Race			
White	1.00 (reference)	1.00 (reference)	1.00 (reference)
Mixed	0.78 (0.68-0.89)	1.10 (0.83-1.45)	0.90 (0.64-1.28)
Asian	1.21 (1.16-1.27)	1.36 (1.24-1.49)	1.18 (1.05-1.33)
Black	0.58 (0.54-0.61)	0.94 (0.82-1.08)	0.69 (0.59-0.81)
Other	0.79 (0.73-0.85)	0.80 (0.67-0.96)	0.74 (0.61-0.90)
Income domain of the Index of Multiple Deprivation[d]			
1 (least)	1.00 (reference)	1.00 (reference)	1.00 (reference)
2	1.12 (1.09-1.15)	1.09 (1.04-1.15)	1.05 (1.00-1.11)
3	1.25 (1.22-1.28)	1.24 (1.18-1.31)	1.17 (1.12-1.24)
4	1.48 (1.45-1.52)	1.43 (1.35-1.51)	1.36 (1.29-1.43)
5 (most)	1.88 (1.83-1.92)	1.74 (1.65-1.84)	1.60 (1.52-1.69)
Charlson comorbidity index[e]			
0	1.00 (reference)	1.00 (reference)	1.00 (reference)
1	0.98 (0.96-1.01)	0.99 (0.93-1.05)	0.99 (0.93-1.05)
2	0.98 (0.96-1.00)	0.99 (0.95-1.03)	0.93 (0.89-0.97)
3	0.98 (0.96-1.01)	0.99 (0.94-1.05)	1.03 (0.97-1.09)
≥4	1.00 (0.97-1.03)	0.96 (0.91-1.03)	1.01 (0.95-1.07)
TNM stage			
	1.00 (reference)	1.00 (reference)	1.00 (reference)
II	0.95 (0.94-0.97)	1.03 (0.99-1.07)	0.95 (0.91-0.99)
III	1.05 (1.03-1.07)	1.04 (0.98-1.11)	1.16 (1.11-1.22)
IV	1.34 (1.27-1.40)	–	–
Laterality			
Left	–	1.00 (reference)	–
Right	–	1.00 (0.96-1.03)	–
Bilateral	–	0.95 (0.83-1.09)	–
Treatment modality ("no" reference for each treatment type)			
Surgery	0.68 (0.66-0.69)	0.43 (0.41-0.45)	0.77 (0.73-0.82)
Radiotherapy	0.69 (0.68-0.70)	0.72 (0.69-0.75)	0.93 (0.84-1.04)
Chemotherapy	0.74 (0.73-0.76)	0.63 (0.60-0.66)	0.48 (0.46-0.51)

Values are OR (95% CI). [a]Numbers refer to tumor diagnoses (not to patients). [b]Each model is adjusted for all variables listed in the table (excluding screen-detected, because a high proportion were missing). Total numbers are smaller because we excluded any patients with missing observations in the variable included in the model. [c]We grouped age ranges 25 to 34, 35 to 44, and 45 to 54 because of small numbers of observations in the younger age groups for some cancer sites. [d]Income domain of the Index of Multiple Deprivation derived in 2015 was used for patients diagnosed with cancer in 2013, and income domain of the Index of Multiple Deprivation derived in 2019 was used for patients diagnosed with cancer after 2013. [e]5 years before diagnosis and excluding cardiovascular disease.

CVD = cardiovascular disease; other abbreviations as in Table 1.

Continued on the next page

accuracy but does not consider the primary care CVD burden and potential gaps between primary and inpatient care. This may have led to underestimations of CVD prevalence,[60] although HES outpatient has limited diagnosis data, and integrating NICOR data did not substantially alter our results. We did not analyze data on CVD severity, as these data are not captured in HES. We excluded patients with missing data on several variables, which resulted in a large amount of missing data, but we performed a complete

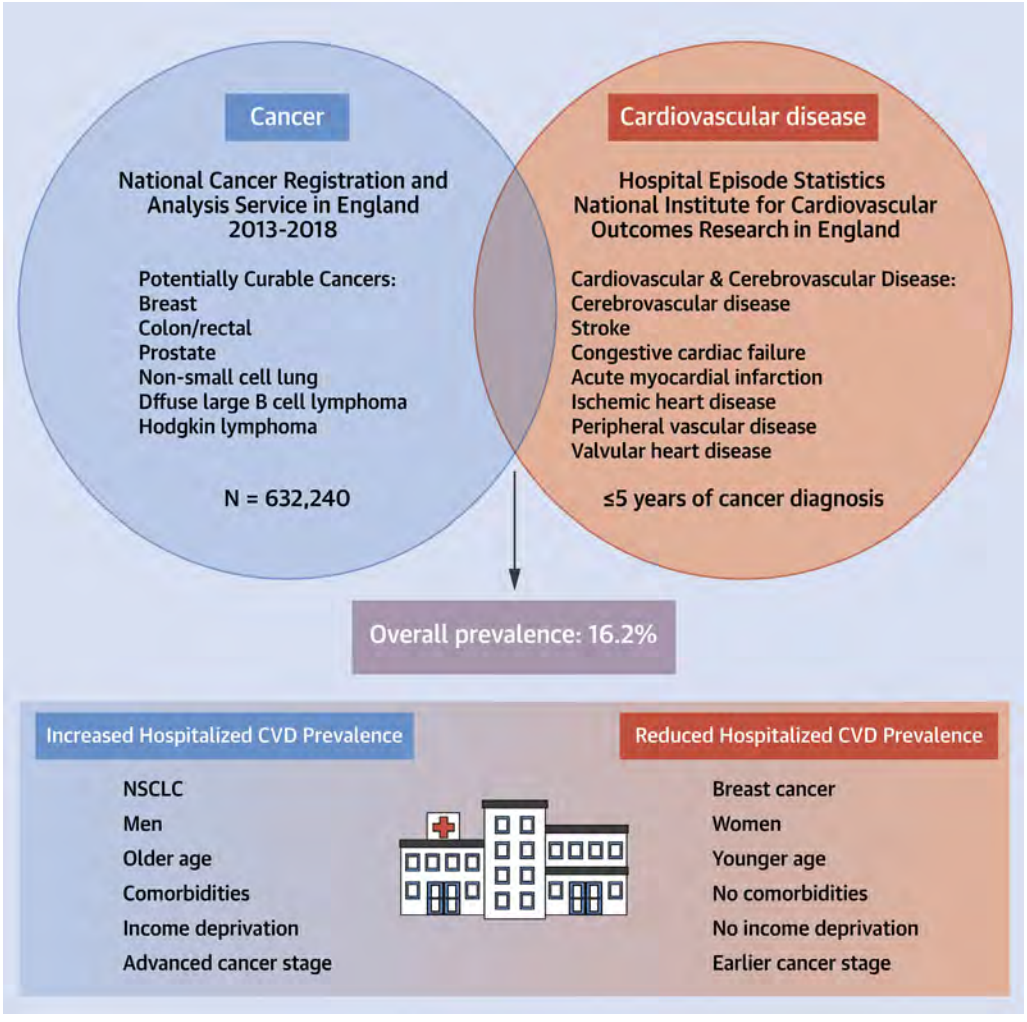
TABLE 3 Continued

Rectal (n = 38,083)	Prostate (n = 162,175)	NSCLC (n = 67,680)	DLBCL (n = 22,564)	Hodgkin Lymphoma (n = 7,724)
6,590	26,607	24,609	5,026	850
0.21 (0.18-0.25)	0.26 (0.23-0.29)	0.24 (0.21-0.27)	0.20 (0.17-0.23)	0.09 (0.07-0.11)
0.54 (0.49-0.59)	0.55 (0.53-0.57)	0.60 (0.57-0.63)	0.56 (0.51-0.63)	0.49 (0.38-0.62)
1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1.72 (1.61-1.85)	1.60 (1.55-1.65)	1.36 (1.30-1.41)	1.68 (1.55-1.82)	1.69 (1.38-2.08)
2.01 (1.83-2.22)	2.42 (2.27-2.57)	1.48 (1.40-1.57)	2.27 (2.03-2.54)	2.18 (1.56-3.05)
1.00 (reference)	–	1.00 (reference)	1.00 (reference)	1.00 (reference)
0.55 (0.52-0.59)	–	0.59 (0.57-0.61)	0.55 (0.51-0.59)	0.55 (0.46-0.65)
1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1.00 (0.59-1.68)	0.84 (0.67-1.06)	0.65 (0.44-0.95)	0.82 (0.43-1.56)	0.21 (0.03-1.58)
1.30 (1.09-1.54)	1.47 (1.35-1.61)	0.91 (0.80-1.03)	1.52 (1.29-1.80)	1.36 (0.98-1.89)
0.81 (0.60-1.10)	0.64 (0.59-0.70)	0.69 (0.57-0.83)	0.70 (0.49-0.99)	0.73 (0.42-1.29)
0.65 (0.46-0.93)	0.84 (0.72-0.97)	0.94 (0.77-1.15)	1.10 (0.80-1.51)	1.14 (0.60-2.17)
1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1.02 (0.94-1.12)	1.11 (1.06-1.15)	1.10 (1.04-1.17)	1.10 (0.99-1.21)	1.08 (0.84-1.41)
1.16 (1.07-1.27)	1.17 (1.13-1.22)	1.16 (1.09-1.23)	1.14 (1.03-1.26)	1.06 (0.82-1.38)
1.38 (1.26-1.51)	1.30 (1.25-1.36)	1.22 (1.16-1.30)	1.28 (1.15-1.42)	1.58 (1.22-2.04)
1.57 (1.43-1.72)	1.59 (1.52-1.66)	1.36 (1.28-1.43)	1.45 (1.30-1.62)	1.74 (1.34-2.27)
1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1.01 (0.91-1.12)	0.94 (0.89-0.99)	1.04 (0.98-1.11)	1.02 (0.89-1.15)	1.14 (0.86-1.52)
1.00 (0.93-1.07)	0.97 (0.94-1.01)	1.03 (0.99-1.07)	1.02 (0.94-1.11)	1.16 (0.95-1.41)
1.00 (0.91-1.10)	0.95 (0.91-1.00)	0.98 (0.93-1.04)	0.97 (0.87-1.09)	1.04 (0.79-1.37)
0.96 (0.87-1.07)	1.02 (0.97-1.07)	1.01 (0.95-1.07)	1.03 (0.92-1.16)	1.27 (0.96-1.68)
1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
0.89 (0.83-0.96)	0.97 (0.94-1.01)	0.89 (0.86-0.93)	0.92 (0.82-1.03)	1.08 (0.81-1.44)
0.86 (0.80-0.93)	1.01 (0.98-1.05)	0.80 (0.77-0.84)	1.06 (0.95-1.19)	1.21 (0.89-1.64)
–	–	–	1.09 (0.99-1.19)	1.33 (1.00-1.78)
–	–	1.00 (reference)	–	–
–	–	1.03 (0.99-1.06)	–	–
–	–	1.02 (0.69-1.51)	–	–
0.62 (0.59-0.66)	0.52 (0.49-0.54)	0.54 (0.51-0.56)	–	–
1.09 (1.03-1.17)	0.87 (0.85-0.90)	0.84 (0.81-0.88)	0.80 (0.74-0.86)	0.71 (0.57-0.90)
0.54 (0.50-0.59)	1.03 (0.96-1.10)	0.55 (0.53-0.58)	0.54 (0.50-0.59)	0.59 (0.48-0.72)

case analysis, which requires a plausible missing-at-random assumption.[61] However, the data we used in our analysis were from 2013, when recording of variables such as cancer stage in NCRD improved to minimize this potential limitation.[62] Moreover, case ascertainment of valve disease may be poor because of inconsistent coding approaches. Additionally, the population included was not racially diverse, and these findings may not be applicable to different geographic areas. We did not investigated the impact, although this will be the primary endpoint of a subsequent study. Finally, we excluded CVD diagnosed after cancer diagnosis to avoid including conditions caused by anticancer treatments.[36]

JACC: CARDIOONCOLOGY, VOL. 4, NO. 2, 2022
JUNE 2022:238–253

CENTRAL ILLUSTRATION Study Design and Key Findings



Battisti NML, et al. J Am Coll Cardiol CardioOnc. 2022;4(2):238–253.

The figure shows the design of the analysis and the key findings. CVD = Cardiovascular Disease; NSCLC = Non-small-cell lung cancer.

CONCLUSIONS

We found significant overlap between CVD and potentially curable cancer diagnoses, along with substantial differences on the basis of age, sex, socioeconomic deprivation, and tumor types (**Central Illustration**). A key feature of our analysis is the use of both cancer registry and CVD audit datasets to elucidate the burden of CVD in cancer cohorts alongside key variables such as comorbidities and Index of Multiple Deprivation. However, further research is needed to investigate the variation in CVD prevalence in patients with cancer. Overall, these results have important implications at 2 levels. At the patient level, for individuals diagnosed with these potentially curable malignancies, the presence of CVD may have a significant impact not only on mortality and treatment benefits and treatment tolerability but also on trial eligibility. On a population level, these findings are important to interpreting overall survival differences, treatment strategies, and outcomes existing within and among countries and to informing health care policy strategies. As part of the Virtual Cardio-Oncology Research Initiative, we plan to evaluate the impact of CVD on the management of these potentially curable malignancies.

ACKNOWLEDGMENTS This project involves data that has been provided by, or derived from patients and collected by the NHS as part of their care and support. The data is collated, maintained and quality assured by the National Cancer Registration and Analysis Service, which is part of Public Health England (PHE) and data has also been provided by the Healthcare Quality Improvement Partnership from the National Cardiac Audit Programme, part of the National Clinical Audit and Patient Outcomes Programme which they commission. Access to the data was facilitated by the PHE Office for Data Release.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This study was funded by a joint research grant from the British Heart Foundation (SP/16/5/32415) and Cancer Research UK (C53325/A21134). The funders did not have any involvement in producing the report. Dr Battisti has received advisory board fees from Pfizer, Abbott and Sanofi; has received travel grants from Exact Sciences, Eli Lilly and Pfizer; and has received speaker fees from Pfizer and Abbvie. Dr Ring has received advisory board and speaker fees from Roche, Novartis, Pfizer, Merck Sharpe & Dohme, AstraZeneca, Seagen, Daiichi Sankyo, and Eli Lilly. Dr Adlam has received research funding and in-kind support from AstraZeneca for unrelated research; has received educational funding from Abbott Vascular to support a clinical research fellow; and has conducted consultancy for General Electric to support general research funds. Mr Sweeting is a full-time employee of AstraZeneca. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr David Adlam, Department of Cardiovascular Sciences, University of Leicester and Leicester National Institute of Health Research Biomedical Research Centre, Glenfield Hospital, Groby Road, Leicester LE3 9QP, United Kingdom. E-mail: da134@leicester.ac.uk. OR Dr Alistair Ring, Breast Unit, Department of Medicine, The Royal Marsden NHS Foundation Trust, Downs Road, Sutton, London SM2 5PT, United Kingdom. E-mail: alistair.ring@rmh.nhs.uk.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: CVD was present in 16.2% of patients with potentially curable malignancies. Male sex, age, and income deprivation were associated with increased CVD prevalence. CVD prevalence was highest for patients with NSCLC and lowest for those with breast cancer.

TRANSLATIONAL OUTLOOK: The overlap between cancer and CVD burden is substantial and may explain cancer treatment patterns and outcomes. Future work is focused on understanding the impact of prevalent CVD on cancer management and the relationships between geography and access to cardio-oncology resources. Understanding the intersection between cancer and CVD is key to informing anticancer treatment decisions, interpreting outcomes, and planning health care provision.

REFERENCES

1. National Cancer Registration and Analysis Service. CancerData. Available at: Accessed May 4, 2022. https://www.cancerdata.nhs.uk

2. Arnold M, Rutherford MJ, Bardot A, et al. Progress in cancer survival, mortality, and incidence in seven high-income countries 1995-2014 (ICBP SURVMARK-2): a population-based study. *Lancet Oncol*. 2019;20:1493–1505.

3. Jones NR, Roalfe AK, Adoki I, Hobbs FDR, Taylor CJ. Survival of patients with chronic heart failure in the community: a systematic review and meta-analysis. *Eur J Heart Fail*. 2019;21:1306–1325.

4. Koene RJ, Prizment AE, Blaes A, Konety SH. Shared risk factors in cardiovascular disease and cancer. *Circulation*. 2016;133:1104–1114.

5. Vincent L, Leedy D, Masri SC, Cheng RK. Cardiovascular disease and cancer: is there increasing overlap? *Curr Oncol Rep*. 2019;21:47.

6. Curigliano G, Cardinale D, Dent S, et al. Cardiotoxicity of anticancer treatments: epidemiology, detection, and management. *CA Cancer J Clin*. 2016;66:309–325.

7. Renzi C, Kaushal A, Emery J, et al. Comorbid chronic diseases and cancer diagnosis: disease-specific effects and underlying mechanisms. *Nat Rev Clin Oncol*. 2019;16:746–761.

8. Blum TG, Rich A, Baldwin D, et al. The European initiative for quality management in lung cancer care. *Eur Respir J*. 2014;43:1254–1277.

9. Iacobucci G. Cancer survival in England: rates improve and variation falls. *BMJ*. 2019;365:l1532.

10. Jones RP, Vauthey JN, Adam R, et al. Effect of specialist decision-making on treatment strategies for colorectal liver metastases. *Br J Surg*. 2012;99:1263–1269.

11. Morris E, Treasure T. Surgical management and outcomes of colorectal cancer liver metastases. *Cancer Epidemiol*. 2018;52:160–161.

12. Royal College of Physicians. National Lung Cancer Audit. Available at: Accessed May 4, 2022. https://www.rcplondon.ac.uk/projects/national-lung-cancer-audit

13. Battisti NML, Wallington M, Ring A, et al. Is age a barrier to chemotherapy? Rates of treatment in older patients with breast, colon or lung cancer in England in 2014: a national registry study. Presented at: Madrid, Spain: European Society for Medical Oncology 2018 Congress; 2018.

14. Ring A, Harder H, Langridge C, Ballinger RS, Fallowfield LJ. Adjuvant chemotherapy in elderly women with breast cancer (AChEW): an observational study identifying MDT perceptions and barriers to decision making. *Ann Oncol*. 2013;24:1211–1219.

15. Allemani C, Matsuda T, Di Carlo V, et al. Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. *Lancet*. 2018;391:1023–1075.

16. Al-Kindi SG, Oliveira GH. Prevalence of preexisting cardiovascular disease in patients with different types of cancer: the unmet need for onco-cardiology. *Mayo Clin Proc*. 2016;91:81–83.

17. Edwards BK, Noone AM, Mariotto AB, et al. Annual report to the nation on the status of cancer, 1975-2010, featuring prevalence of comorbidity and impact on survival among persons with

lung, colorectal, breast, or prostate cancer. *Cancer*. 2014;120:1290–1314.

18. McGale P, Darby SC, Hall P, et al. Incidence of heart disease in 35,000 women treated with radiotherapy for breast cancer in Denmark and Sweden. *Radiother Oncol*. 2011;100:167–175.

19. Zöller B, Ji J, Sundquist J, Sundquist K. Risk of coronary heart disease in patients with cancer: a nationwide follow-up study from Sweden. *Eur J Cancer*. 2012;48:121–128.

20. Sweeting MJ, Oliver-Williams C, Teece L, et al. Data resource profile: the Virtual Cardio-Oncology Research Initiative (VICORI) linking national English cancer registration and cardiovascular audits. *Int J Epidemiol*. 2021;50(6):1768–1779.

21. Henson KE, Elliss-Brookes L, Coupland VH, et al. Data resource profile: National Cancer Registration Dataset in England. *Int J Epidemiol*. 2019;49, 16-16h.

22. Herbert A, Wijlaars L, Zylbersztejn A, Cromwell D, Hardelid P. Data resource profile: Hospital Episode Statistics admitted patient care (HES APC). *Int J Epidemiol*. 2017;46:1093-1093i.

23. National Institute for Cardiovascular Outcomes Research. Home page. Accessed May 4, 2022. https://www.nicor.org.uk

24. Wilkinson C, Weston C, Timmis A, Quinn T, Keys A, Gale CP. The Myocardial Ischaemia National Audit Project (MINAP). *Eur Heart J Qual Care Clin Outcomes*. 2020;6:19–22.

25. National Institute for Cardiovascular Outcomes Research. Adult cardiac surgery (surgery audit). Accessed May 4, 2022. https://www.nicor.org.uk/adult-cardiac-surgery-surgery-audit/

26. National Institute for Cardiovascular Outcomes Research. Adult percutaneous coronary interventions (angioplasty audit). Accessed May 4, 2022. https://www.nicor.org.uk/adult-percutaneous-coronary-interventions-angioplasty-audit/

27. National Institute for Cardiovascular Outcomes Research. Heart failure (heart failure audit). Accessed May 4, 2022. https://www.nicor.org.uk/heart-failure-heart-failure-audit/

28. National Institute for Cardiovascular Outcomes Research. 2018/19 data quality reports for each hospital. Accessed May 4, 2022. https://www.nicor.org.uk/2018-19-data-quality-reports-for-each-hospital/

29. NHS Digital. The processing cycle and HES data quality. Accessed May 4, 2022. https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/hospital-episode-statistics/the-processing-cycle-and-hes-data-quality

30. National Cancer Registration and Analysis Service. National Radiotherapy Dataset (RTDS). Accessed May 4, 2022. http://www.ncin.org.uk/collecting_and_using_data/rtds

31. World Health Organization. *International Statistical Classification of Diseases and Related Health Problems (10th revision)*. Geneva, Switzerland: World Health Organization; 2010.

32. Office for National Statistics. English indices of deprivation. Accessed May 4, 2022. https://www.gov.uk/government/collections/english-indices-of-deprivation

33. Bright CJ, Lawton S, Benson S, et al. Data resource profile: the Systemic Anti-Cancer Therapy (SACT) dataset. *Int J Epidemiol*. 2019;49:15-15l.

34. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373–383.

35. Unger JM, Hershman DL, Fleury ME, Vaidya R. Association of patient comorbid conditions with cancer clinical trial participation. *JAMA Oncol*. 2019;5:326–333.

36. Welch CA, Sweeting MJ, Lambert PC, et al. Impact on survival of modelling increased surgical resection rates in patients with non-small-cell lung cancer and cardiovascular comorbidities: a VICORI study. *Br J Cancer*. 2020;123:471–479.

37. Adlam D, Peake MD. Cancer and heart disease: new bedfellows in the cardiovascular landscape. *Eur Heart J Qual Care Clin Outcomes*. 2017;3:168–170.

38. Koo MM, Swann R, McPhail S, et al. The prevalence of chronic conditions in patients diagnosed with one of 29 common and rarer cancers: a cross-sectional study using primary care data. *Cancer Epidemiol*. 2020;69:101845.

39. Bluethmann SM, Mariotto AB, Rowland JH. Anticipating the "silver tsunami": prevalence trajectories and comorbidity burden among older cancer survivors in the United States. *Cancer Epidemiol Biomarkers Prev*. 2016;25:1029–1036.

40. Savji N, Rockman CB, Skolnick AH, et al. Association between advanced age and vascular disease in different arterial territories: a population database of over 3.6 million subjects. *J Am Coll Cardiol*. 2013;61:1736–1743.

41. Hershman DL, McBride RB, Eisenberger A, Tsai WY, Grann VR, Jacobson JS. Doxorubicin, cardiac risk factors, and cardiac toxicity in elderly patients with diffuse B-cell non-Hodgkin's lymphoma. *J Clin Oncol*. 2008;26:3159–3165.

42. Pinder MC, Duan Z, Goodwin JS, Hortobagyi GN, Giordano SH. Congestive heart failure in older women treated with adjuvant anthracycline chemotherapy for breast cancer. *J Clin Oncol*. 2007;25:3808–3815.

43. Tan-Chiu E, Yothers G, Romond E, et al. Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. *J Clin Oncol*. 2005;23:7811–7819.

44. Perez EA, Suman VJ, Davidson NE, et al. Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the North Central Cancer Treatment Group N9831 adjuvant breast cancer trial. *J Clin Oncol*. 2008;26:1231–1238.

45. Chavez-MacGregor M, Zhang N, Buchholz TA, et al. Trastuzumab-related cardiotoxicity among older patients with breast cancer. *J Clin Oncol*. 2013;31:4222–4228.

46. Zou B, Schuster JP, Niu K, Huang Q, Rühle A, Huber PE. Radiotherapy-induced heart disease: a review of the literature. *Precis Clin Med*. 2019;2:270–282.

47. Oren M, Oren O, Mintzer DM. The use of cardiovascular disease states as exclusion criteria in breast cancer trials: a 4-decade perspective. *J Clin Oncol*. 2017;35:e18053.

48. Bonsu J, Charles L, Guha A, et al. Representation of patients with cardiovascular disease in pivotal cancer clinical trials. *Circulation*. 2019;139:2594–2596.

49. U.S. Food and Drug Administration. Cancer clinical trial eligibility criteria: patients with organ dysfunction or prior or concurrent malignancies. Accessed May 4, 2022. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cancer-clinical-trial-eligibility-criteria-patients-organ-dysfunction-or-prior-or-concurrent

50. D'Agostino RB Sr, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation*. 2008;117:743–753.

51. Yancik R. Cancer burden in the aged: an epidemiologic and demographic overview. *Cancer*. 1997;80:1273–1283.

52. Satariano WA, Ragland DR. The effect of comorbidity on 3-year survival of women with primary breast cancer. *Ann Intern Med*. 1994;120:104–110.

53. Asmis TR, Ding K, Seymour L, et al. Age and comorbidity as independent prognostic factors in the treatment of non small-cell lung cancer: a review of National Cancer Institute of Canada Clinical Trials Group trials. *J Clin Oncol*. 2008;26:54–59.

54. Hines RB, Chatla C, Bumpers HL, et al. Predictive capacity of three comorbidity indices in estimating mortality after surgery for colon cancer. *J Clin Oncol*. 2009;27:4339–4345.

55. Frasci G, Lorusso V, Panza N, et al. Gemcitabine plus vinorelbine versus vinorelbine alone in elderly patients with advanced non-small-cell lung cancer. *J Clin Oncol*. 2000;18:2529–2536.

56. Wu AH, Kurian AW, Kwan ML, et al. Diabetes and other comorbidities in breast cancer survival by race/ethnicity: the California Breast Cancer Survivorship Consortium (CBCSC). *Cancer Epidemiol Biomarkers Prev*. 2015;24:361–368.

57. Forrest LF, Sowden S, Rubin G, White M, Adams J. Socio-economic inequalities in stage at diagnosis, and in time intervals on the lung cancer pathway from first symptom to treatment: systematic review and meta-analysis. *Thorax*. 2017;72:430–436.

58. Exarchakou A, Rachet B, Belot A, Maringe C, Coleman MP. Impact of national cancer policies on

cancer survival trends and socioeconomic inequalities in England, 1996-2013: population based study. *BMJ*. 2018;360:k764.

59. Peake MD. Deprivation, distance and death in lung cancer. *Thorax*. 2015;70:108–109.

60. Herrett E, Shah AD, Boggon R, et al. Completeness and diagnostic validity of recording acute myocardial infarction events in primary care, hospital care, disease registry, and national mortality records: cohort study. *BMJ*. 2013;346:f2350.

61. Carpenter JR, Kenward MG. *Multiple Imputation and Its Application*. Hoboken, New Jersey: John Wiley; 2012.

62. McPhail S, Johnson S, Greenberg D, Peake M, Rous B. Stage at diagnosis and early mortality from cancer in England. *Br J Cancer*. 2015;112(suppl 1):S108–S115.

KEY WORDS breast cancer, colorectal cancer, lung cancer, lymphoma, prostate cancer

APPENDIX For acknowledgments, supplemental tables, a supplemental figure, and references, please see the online version of this paper.

Breast Cancer Research and Treatment (2021) 188:149–163
https://doi.org/10.1007/s10549-021-06192-w

CLINICAL TRIAL

Incidence of cardiotoxicity and validation of the Heart Failure Association-International Cardio-Oncology Society risk stratification tool in patients treated with trastuzumab for HER2-positive early breast cancer

Nicolò Matteo Luca Battisti[1] · Maria Sol Andres[2] · Karla A. Lee[1] · Sivatharshini Ramalingam[2] · Tamsin Nash[1] · Stephanie Mappouridou[1] · Nishanthi Senthivel[1] · Kalaprapa Asavisanu[1] · Mariam Obeid[1] · Elli-Sophia Tripodaki[1] · Vasileios Angelis[1] · Emily Fleming[1] · Emily F. Goode[1] · Susan John[1] · Stuart D. Rosen[2] · Mark Allen[1] · Susannah Stanway[1] · Alexander R. Lyon[2] · Alistair Ring[1]

Received: 17 February 2021 / Accepted: 10 March 2021 / Published online: 5 April 2021

Abstract

Purpose Trastuzumab improves survival in patients with HER2+ early breast cancer. However, cardiotoxicity remains a concern, particularly in the curative setting, and there are limited data on its incidence outside of clinical trials. We retrospectively evaluated the cardiotoxicity rates [left ventricular ejection fraction (LVEF) decline, congestive heart failure (CHF), cardiac death or trastuzumab discontinuation] and assessed the performance of a proposed model to predict cardiotoxicity in routine clinical practice.

Methods Patients receiving curative trastuzumab between 2011 and 2018 were identified. Demographics, treatments, assessments and toxicities were recorded. Fisher's exact test, Chi-squared and logistic regression were used.

Results 931 patients were included in the analysis. Median age was 54 years (range 24–83) and Charlson comorbidity index 0 (0–6), with 195 patients (20.9%) aged 65 or older. 228 (24.5%) were smokers. Anthracyclines were given in 608 (65.3%). Median number of trastuzumab doses was 18 (1–18). The HFA-ICOS cardiovascular risk was low in 401 patients (43.1%), medium in 454 (48.8%), high in 70 (7.5%) and very high in 6 (0.6%). Overall, 155 (16.6%) patients experienced cardiotoxicity: LVEF decline ≥ 10% in 141 (15.1%), falling below 50% in 55 (5.9%), CHF NYHA class II in 42 (4.5%) and class III–IV in 5 (0.5%) and discontinuation due to cardiac reasons in 35 (3.8%). No deaths were observed. Cardiotoxicity rates increased with HFA-ICOS score (14.0% low, 16.7% medium, 30.3% high/very high; $p = 0.002$).

Conclusions Cardiotoxicity was relatively common (16.6%), but symptomatic heart failure on trastuzumab was rare in our cohort. The HFA-ICOS score identifies patients at high risk of cardiotoxicity.

Keywords Breast cancer · Trastuzumab · Cardiotoxicity · Early stage

Introduction

Trastuzumab is a monoclonal antibody targeting the human epidermal growth factor receptor 2 (HER2) and is the standard of care for the management of early-stage and advanced HER2-positive breast cancer [1]. However, treatment with HER2-directed agents is associated with a risk of cardiotoxicity. This most frequently involves an asymptomatic decrease in the left ventricular ejection fraction (LVEF) detected during surveillance before presentation with symptomatic heart failure. Less frequently, rapid development of congestive heart failure (CHF) despite surveillance may develop [2, 3]. Cardiotoxicity associated with anti-HER2 agents is usually reversible with cessation of trastuzumab treatment and cardiac medication, but this may compromise optimal breast cancer treatment [4]. Factors associated with a higher risk of cardiotoxicity in patients receiving trastuzumab include older age, previous or concurrent anthracycline use, pre-existing cardiac dysfunction, pre-existing significant cardiovascular (CV) disease, high body mass

✉ Alistair Ring
alistair.ring@rmh.nhs.uk

Extended author information available on the last page of the article

index (BMI), antihypertensive therapy and, in older patients, diabetes mellitus [5–11].

A metanalysis of adjuvant trials reported a risk of advanced heart failure [New York Heart Association (NYHA) class III-IV] of 0.4–2.5% in patients receiving trastuzumab [12]. Even when anthracyclines are not given, a trial investigating the use of trastuzumab along with taxane-based chemotherapy showed an incidence of cardiotoxicity of 3% although this was severe only in 0.5% of trial participants [13]. In contrast, previous real-world experiences have reported a rate of cardiovascular complications in 10–15% of patients receiving this agent in the curative setting [14].

Age is a predictor of impaired cardiac function with trastuzumab treatment. This is a concern due to the higher burden of comorbidities and increased risk of adverse outcomes in older individuals [15]. Nonetheless, trastuzumab improves survival and reduces risk of recurrence and is otherwise well tolerated in older patients. The rate of cardiac events in a systematic review of randomised studies including data on patients aged over 60 years was 5% [16]. However, the incidence is unclear outside of clinical trials, which tend to recruit patients who are younger, with normal baseline cardiac function and who have a lower burden of comorbidities including pre-existing CV disease.

Therefore, predicting the cardiotoxicity of anti-HER2 agents is of considerable importance. Cardiac risk scores have been developed based on prospective trial [12] and retrospective registry data [14]. However, independent validation is needed before they can be considered for general use. The Heart Failure Association (HFA) of the European Society of Cardiology (ESC) together with the International Cardio-Oncology Society (ICOS) have recently developed a risk stratification tool (HFA-ICOS Risk Tool) to evaluate the likelihood of cardiotoxicity at baseline for patients receiving HER2-directed treatments (Table 1) [17]. In this study we investigated the rates of cardiotoxicity secondary to trastuzumab for early-stage HER2-positive breast cancer in a breast cancer service, comparing rates in older versus younger patients, and assessed the performance of HFA-ICOS cardiovascular risk prediction tool in this population.

Methods

This analysis is a retrospective study of patients who received trastuzumab for HER2-positive early breast cancer (EBC) between 01/01/2011 and 31/12/2018 at the Royal Marsden Hospital NHS Foundation Trust. Eligible patients had curable disease (TNM stages: T1-4, N0-3, M0) and received trastuzumab in the neoadjuvant or adjuvant setting. Patients who received part of the course of treatment elsewhere or those with advanced-stage breast cancer were not eligible for the analysis. This analysis was approved as a service evaluation (SE842) at the Royal Marsden NHS Foundation Trust.

Baseline data collection

Baseline patient characteristics at initiation of trastuzumab were collected and included: date of birth, age at diagnosis, date of last follow-up, date of death, weight, body mass index (BMI), comorbidities, smoking history, obesity, alcohol consumption, concurrent medications, Eastern Cooperative Oncology Group Performance Score (ECOG PS), menopausal status. Specifically, data on CV comorbidities and risk factors were collected and included: diabetes mellitus, hypertension, hypercholesterolemia, coronary artery disease, cerebrovascular disease, peripheral artery disease, heart failure and NYHA classification, rheumatic heart disease, arrhythmias, congenital heart disease, valvular heart disease, cardiomyopathy, aortic aneurysm, thromboembolic disease, pulmonary hypertension, pericardial disease and chronic kidney disease. A non-age adjusted Charlson Comorbidity Index (CCI) was calculated for each patient based on comorbidities at baseline. Specific data on medications relevant to cardiovascular risk were recorded and included: beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, mineralocorticoid receptor blockers, diuretics, digitalis, calcium channel blockers, antiplatelets, anticoagulants and statins. Blood tests results including haemoglobin, white blood count (WBC) and creatinine measurements and LVEF measured on multiple-gated acquisition (MUGA) scan or echocardiogram as per local practice were also recorded at baseline.

Baseline data were collected regarding the primary tumour including: date of diagnosis, histology, grade, ER status and Allred score, PR status and Allred score, HER2 testing method, best stage (i.e. the worst stage between clinical stage and pathological stage), laterality.

Radiotherapy and systemic therapy data were collected. These included use of chemotherapy, anthracyclines, taxanes, platinum compounds, pertuzumab, radiotherapy, endocrine agents, along with setting (adjuvant vs. neoadjuvant), cumulative dose of anthracyclines, number of chemotherapy cycles and number of doses of trastuzumab.

The baseline cardiovascular risk of these patients was classified as low/medium/high/very high based on the recommendations of the HFA-ICOS Risk Tool developed for HER2-targeted agents [17].

Follow-up and outcomes

Data on LVEF from MUGA scan or echocardiogram performed as per National Cancer Research Institute recommendations in the UK [18] until trastuzumab completion or discontinuation were recorded (i.e. baseline, 16 and

Table 1 Heart Failure Association-International Cardio-Oncology Society baseline cardiovascular risk stratification tool for anti-HER2 therapies

Domain class	Risk factor	Score
Previous cardiovascular disease	Heart failure or cardiomyopathy	VERY HIGH
	Myocardial infarction or CABG	HIGH
	Stable angina	HIGH
	Severe valvular heart disease	HIGH
	Baseline LVEF < 50%	HIGH
	Borderline LVEF 50–54%	MEDIUM (2 points)
	Arrhythmia[b]	MEDIUM (2 points)
Cardiac biomarkers (where available)	Elevated baseline troponin[c]	MEDIUM (2 points)
	Elevated baseline BNP or NT-proBNP[c]	MEDIUM (2 points)
Demographic and cardiovascular risk factors	Age ≥ 80 years	HIGH
	Age 65–79 years	MEDIUM (2 points)
	Hypertension[d]	MEDIUM (1 point)
	Diabetes mellitus[e]	MEDIUM (1 point)
	Chronic kidney disease[f]	MEDIUM (1 point)
Current cancer treatment regimen	Includes Anthracycline before HER2-targeted therapy[g]	MEDIUM (1 point)[g]
Previous cardiotoxic cancer treatment	Prior trastuzumab cardiotoxicity	VERY HIGH
	Prior (remote) anthracycline exposure[h]	MEDIUM (2 points)
	Prior radiotherapy to left chest or mediastinum	MEDIUM (2 points)
Lifestyle risk factors	Current smoker or significant smoking history	MEDIUM (1 point)
	Obesity (BMI > 30)	MEDIUM (1 point)

LOW RISK no risk factor OR one MEDIUM[1] risk factor, *MEDIUM RISK* MEDIUM risk factors with a total of 2–4 points, *HIGH RISK* MEDIUM risk factors with a total of ≥ 5 points OR any HIGH risk factor, *VERY HIGH RISK* any VERY HIGH risk factorCABG: coronary artery bypass graft, *BNP* brain natriuretic peptide, *NT-proBNP* N-terminal pro b-type natriuretic peptide, *BMI* body mass index

[a]Baseline cardiac biomarkers have been measured only in 27 patients: elevated troponin has not documented in any patients and elevated BNP or NT-proBNP have been documented in 7 patients (0.75%)

[b]Atrial fibrillation, atrial flutter, ventricular tachycardia or ventricular fibrillation

[c]Elevated above the upper limit of normal for local laboratory reference range

[d]Systolic blood pressure (BP) > 140mmg Hg or diastolic BP > 90 mm Hg, or on treatment

[e]HbA1c > 7.0% or > 53 mmol/mol or on treatment

[f]Estimated glomerular filtration rate < 60 ml/min/1.73m^2

[g]HIGH risk if anthracycline chemotherapy and trastuzumab delivered concurrently

[h]Previous malignancy (not current treatment protocol)

23 weeks for patients receiving taxanes alone and before and after anthracycline use for those receiving sequential chemotherapy regimens). Cardiac adverse outcomes were defined as: death due to cardiac reasons, LVEF decline of ≥ 10%, LVEF decline to below 50%, congestive heart failure (CHF) (NYHA class II and III–IV) and trastuzumab discontinuation (temporary or permanent) due to cardiac toxicity. Reasons for discontinuing trastuzumab not related to cardiotoxicity and management of cardiac events with specialist referrals and medications were also recorded.

Statistical analysis

Analyses were performed in Stata/MP 16.0 [19]. A $p < 0.05$ was considered statistically significant. Baseline patients and breast cancer characteristics were tabulated and compared among age groups (≥ 65 and < 65 years) and HFA-ICOS CV risk groups (low vs. medium vs. high vs. very high) using Chi-squared, Fisher's statistics, two-sample *t* tests and 3-way ANOVA. Similarly, exposure to anticancer treatments was compared among age and HFA-ICOS CV risk groups. An age cut-off of 65 years was used to be consistent with previous analyses [15] and since individuals aged ≥ 65 years were under-represented in the pivotal trials of adjuvant trastuzumab [20]. Baseline LVEF measurements were compared with those at trastuzumab completion in the overall population and according to age group for those patients undergoing a MUGA scan or an echocardiogram at treatment initiation and specifically for those undergoing a baseline echocardiogram.

Cardiac event rates occurring at any time during the course of trastuzumab and subsequent follow-up were

estimated and compared according to age (≥ 65 vs. < 65 years) and HFA-ICOS CV risk (low vs. medium vs. high/very high). These rates were also compared based on menopausal status and use of statins at baseline. Reasons for trastuzumab discontinuation and management of cardiac events were also compared among these patient groups.

Logistical regression was used to calculate the odds of cardiac events based on HFA-ICOS risk category. The performance of the HFA-ICOS Risk Tool to predict cardiotoxicity was evaluated by calculating sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). We also composed receiver-operating characteristic (ROC) curves and calculated the area under the curve for the prediction model.

Results

Population characteristics

Between January 2011 and December 2018, 1094 patients initiated trastuzumab in the curative setting for HER2+ EBC at The Royal Marsden NHS Foundation Trust. The analysis was restricted to 931 patients who completed the entire course of trastuzumab at our Institution for whom cardiac assessments were available (Fig. 1).

Patient characteristics and tumour characteristics are shown in Table 2. No significant differences in patient and tumour characteristics were observed in those aged ≥ 65 years compared with their younger counterparts. Comorbidities and CV risk factors are outlined in Table 3. Patients aged 65 years and older had a higher prevalence of diabetes mellitus, hypertension and hypercholesterolemia compared with the younger patients (< 65 years old). At trastuzumab initiation, a higher proportion of patients aged ≥ 65 years were on cardioprotective medications including beta-blockers, ACE inhibitors, angiotensin receptor blockers and mineralocorticoid receptor blockers [< 65 years: 86/736 (11.7%)]; ≥ 65 years: 60/195 (30.8%); $p = 0.001$] (Table 3).

Of the 931 patients, based on the HFA-ICOS risk stratification tool 401 (43.1%) had a low baseline CV risk, 454 patients (48.8%) were medium-risk, 70 patients (7.5%) were high-risk, and 6 patients (0.6%) were very high-risk.

Treatment characteristics and cardiac assessments

Trastuzumab was given in the adjuvant setting only in 584 patients (62.7%), whereas 347 (37.3%) received trastuzumab neoadjuvantly and continued treatment in the adjuvant setting. The median number of doses given was 18 (range 1–18). The majority of patients received a sequential combination of anthracyclines and taxanes [594 (63.8%)],

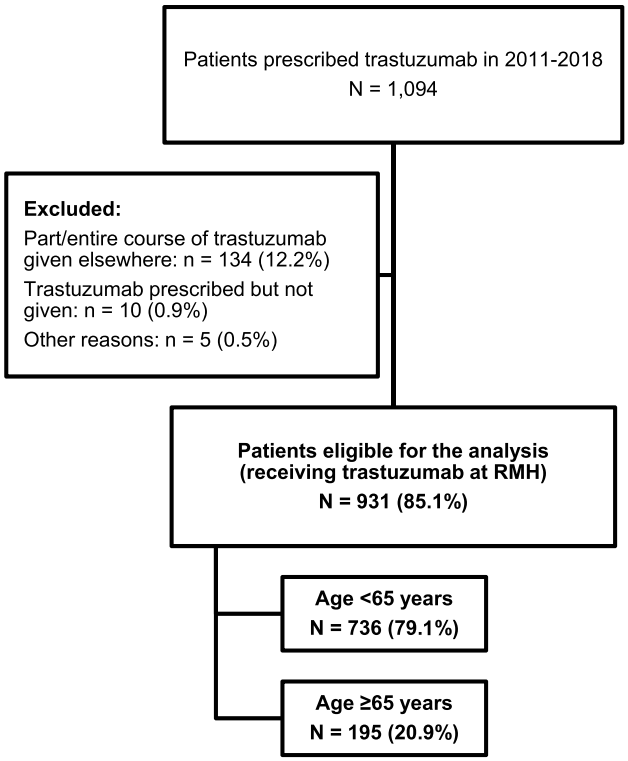


Fig. 1 CONSORT diagram

while 288 (30.9%) received taxanes alone. Pertuzumab was added to trastuzumab in 158 patients (17.0%) and adjuvant radiotherapy was given to 689 patients (74.0%). Among 638 patients with ER-positive disease, tamoxifen was initially prescribed for 379 patients (59.4%) and an aromatase inhibitor for 226 (35.4%).

Table 4 report the treatments given in the overall population and based on age and HFA-ICOS risk category. Anthracyclines were added to a taxane less frequently in older patients [≥ 65 years 68 (34.9%) vs. < 65 years 526 (71.5%); $p = 0.001$] and in those with increasing HFA-ICOS risk score [low 271 (67.6%) vs. medium 291 (64.1%) vs. high 31 (44.3%) vs. very high 1 (16.7%); $p = 0.001$]. Similarly, older patients and those with higher CV risk were more likely to receive trastuzumab only in the adjuvant setting rather than in the neoadjuvant setting.

LVEF at baseline and upon trastuzumab completion in the overall population and according to age group are reported in Fig. 2.

Cardiac events and their management

Cardiac adverse events occurred in 155 patients (16.6%) (Table 5, Fig. 3). No cardiac deaths were observed in this cohort. One hundred and forty-one patients (15.1%) experienced a LVEF decline ≥ 10% and 55 (5.91%) below 50%.

Table 2 Patient and tumour characteristics at baseline in the overall population and according to age group

Characteristics	Overall $N=931$		Age group				p value
			<65 years $N=736$		≥ 65 years $N=195$		
Continuous variables							
Age (years)							
Median	54		50		69		–
IQR	46–63		43–56		67–73		
Mean	54.3		50.0		70.9		
Standard deviation	11.9		9.0		4.6		
Range	24–83		24–64		65–83		
Weight (kg)[a]							
Median	69		69.0		68.8		0.555
IQR	60.8–78.9		60.6–79.0		61.5–77.7		
Mean	71.0		71.3		70.1		
Standard deviation	14.8		15.4		12.4		
Range	42.5–140.0		42.5–140.0		43.7–106.6		
BMI (kg/m^2)[b]							
Median	25.4		25.4		26.7		0.073
IQR	22.7–30.0		22.0–30.0		23.8–30.2		
Mean	26.8		26.7		27.2		
Standard deviation	5.50		5.70		4.7		
Range	15.9–51.8		15.9–51.8		17.3–42.2		
Charlson comorbidity index							
Median	0		0		0		0.259
IQR	0–2		0–0		0–1		
Mean	0.9		0.9		1.0		
Standard deviation	1.1		1.0		1.1		
Range	0–6		0–5		0–6		
	N	%	*N*	%	*N*	%	
Categorical variables							
Sex							
Female	930	99.9	736	100.00	194	99.5	–
Male	1	0.1	0	0.00	1	0.5	–
ECOG PS							
0	826	88.7	679	92.3	147	75.4	0.001
1	102	11.0	57	7.7	45	23.1	0.001
2	3	0.3	0	0.0	3	1.5	0.009
Menopausal status							
Pre/perimenopausal	427	45.9	427	58.0	0	0.0	–
Postmenopausal	504	54.1	309	42.0	195	100.0	0.001
Status (on 13/05/2020)							
Dead	51	5.5	36	4.9	15	7.7	0.155
Alive	880	94.5	700	95.1	180	92.3	–
Previous (remote) use of chemotherapy	45	4.8	35	4.8	10	5.1	0.851
Previous (remote) use of anthracyclines	29	3.1	23	3.1	6	3.1	0.999
Previous (remote) use of trastuzumab	9	1.0	9	1.2	0	0.0	0.217
Histology							
Ductal	885	95.1	706	95.9	179	91.8	0.022
Lobular	38	4.1	25	3.4	13	6.7	0.064
Mixed ductal/lobular	5	0.5	3	0.4	2	1.0	0.282

Table 2 (continued)

	N	%	*N*	%	*N*	%	
Other	2	0.2	1	0.1	1	0.5	0.376
Missing	1	0.1	1	0.1	0	0.0	–
Grade							
1	15	1.6	12	1.6	3	1.5	0.999
2	332	35.7	263	35.7	69	35.4	0.867
3	570	61.2	448	60.9	122	62.6	0.868
Missing	14	1.5	13	1.8	1	0.5	–
ER status							
Negative	293	31.5	226	30.7	67	34.4	0.341
Positive	638	68.5	510	69.3	128	65.6	0.341
PgR status							
Negative	447	48.0	340	46.2	107	54.9	0.017
Positive	452	48.5	373	50.7	79	40.5	0.017
Missing	32	3.4	23	3.1	9	4.6	–
HER2 testing method							
IHC	611	65.6	494	67.1	117	60.0	–
ISH	201	21.6	146	19.9	55	28.2	–
Unknown	119	12.8	96	13.0	23	11.8	–
Best stage[c]							
I	212	22.8	163	22.1	49	25.1	0.386
II	551	59.2	442	60.0	109	55.9	0.324
III	162	17.4	127	17.3	35	17.9	0.831
Missing	6	0.6	4	0.5	2	1.0	–
Laterality							
Right	450	48.3	355	48.2	95	48.7	0.936
Left	467	50.2	370	50.3	97	49.7	0.936
Bilateral[d]	14	1.5	11	1.5	3	1.5	0.999

BMI body mass index, *ECOG PS* Eastern Cooperative Oncology Group Performance Status, *ER* oestrogen receptor, *PgR* progesterone receptor, *HER2* human epidermal growth factor receptor 2, *ISH* in situ hybridisation, *IHC* immunohistochemistry

[a]Recorded in 929/931 patients

[b]Recorded in 928/931 patients

[c]Corresponds to the "worst" stage between clinical stage (for patients receiving neoadjuvant systemic therapy) or pathological stage (for those receiving only adjuvant systemic therapy)

[d]Includes patients with bilateral HER2-positive disease (and not patients with monolateral HER2-positive disease plus contralateral HER2-negative disease)

Forty-seven patients (5.0%) developed symptomatic heart failure. In this cohort, 42 patients (4.5%) had mild symptoms (NYHA class II) and 5 patients (0.5%) had more severe symptomatic heart failure (NYHA class III–IV). No differences in cardiac events were observed based on tumour laterality [right: 71/450 (15.8%); left: 81/467 (17.3%); bilateral: 3/14 (21.5%); $p = 0.726$]. The median time to cardiac toxicity was 19.9 weeks (mean: 21.9 weeks; range: 1–120 weeks).

Trastuzumab was discontinued due to cardiotoxicity in 35 patients (3.76%). No significant differences in cardiotoxicity were seen according to age group.

Table 6 outlines the management of cardiotoxicity events. One hundred and seventeen patients (12.6%) required a referral to a cardiologist provided by a specialist cardio-oncology service. Beta-blockers (preferably carvedilol) were prescribed in 57 patients (6.1%), ACE inhibitors or angiotensin receptor blockers in 99 (10.6%), mineralocorticoid receptor blockers (eplerenone) in 5 patients (0.54%), diuretics in 16 patients (1.7%) and statins were started in 17 patients (1.8%) either by the treating oncologist or by the cardiologist. No significant differences were observed in the management of cardiac events based on age. In the older age group, cardioprotective medications (including beta-blockers, ACE inhibitors, angiotensin receptor blockers or mineralocorticoid receptor blockers) were prescribed in 37 patients out of 39 developing cardiac toxicity (94.9%). The use of cardioprotective medications following this specific toxicity increased with increasing HFA-ICOS risk category.

Table 3 Comorbidities, cardiovascular risk factors and concurrent medications at baseline in the overall population and according to age group

			Overall $N=931$		Age group				p value
					< 65 years $N=736$		≥ 65 years $N=195$		
			N	%	N	%	N	%	
Comorbidities and cardiovascular risk factors									
Diabetes mellitus			44	4.7	28	3.8	16	8.2	0.014
Hypertension			176	18.9	96	13.0	80	41.0	0.001
Hypercholesterolemia			91	9.8	44	6.0	47	24.1	0.001
Coronary artery disease			12	1.3	5	0.7	7	3.6	0.005
Cerebrovascular disease			4	0.4	2	0.2	2	1.0	0.195
Peripheral artery disease			1	0.1	0	0.0	1	0.5	0.209
Heart failure	Overall		2	0.21	1	0.14	1	0.51	0.375
	NYHA class	1	1	0.11	1	0.14	0	0.00	–
		3	1	0.11	0	0.00	1	0.51	–
Rheumatic heart disease			1	0.1	1	0.1	0	0.0	0.999
Abnormal heart rhythm			23	2.5	12	1.6	11	5.6	0.003
Congenital heart disease			7	0.7	5	0.7	2	1.0	0.641
Valvular heart disease			9	1.0	6	0.8	3	1.5	0.406
Cardiomyopathy			4	0.4	4	0.5	0	0.0	0.585
Aortic aneurysm			1	0.1	0	0.0	1	0.5	0.209
Thromboembolic disease			9	01.0	7	0.9	2	1.0	0.999
Venous thromboembolism			6	0.6	5	0.7	1	0.5	0.999
Pulmonary hypertension			1	0.1	0	0.0	1	0.5	0.209
Pericardial disease			1	0.1	1	0.1	0	0.0	0.999
Chronic kidney disease			5	0.5	3	0.4	2	1.0	0.282
Cigarette smoking									
Overall			228	24.5	179	24.3	49	24.5	0.851
Current			42	4.5	38	5.2	4	2.0	–
Past			186	20.0	141	19.2	45	23.1	–
Regular alcohol consumption			385	41.3	299	40.6	86	44.1	0.414
Concurrent medications									
Cardioprotective medications[a]			146	15.7	86	11.7	60	30.8	0.001
Beta-blockers			54	5.8	30	4.1	24	12.3	0.001
ACE inhibitors			77	8.3	47	6.4	30	15.4	0.001
Angiotensin receptor blockers			38	4.1	18	2.4	20	10.3	0.001
Mineralocorticoid receptor blockers			1	0.1	0	0.0	1	0.5	0.209

Table 3 (continued)

	Overall $N=931$		Age group				p value
			< 65 years $N=736$		≥ 65 years $N=195$		
	N	%	N	%	N	%	
Diuretics	50	5.4	25	3.4	25	12.8	0.001
Digitalis	3	0.3	1	0.1	2	1.0	0.113
Calcium channel blockers	82	8.8	46	6.2	36	18.5	0.001
Antiplatelets	33	3.5	20	2.7	13	6.7	0.014
Anticoagulants	12	1.3	7	0.9	5	2.6	0.143
Statins	83	8.9	38	5.2	45	23.1	0.001

NYHA New York Heart Association, *ACE* angiotensin-converting enzyme

[a]Cardioprotective medications include beta-blockers, ACE inhibitors, angiotensin receptor blockers and mineralocorticoid receptor blockers

Performance of the HFA-ICOS risk prediction model

Increasing CV risk based on the HFA-ICOS category correlated with increasing rates of cardiac events on trastuzumab: the overall rates of cardiotoxicity was 14.0% in patients classified as low risk versus 16.7% with medium risk versus 30.3% classified as baseline as high or very high risk ($p=0.002$) (Fig. 4).

The HFA-ICOS score also correlated with increasing rates of cardiac toxicity: 7.6% for low-risk patients with a score of 0 ($n=66$); 15.2% for low-risk patients with a score of 1 ($n=335$); 16.0% for medium-risk patients with a score of 2 ($n=263$); 18.3% for medium-risk patients with a score of 3 ($n=120$); 16.9% for medium-risk patients with a score of 4 ($n=71$); 30.3% for high- to very high-risk patients with a score ≥ 5 ($n=76$) ($p=0.0147$) (Fig. 5).

The HFA-ICOS Risk Tool had a sensitivity of 14.8%, a specificity of 93.2%, a PPV of 30.3% and a NPV of 84.6% when predicting any cardiac event on trastuzumab in patients classified as low/medium risk versus those classified as high/very high risk. Area under the ROC curve for the predictive model for any cardiac toxicity was 0.56.

Discussion

This is a large retrospective single-centre study analysing cardiotoxicity incidence and outcomes for patients receiving trastuzumab for curable HER2-positive breast cancer, with a particular focus on outcomes for the older age group and according to baseline HFA-ICOS Risk. A significant proportion of these patients (43.1%) had a low cardiovascular risk profile based on the HFA-ICOS assessment tool. Nonetheless, more than a half had medium, high or very high risk and establishing the rates of cardiotoxicity in the real world is crucial especially in the curative setting.

A key result of our analysis is that the incidence of clinically serious symptomatic heart failure in patients receiving curative trastuzumab outside clinical trials is low (5.0%), with no fatal cardiotoxicity, although various degrees of cardiac toxicity may occur in up to 16.6% of patients on this treatment. These results are comparable to a recent pooled analysis of the trastuzumab registration trials which showed a small to modest risk of cardiotoxicity ranging between 5.5 and 19.4% [20]. The importance of this analysis is that it includes a real-world population of patients not enrolled in clinic trials and therefore may be particularly useful to inform routine clinical practice.

Benchmarking the incidence of cardiac events for patients receiving trastuzumab in the curative setting is also important in the context of the studies investigating de-escalation strategies. In our series one third of patients received taxanes alone and in a similar population with node-negative EBC,

Table 4 Treatment characteristics and exposure in the overall population and according to age and HFA/ICOS risk group

Treatment characteristics	Category	Overall $N=931$		Age group				p value	HFA-ICOS risk group								p value
				< 65 years $N=736$		≥ 65 years $N=195$			Low $N=401$		Medium $N=454$		High $N=70$		Very high $N=6$		
		N	%	*N*	%	*N*	%		*N*	%	*N*	%	*N*	%	*N*	%	
Concurrent chemotherapy	No chemotherapy	10	1.1	7	0.9	3	1.5	0.445	3	0.7	6	1.3	0	0.0	1	16.7	0.002
	Anthracycline + taxanes	594	63.8	526	71.5	68	34.9	0.001	271	67.6	291	64.1	31	44.3	1	16.7	0.001
	Taxanes alone	288	30.9	174	23.6	114	58.5	0.001	111	27.7	141	31.1	33	47.1	3	50.0	0.001
	Anthracyclines alone	14	1.5	13	1.8	1	0.5	0.323	6	1.5	8	1.8	0	0.0	0	0.0	0.714
	Including carboplatin	29	3.1	25	3.4	4	2.0	0.486	12	3.0	14	3.1	2	2.9	1	16.7	0.297
	Other regimen	25	2.7	16	2.2	9	4.6	0.078	10	2.5	8	1.8	6	8.6	1	16.7	0.002
Epirubicin dose ≥ 450 mg/m^2		21	2.3	18	2.4	3	1.5	0.721	6	2.2	13	4.3	2	6.2	0	0.0	0.416
Pertuzumab use		158	17.0	143	19.4	15	7.7	0.001	74	18.4	74	16.3	9	12.9	1	16.7	0.657
Setting	Adjuvant only	584	62.7	434	59.0	150	76.9	0.001	235	58.6	291	64.1	54	77.1	4	66.7	0.023
	Neoadjuvant + adjuvant	347	37.3	302	41.0	45	23.1	0.001	166	41.4	163	35.9	16	22.9	2	33.3	0.023
Radiotherapy use	No	242	26.0	179	24.3	63	32.3	0.027	106	26.4	111	24.4	24	34.3	1	16.7	0.337
	Yes	689	74.0	557	75.7	132	67.7	0.027	295	73.6	343	75.5	46	65.7	5	83.3	0.337
Endocrine therapy	No endocrine therapy	326	35.0	255	34.6	71	36.4	0.673	125	31.2	176	38.8	24	34.3	1	16.7	0.097
	Tamoxifen[a]	379	40.7	338	45.9	41	21.0	0.001	212	52.9	149	32.8	14	20.0	4	66.7	0.001
	Aromatase inhibitor[a]	226	24.3	143	19.4	83	42.6	0.001	64	16.0	129	28.4	32	45.7	1	16.7	0.001
Chemotherapy cycles	Median	6		6		4		0.001	6		6		5		5		0.001
	IQR	4–8		4–8		4–6			4–8		4–8		4–6		4–6		
	Mean	5.9		6.2		4.9			6.1		5.9		5.1		4.7		
	SD	1.9		1.8		2.0			1.9		1.9		2.0		2.7		
	Range	0–10		0–10		0–10			0–10		0–10		1–8		0–8		
Epirubicin cumulative dose (mg/m^2)[b]	Median	360		360		360		0.798	360		360		360		360		0.852
	IQR	300–360		300–360		300–360			300–360		300–360		300–360		360–360		
	Mean	333.4		333.1		335.4			329.7		336.0		338.9		360.0		
	SD	67.8		67.7		69.6			61.5		73.4		66.7		0.0		
	Range	90–600		90–600		90–600			90–600		90–600		180–600		360–360		
Trastuzumab doses	Median	18		18		18		0.001	18		18		18		18		0.193
	IQR	18–18		18–18		17–18			18–18		18–18		17–18		14–18		
	Mean	17.3		17.5		16.8			17.6		17.3		16.4		15.0		
	SD	2.1		1.7		3.1			1.4		2.2		3.7		5.6		
	Range	1–18		3–18		1–18			3–18		1–18		4–18		4–18		

[a]Initial choice of endocrine agent (regardless of subsequent changes based on menopausal status and tolerance)

[b]Two patients who received doxorubicin instead of epirubicin have been excluded from this analysis

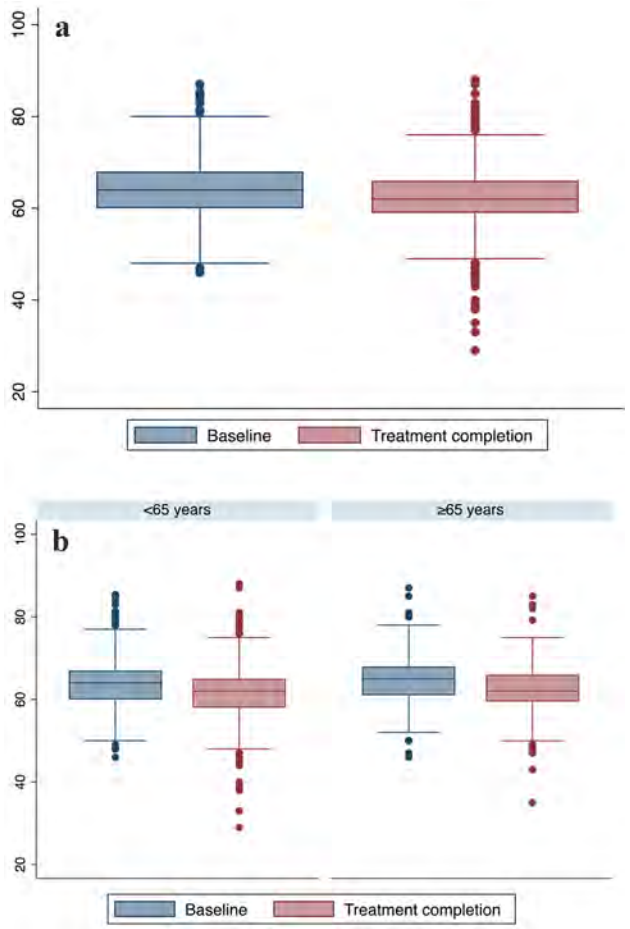


Fig. 2 Left ventricular ejection fraction at baseline and upon trastuzumab completion in the overall population (**a**) and according to age group (**b**)

the APT study reported even lower rates of cardiac toxicity, with 0.5% of patients experiencing grade 3 left ventricular systolic dysfunction and 3% reporting asymptomatic LVEF decline [13]. In our series only 3.8% of patients did not complete a full one-year course of trastuzumab due to cardiac toxicity. The PERSEPHONE study suggested non-inferior efficacy of 6 months of treatment compared with 12 months along with a substantial reduction in cardiac events from 12 to 9% [21].

This study suggests that there are no differences in the rates of cardiac adverse events according to age. This is consistent with previous analyses showing that most patients aged ≥ 66 years are able to complete a one-year course of trastuzumab without complications [22], although comorbidities remain critical in determining the risk of cardiotoxicity [23]. One variable that may explain the lack of effect of age alone is the rate of anthracycline chemotherapy which was significantly lower in the patients ≥ 65 years (34.9%) versus the younger patients < 65 years (71.5%). Therefore, the increased risk portended by increasing age may be balanced by the higher anthracycline chemotherapy use in the younger patients.

Our analysis also included a substantial proportion of patients with medium/high cardiovascular risk (56.9%). The registration trials of trastuzumab mandated stringent cardiac monitoring, limited the cumulative dose of anthracyclines to 300 mg/m^2 and excluded subjects with abnormal baseline cardiac function. This consideration makes real-world experiences useful since the risk of cardiac toxicity on trastuzumab varies according to the use of previous chemotherapy, pre-existing heart disease and cardiovascular risk factors [24]. Therefore, identifying the baseline

Table 5 Rates of cardiac events at any time following trastuzumab initiation in the overall population and according to age group and HFA-ICOS risk group

Cardiac events[a]	Overall *N* = 931		Age group				*p* value	HFA-ICOS risk category								*p* value
			< 65 years *N* = 736		≥ 65 years *N* = 195			Low *N* = 401		Medium *N* = 454		High *N* = 70		Very high *N* = 6		
	N	%	*N*	%	*N*	%		*N*	%	*N*	%	*N*	%	*N*	%	
Overall	155	16.6	116	15.8	39	20.0	0.161	56	14.0	76	16.7	20	28.57	3	50.0	0.003
LVEF decline ≥ 10%	141	15.1	106	14.4	35	17.9	0.218	51	12	70	15.42	17	24.3	3	50.0	0.007
LVEF decline below 50%	55	5.9	43	5.8	12	6.1	0.865	18	4.5	29	6.4	6	8.6	2	33.3	0.014
CHF																
NYHA class II	42	4.5	34	4.6	8	4.1	0.757	12	3.0	24	5.3	4	5.7	2	33.3	0.002
NYHA class III–IV	5	0.5	3	0.4	2	1.0	0.294	0	0.0	4	0.9	1	1.4	0	0.0	0.236
Trastuzumab discontinuation due to cardiotoxicity																
Overall	35	3.8	26	3.5	9	4.6	0.040	9	2.2	17	3.7	7	10.0	2	33.3	0.001
Temporary	23	2.5	18	2.4	5	2.6	0.999	5	1.2	12	2.6	4	5.7	2	33.3	0.001
Permanent	12	1.3	8	1.1	4	2.0	0.289	4	1.0	5	1.1	3	4.3	0	0.0	0.144

LVEF left ventricular ejection fraction, *CHF* congestive heart failure, *NYHA* New York Heart Association

[a]Cardiac event categories are not mutually exclusive (e.g. patients may have had a LVEF decline > 10% AND below 50%)

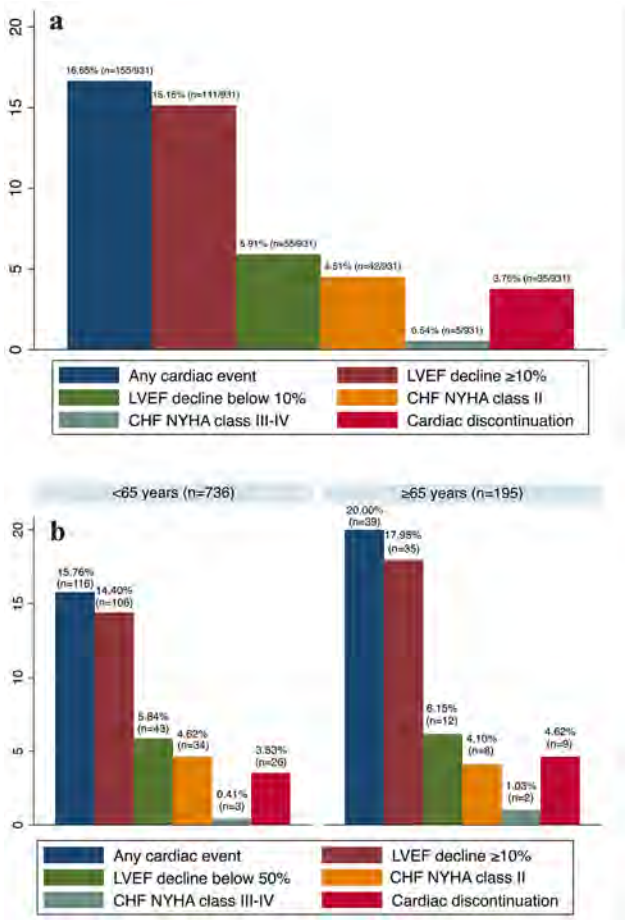


Fig. 3 Rates of cardiac events at any time following trastuzumab initiation in the overall population (**a**) and according to age group (**b**). *LVEF* left ventricular ejection fraction, *CHF* congestive heart failure, *NYHA* New York Heart Association

cardiovascular risk and developing prediction models able to identify those patients at higher risk of experiencing cardiac events remains particularly valuable [17].

The HFA-ICOS risk score had a good correlation with the incidence of cardiotoxicity in our analysis, with 30.3% of patients with a high- to very high-risk score experiencing any cardiac event compared with 16.7% of those with medium risk and 14.0% of those with low risk. We documented a similar pattern also for specific types of cardiac adverse events, including LVEF decline, CHF and trastuzumab discontinuations. Importantly, the HFA-ICOS score had a high NPV (86.0%) which is highly desirable to identify those patients who are not at lower risk of cardiac toxicity in this setting. The score did not discriminate between the low and medium-risk cohorts who had similar event rates and did not identify the cohort at absolute low risk (< 5%). In practical terms the low sensitivity of the HFA-ICOS score would suggest that this should not be used to de-escalate cardiac monitoring in patients with lower cardiovascular risk (as a 14% risk of cardiovascular events is still an appreciable rate in a curative setting). On the other hand, our findings might imply that enhanced monitoring (for example involving natriuretic peptides measurements, blood pressure control and earlier cardiology reviews if indicated) could be an appropriate strategy in those deemed at higher risk of cardiac toxicity. These findings would benefit from prospective validation in a larger cohort of patients.

This study has a number of limitations. At our institution, the measurement of cardiac biomarkers such as troponin and natriuretic peptides is not routine practice; therefore, despite their desirability where available [17], they have not been included in the model. In this series, baseline cardiac assessments involved either MUGA scans or echocardiograms to measure LVEF which may have introduced bias. Measuring the global longitudinal strain (GLS) using speckle tracking echocardiography has become standard practice in our hospital only since 2016 and therefore this parameter has not been captured in our cohort. GLS has recently emerged as a new marker of subclinical ventricular dysfunction demonstrating a stronger association with prognosis compared with LVEF in patients with cardiac conditions not related to cancer [25]. Various observational studies suggested its potential role accurately to predict the cardiotoxicity of anticancer agents and guide cardioprotective treatment [26, 27]. Our analysis is retrospective and therefore may be subject to selection bias as we included patients who were deemed fit to receive trastuzumab. Finally, excluding patients who did not receive a full course of trastuzumab at our institution may have also contributed to selection bias.

This analysis has some major strengths as well. We have demonstrated within a large cohort that overall rates of serious cardiotoxicity associated with trastuzumab are low, but absolute rate of all cardiotoxicity is clinically significant (16.6%), and dependent on the individual cardiovascular risk profile at baseline. Our study provides evidence that rates of cardiotoxicity on trastuzumab do not differ based on age in a real-world population. Furthermore, we have included patients receiving contemporary chemotherapy and targeted treatment regimens which make our findings applicable to current practice. Our study fills a gap of knowledge by providing evidence of external validation of a prediction model of cardiac toxicity in a population receiving treatment with substantial chances of cure [1]. This aspect is particularly valuable in the older patient population where competing risks of morbidity and mortality are more relevant.

These data should be considered when discussing risks and benefits of trastuzumab in older patients with HER2-positive EBC and prospective validation of the use of the HFA-ICOS Risk Tool is warranted.

Table 6 Management of trastuzumab-related cardiac toxicity in the overall population and according to age group and HFA-ICOS risk group

Variable	Category	Overall $N=931$		Age group				p value	HFA-ICOS risk group								p value
				< 65 years $N=736$		≥ 65 years $N=195$			Low $N=401$		Medium $N=454$		High $N=70$		Very high N=6		
		N	%	N	%	N	%		N	%	N	%	N	%	N	%	
Referral to cardiologist		166	17.8	129	17.5	37	19.0	0.674	54	13.5	86	18.9	20	28.6	6	100.0	0.001
Referral	Baseline	49	5.2	33	4.5	16	8.2	0.047	13	3.2	21	4.6	11	15.7	4	66.7	0.001
	Reactive[a]	117	12.6	96	13.0	21	10.8	0.466	41	10.2	65	14.3	9	12.9	2	33.3	0.131
Medications prescribed	Beta-blocker	57	6.1	42	5.7	15	7.7	0.314	11	2.7	38	8.4	7	10.0	1	16.7	0.002
	ACE inhibitor	81	8.7	63	8.6	18	9.2	0.775	25	6.2	41	9.0	12	17.1	3	50.0	0.001
	Angiotensin receptor blocker	18	1.9	14	1.9	4	2.0	0.778	6	1.5	10	2.2	2	2.9	0	0.0	0.799
	Mineralocorticoid receptor blocker	5	0.5	5	0.7	0	0.0	0.590	1	0.2	4	0.9	0	0.0	0	0.0	0.565
	Diuretic	16	1.7	13	1.8	3	1.5	0.999	1	0.2	14	3.1	1	1.4	0	0.0	0.016
	Ivabradine	3	0.3	3	0.4	0	0.0	0.999	1	0.2	2	0.4	0	0.0	0	0.0	0.917
	Digitalis	2	0.2	1	0.1	1	0.5	0.375	0	0.0	0	0.0	1	1.4	1	16.7	0.001
	Calcium channel blocker	4	0.4	3	0.4	1	0.5	0.999	0	0.0	2	0.4	2	2.9	0	0.0	0.010
	Antiplatelets	17	1.8	12	1.6	5	2.6	0.373	3	0.7	10	2.2	4	5.7	0	0.0	0.030
	Anticoagulants	8	0.9	3	0.4	5	2.6	0.012	0	0.0	6	1.3	2	2.9	0	0.0	0.047
	Statins	17	1.8	10	1.4	7	3.6	0.063	1	0.2	11	2.4	5	7.1	0	0.0	0.001

[a]Reactive referrals due to cardiac reasons

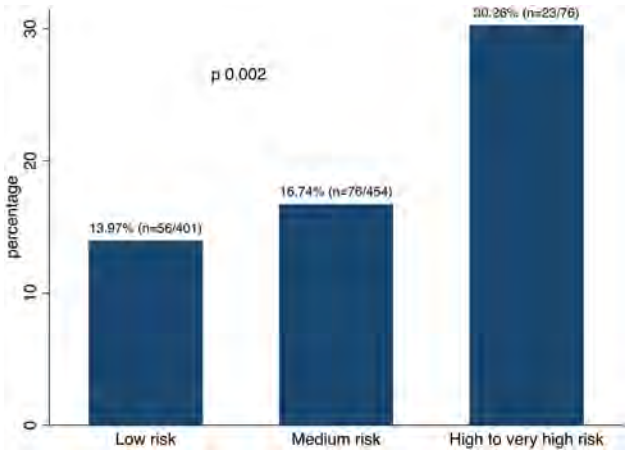


Fig. 4 Rates of overall cardiac events by HFA-ICOS risk category

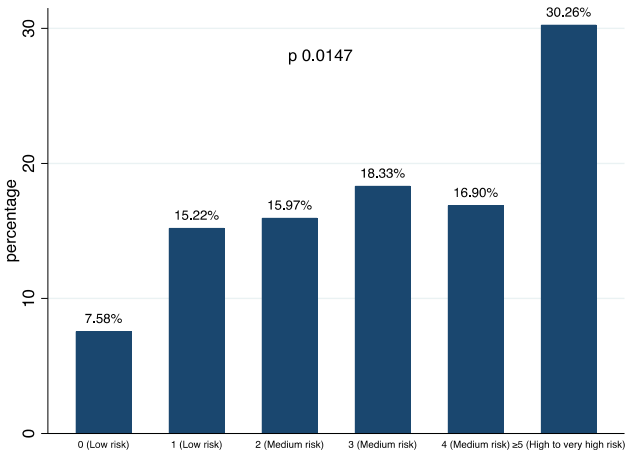


Fig. 5 Rates of overall cardiac events by HFA-ICOS risk score

Acknowledgements The authors wish to acknowledge the support of the Royal Marsden NIHR Biomedical Research Centre for Cancer and The Cridlan Ross Smith Charitable Trust. ARL is supported by the Leducq Transatlantic Cardio-Oncology Network.

Author contributions NMLB, MA, ARL and AR conceived and designed the analysis. NMLB, KAL, TN, SM, NS, KA, MO, EST, VA, EF, EFG, SJ collected the data. NMLB performed the analysis. NMLB, MSA, KAL, SR, TN, SM, NS, KA, MO, EST, VA, EF, EFG, SJ, SDR, MA, SS, ARL and AR wrote the paper.

Funding Dr. Battisti is supported by a fellowship of The Cridlan Ross Smith Charitable Trust. Dr. Battisti and Dr. Ring wish to acknowledge the support of The Royal Marsden NIHR Biomedical Research Centre for Cancer. Dr. Tripodaki is funded by a scholarship from the Hellenic Society of Clinical Oncology (HESMO). The remaining authors have no funding to report.

Data availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Code availability The statistical analysis code generated during the current study is available from the corresponding author on reasonable request.

Declarations

Conflict of interest Dr. Battisti has received travel grants from Genomic Health and Pfizer and speaker fees from Pfizer and AbbVie. Dr. Lyon has received speaker, advisory board or consultancy fees and/or research grants from Pfizer, Novartis, Servier, Astra Zeneca, Bristol Myers Squibb, GSK, Amgen, Takeda, Roche, Janssens-Cilag Ltd, Clinigen Group, Eli Lily, Eisai Ltd, Ferring Pharmaceuticals, Boehringer Ingelheim, Akcea Therapeutics, Myocardial Solutions, iO-WNA Health and Heartfelt Technologies Ltd. Dr. Ring has received advisory board and speaker fees from Roche, Novartis, Pfizer, MSD and Lilly. Dr. Andres, Dr. Lee, Dr Ramalingam, Dr. Nash, Dr Mappouridou, Dr. Senthivel, Dr. Asavisanu, Dr. Obeid, Dr. Tripodaki, Dr. Angelis, Dr. Fleming, Dr. Goode, Dr. John, Professor Rosen, Dr. Allen, Dr. Stanway have no conflicts of interest.

Ethical approval This analysis was approved as a Service Evaluation by The Committee for Clinical Review of The Royal Marsden NHS Foundation Trust.

Informed consent No individual person's data are included in the manuscript in any form and therefore no consents for publication were required.

References

1. Hayes DF (2019) HER2 and breast cancer: a phenomenal success story. N Engl J Med 381(13):1284–1286
2. Perez EA, Rodeheffer R (2004) Clinical cardiac tolerability of trastuzumab. J Clin Oncol 22(2):322–329
3. Keefe DL (2002) Trastuzumab-associated cardiotoxicity. Cancer 95(7):1592–1600
4. Eiger D, Pondé NF, Agbor-Tarh D, Moreno-Aspitia A, Piccart M, Hilbers FS et al (2020) Long-term cardiac outcomes of patients with HER2-positive breast cancer treated in the adjuvant lapatinib and/or trastuzumab Treatment Optimization Trial. Br J Cancer 122(10):1453–1460
5. Bowles EJ, Wellman R, Feigelson HS, Onitilo AA, Freedman AN, Delate T et al (2012) Risk of heart failure in breast cancer patients after anthracycline and trastuzumab treatment: a retrospective cohort study. J Natl Cancer Inst 104(17):1293–1305
6. Ewer SM, Ewer MS (2008) Cardiotoxicity profile of trastuzumab. Drug Saf 31(6):459–467
7. Guenancia C, Lefebvre A, Cardinale D, Yu AF, Ladoire S, Ghiringhelli F et al (2016) Obesity as a risk factor for anthracyclines and trastuzumab cardiotoxicity in breast cancer: a systematic review and meta-analysis. J Clin Oncol 34(26):3157–3165
8. Romond EH, Jeong JH, Rastogi P, Swain SM, Geyer CE Jr, Ewer MS et al (2012) Seven-year follow-up assessment of cardiac function in NSABP B-31, a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel (ACP) with ACP plus trastuzumab as adjuvant therapy for patients with node-positive, human epidermal growth factor receptor 2-positive breast cancer. J Clin Oncol 30(31):3792–3799
9. Russell SD, Blackwell KL, Lawrence J, Pippen JE Jr, Roe MT, Wood F et al (2010) Independent adjudication of symptomatic heart failure with the use of doxorubicin and cyclophosphamide followed by trastuzumab adjuvant therapy: a combined review

of cardiac data from the National Surgical Adjuvant breast and Bowel Project B-31 and the North Central Cancer Treatment Group N9831 clinical trials. J Clin Oncol 28(21):3416–3421
10. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A et al (2001) Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 344(11):783–792
11. Suter TM, Procter M, van Veldhuisen DJ, Muscholl M, Bergh J, Carlomagno C et al (2007) Trastuzumab-associated cardiac adverse effects in the herceptin adjuvant trial. J Clin Oncol 25(25):3859–3865
12. Moja L, Tagliabue L, Balduzzi S, Parmelli E, Pistotti V, Guarneri V et al (2012) (2012) Trastuzumab containing regimens for early breast cancer. Cochrane Database Syst Rev. 4:Cd006243
13. Dang C, Guo H, Najita J, Yardley D, Marcom K, Albain K et al (2016) Cardiac outcomes of patients receiving adjuvant weekly paclitaxel and trastuzumab for node-negative, ERBB2-positive breast cancer. JAMA Oncol 2(1):29–36
14. Tarantini L, Cioffi G, Gori S, Tuccia F, Boccardi L, Bovelli D et al (2012) Trastuzumab adjuvant chemotherapy and cardiotoxicity in real-world women with breast cancer. J Card Fail 18(2):113–119
15. Reeder-Hayes KE, Meyer AM, Hinton SP, Meng K, Carey LA, Dusetzina SB (2017) Comparative toxicity and effectiveness of trastuzumab-based chemotherapy regimens in older women with early-stage breast cancer. J Clin Oncol 35(29):3298–3305
16. Brollo J, Curigliano G, Disalvatore D, Marrone BF, Criscitiello C, Bagnardi V et al (2013) Adjuvant trastuzumab in elderly with HER-2 positive breast cancer: a systematic review of randomized controlled trials. Cancer Treat Rev 39(1):44–50
17. Lyon AR, Dent S, Stanway S, Earl H, Brezden-Masley C, Cohen-Solal A et al (2020) Baseline cardiovascular risk assessment in cancer patients scheduled to receive cardiotoxic cancer therapies: a position statement and new risk assessment tools from the Cardio-Oncology Study Group of the Heart Failure Association of the European Society of Cardiology in collaboration with the International Cardio-Oncology Society. Eur J Heart Fail. https://doi.org/10.1002/ejhf.1920
18. Jones AL, Barlow M, Barrett-Lee PJ, Canney PA, Gilmour IM, Robb SD et al (2009) Management of cardiac health in trastuzumab-treated patients with breast cancer: updated United Kingdom National Cancer Research Institute recommendations for monitoring. Br J Cancer 100(5):684–692
19. StataCorp. (2019) Stata statistical software: release 16. StataCorp, College Station
20. de Azambuja E, Ponde N, Procter M, Rastogi P, Cecchini RS, Lambertini M et al (2020) A pooled analysis of the cardiac events in the trastuzumab adjuvant trials. Breast Cancer Res Treat 179(1):161–171
21. Earl HM, Hiller L, Vallier AL, Loi S, McAdam K, Hughes-Davies L et al (2019) 6 versus 12 months of adjuvant trastuzumab for HER2-positive early breast cancer (PERSEPHONE): 4-year disease-free survival results of a randomised phase 3 non-inferiority trial. Lancet 393(10191):2599–2612
22. Vaz-Luis I, Keating NL, Lin NU, Lii H, Winer EP, Freedman RA (2014) Duration and toxicity of adjuvant trastuzumab in older patients with early-stage breast cancer: a population-based study. J Clin Oncol 32(9):927–934
23. Serrano C, Cortés J, De Mattos-Arruda L, Bellet M, Gómez P, Saura C et al (2012) Trastuzumab-related cardiotoxicity in the elderly: a role for cardiovascular risk factors. Ann Oncol 23(4):897–902
24. Henry ML, Niu J, Zhang N, Giordano SH, Chavez-MacGregor M (2018) Cardiotoxicity and cardiac monitoring among chemotherapy-treated breast cancer patients. JACC Cardiovasc Imaging 11(8):1084–1093
25. Laufer-Perl M, Gilon D, Kapusta L, Iakobishvili Z (2021) The Role of speckle strain echocardiography in the diagnosis of early subclinical cardiac injury in cancer patients-is there more than just left ventricle global longitudinal strain? J Clin Med. 10(1):154
26. Čelutkienė J, Pudil R, López-Fernández T, Grapsa J, Nihoyannopoulos P, Bergler-Klein J et al (2020) Role of cardiovascular imaging in cancer patients receiving cardiotoxic therapies: a position statement on behalf of the Heart Failure Association (HFA), the European Association of Cardiovascular Imaging (EACVI) and the Cardio-Oncology Council of the European Society of Cardiology (ESC). Eur J Heart Fail. https://doi.org/10.1002/ejhf.1957
27. Thavendiranathan P, Negishi T, Somerset E, Negishi K, Penicka M, Lemieux J et al (2021) Strain-guided management of potentially cardiotoxic cancer therapy. J Am Coll Cardiol 77(4):392–401

Authors and Affil tions

Nicolò Matteo Luca Battisti[1] · Maria Sol Andres[2] · Karla A. Lee[1] · Sivatharshini Ramalingam[2] · Tamsin Nash[1] · Stephanie Mappouridou[1] · Nishanthi Senthivel[1] · Kalaprapa Asavisanu[1] · Mariam Obeid[1] · Elli-Sophia Tripodaki[1] · Vasileios Angelis[1] · Emily Fleming[1] · Emily F. Goode[1] · Susan John[1] · Stuart D. Rosen[2] · Mark Allen[1] · Susannah Stanway[1] · Alexander R. Lyon[2] · Alistair Ring[1]

Nicolò Matteo Luca Battisti
nicolo.battisti@rmh.nhs.uk

Maria Sol Andres
M.Andres@rbht.nhs.uk

Karla A. Lee
karla.lee@nhs.net

Sivatharshini Ramalingam
tharshini.ramalingam@nhs.net

Tamsin Nash
tamsin.nash@nhs.net

Stephanie Mappouridou
stephanie.mappouridou@nhs.net

Nishanthi Senthivel
Nishanthi.Senthivel@rmh.nhs.uk

Kalaprapa Asavisanu
Kalaprapa.asavisanu@nhs.net

Mariam Obeid
Mariam.Obeid@rmh.nhs.uk

Elli-Sophia Tripodaki
ellisophia@hotmail.com

Vasileios Angelis
Vasileios.Angelis@rmh.nhs.uk

Emily Fleming
Emily.Fleming@rmh.nhs.uk

Emily F. Goode
emily.goode@icr.ac.uk

Susan John
susanjohnm93@gmail.com

Stuart D. Rosen
stuart.rosen@imperial.ac.uk

Mark Allen
mark.allen@rmh.nhs.uk

Susannah Stanway
susannahstanway@gmail.com

Alexander R. Lyon
a.lyon@imperial.ac.uk

[1] Breast Unit, Department of Medicine, The Royal Marsden NHS Foundation Trust, Downs Road, Sutton SM2 5PT, Surrey, UK

[2] Cardio-Oncology Service, Royal Brompton and Harefield NHS Foundation Trust, Sydney Street, Chelsea, London SW3 6NP, UK