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TITLE

Observational cohort study in older women with early breast cancer: use of radiation therapy and impact on health-related quality of life and mortality.

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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.

Keywords: Breast cancer, older, frailty, comorbidity, health-related quality of life, adjuvant radiotherapy.

Disclaimer

Clinical Trial Registration: ISRCTN 46099296

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INTRODUCTION

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).

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 ≥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).

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 ≥3cm, 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 ≥4 lymph nodes were involved (Supplementary Table 3a).[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 (Figure 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). 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 3a). 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 (Figure 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 figures 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; Figure 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; Figure 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 Figure 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 Figure 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 Figure 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), 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 Figure 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 Figure 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 Figure 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 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 ≥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 ≥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 pT1-3 N0-1 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 ≥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.

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.

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FIGURE AND TABLE CAPTIONS

- Figure 1 - STROBE flow diagram for the radiotherapy vs no radiotherapy analyses.
- Table 1 - Postoperative tumour, patient and treatment characteristics by surgery type.
- 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.
  - Table 2b - Results from the multivariable logistic regression model.
- 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.
  - Table 3b - Use of radiotherapy after breast-conserving surgery by combined risk of recurrence and fitness.
  - Table 3c - Use of radiotherapy after mastectomy by risk of recurrence and fitness.
  - Table 3d - Use of radiotherapy after mastectomy by combined risk of recurrence and fitness.
- Figure 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).
- Figure 3 – Funnel plot of radiotherapy use by site (N=56). Proportion of patients enrolled in cohort study receiving radiotherapy against number of patients enrolled.

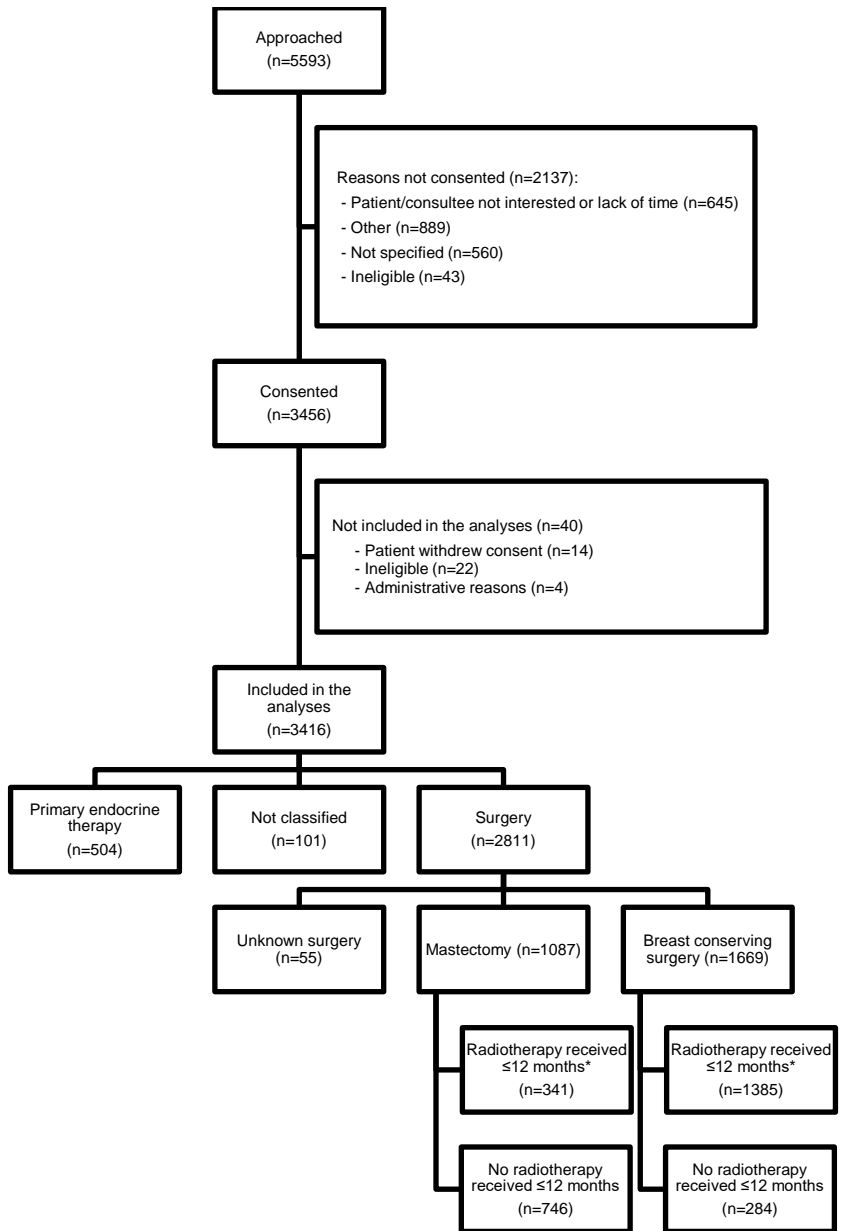**Figure 1 - STROBE flow diagram for the radiotherapy vs no radiotherapy analyses.**

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                    │   Approached    │
                    │   (n=5593)      │
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                             │      ┌──────────────────────────────────────────────────────┐
                             │      │ Reasons not consented (n=2137):                        │
                             ├──────│  - Patient/consultee not interested or lack of time (n=645) │
                             │      │  - Other (n=889)                                       │
                             │      │  - Not specified (n=560)                               │
                             │      │  - Ineligible (n=43)                                   │
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                    │   Consented     │
                    │   (n=3456)      │
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                             │      │ Not included in the analyses (n=40)           │
                             ├──────│  - Patient withdrew consent (n=14)            │
                             │      │  - Ineligible (n=22)                          │
                             │      │  - Administrative reasons (n=4)               │
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                    │ Included in the │
                    │   analyses      │
                    │   (n=3416)      │
                    └────────┬────────┘
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Primary endocrine therapy (n=504)	Not classified (n=101)	Surgery (n=2811)

Under Surgery (n=2811):

Unknown surgery (n=55)	Mastectomy (n=1087)	Breast conserving surgery (n=1669)

	Radiotherapy received ≤12 months* (n=341)	Radiotherapy received ≤12 months* (n=1385)
	No radiotherapy received ≤12 months (n=746)	No radiotherapy received ≤12 months (n=284)

Table 1 - Postoperative tumour, patient and treatment characteristics by surgery type.

		BCS	Mastectomy	Unknown	Total
		N = 1669	N = 1087	N = 55	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%)

		BCS	Mastectomy	Unknown	Total
		N = 1669	N = 1087	N = 55	N = 2811
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%)

		BCS	Mastectomy	Unknown	Total
		N = 1669	N = 1087	N = 55	N = 2811
	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%)

		BCS	Mastectomy	Unknown	Total
		N = 1669	N = 1087	N = 55	N = 2811
	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%)

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**	-	-

Variable	Level	OR (95% CI)	P-value
	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

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

Variable	Level	OR (95% CI)	P-value
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 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 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%)

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.

Figure 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).*
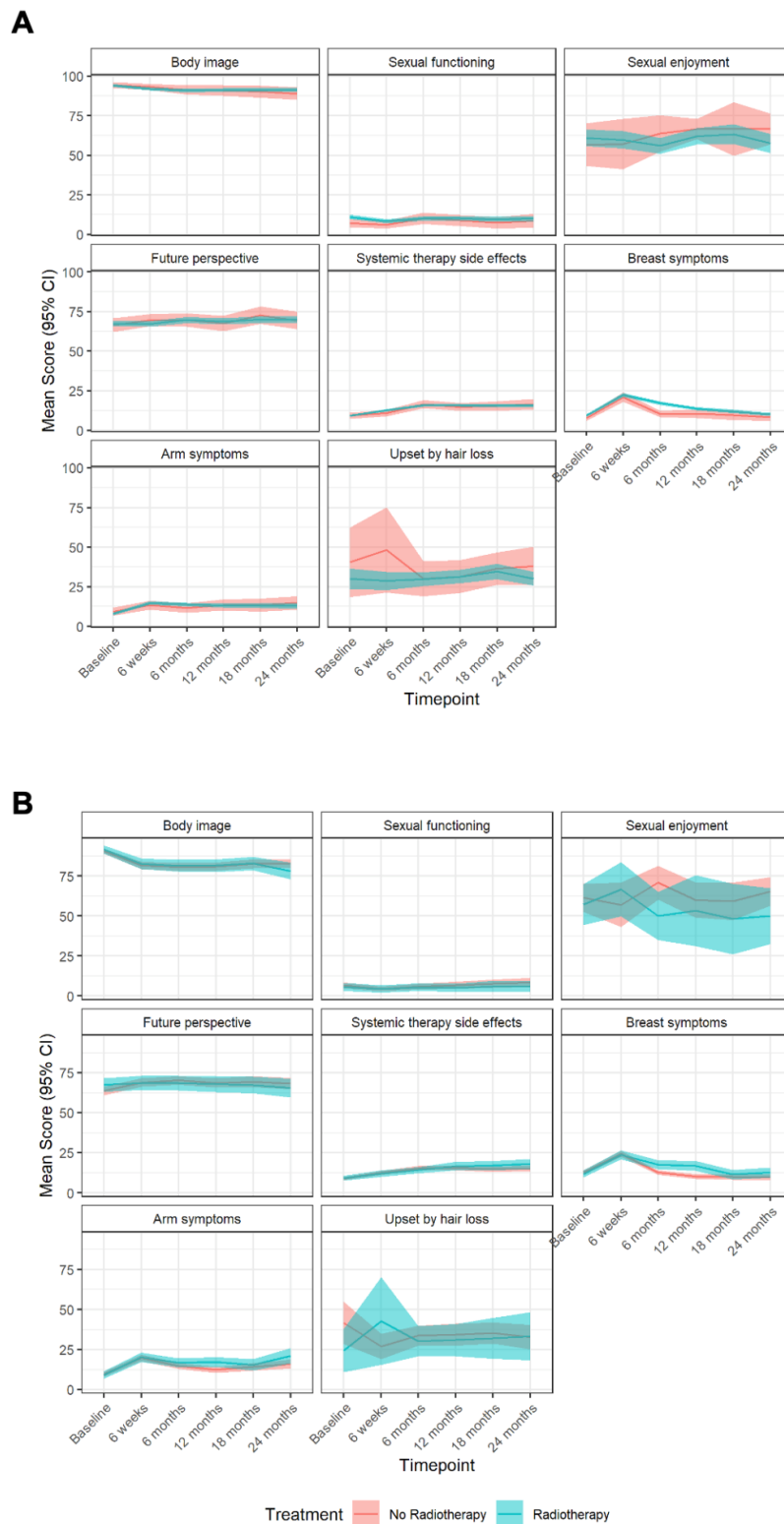
A high score for a functional scale represents a high/healthy level of functioning; a high score for the global health status/QoL represents a high QoL, whilst a high score for a symptom scale represents a high level of symptomology/problems.

Figure 3 – Funnel plot of radiotherapy use by site (N=56). Proportion of patients enrolled in cohort study receiving radiotherapy against number of patients enrolled.
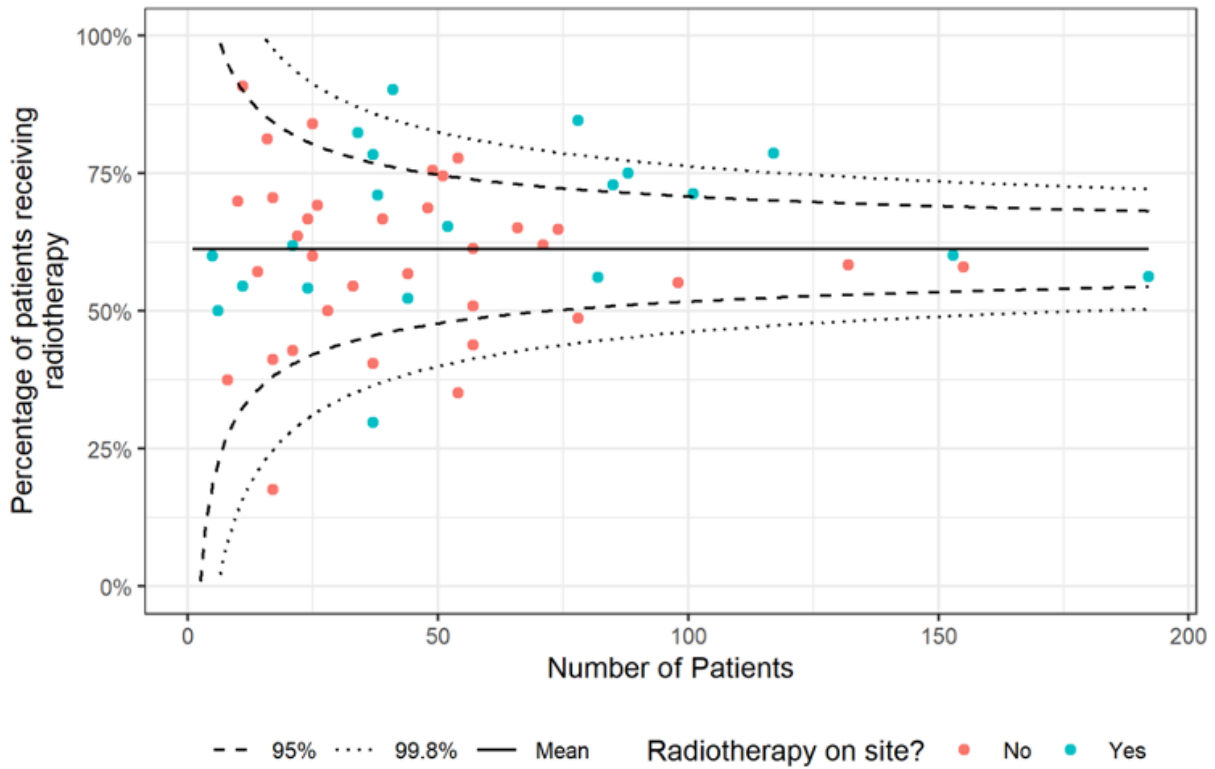
Supplementary Table 1 - List of participating sites.

	Site Name	Local PI
1	Sheffield	Lynda Wyld and Matt Winter
2	Barnsley	Julia Dicks
3	Doncaster	Clare Rogers
4	Milton Keynes	Amanda Taylor
5	Scunthorpe and Grimsby	Rajesh Vijh (Scunthorpe), Jenny Smith (Grimsby)
6	Leicester	Monika Kaushik
7	Derby	Kwok Leung Cheung
8	East Lancashire	Julie Iddon
9	Harrogate	Matthew Adelekan
10	St Helens and Knowsley	Riccardo Audisio
11	York	Rana Nasr (York and Scarborough)

12	Liverpool	Chris Holcombe
13	Airedale	Claire Murphy
14	Leeds	Kieran Horgan
15	Bradford	Rick Linforth
16	Cardiff	Helen Sweetland
17	Aneurin Bevan Health Board	Simon Waters (Royal Gwent), Theresa Howe (Nevill Hall)
18	Royal Lancaster	Rishi Parmeshwar
19	Coventry	Abigail Tomlins
20	Grantham	Anzors Gvaramadze
21	Lincoln	Anzors Gvaramadze
22	Pilgrim	Anzors Gvaramadze
23	Hull	Peter Kneeshaw
24	Nottingham	Lisa Whisker
25	Southport	Anwar Haq
26	Leighton	Vanessa Pope
27	Royal Marsden	Jenny Rusby
28	Cheltenham General	Sarah Vestey
29	Guys and St Thomas	Michael Douek
30	Dorset County	Caroline Osborne
31	Mid Essex	Sascha Miles-Dua
32	Mid Yorkshire	Jay Naik
33	Bristol	Zoe Winters
34	Chesterfield	Iman Azmy
35	Rotherham	Inder Kumar
36	Darent Valley	Seema Seetharam
37	Kingston	Karyn Shenton
38	Colchester	Mukesh Mukesh
39	Yeovil	Caroline Osborne
40	Croydon	Sanjay Joshi
41	North Tees	Colm Hennessy
42	South Tees	Imtiaz Cheema
43	Luton and Dunstable	Mei-Lin Ah-See
44	Weston General	Rachel Ainsworth

45	Tameside	Stephanie Ridgway
46	Macclesfield	Lisa Barraclough
47	Wrightington, Wigan and Leigh	Angela Power
48	Birmingham	Fiona Hoar
49	Kings Mill	Rebecca Boulton
50	Wythenshawe	Nigel Bundred
51	Aintree	Peter Robson
52	Brighton	Gargi Patel
53	St Margaret's	Ashraf Patel
54	St Marys	Steve Parker
55	Oxford	Asha Adwani
56	Frimley and Wexham	Ruth Davis (Wexham), Raouf Daoud (Frimley)

Supplementary Table 2 – Summary of the Quality-of-Life instruments used in the Age Gap 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 ELD-14	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

Supplementary Table 3 – Definitions of risk of recurrence and fitness.

Supplementary Table 3a – Definition of risk of recurrence categories.

Tumour characteristics	Risk of recurrence	
	High*	Low
	BREAST CONSERVING COHORT	
Tumour size	≥3cm	<3cm
ER	Negative	Positive
HER2	Positive	Negative
Grade	3	1-2
Nodal involvement	Yes	No
	MASTECTOMY COHORT	
Tumour size	≥5cm	<5cm
Lymph nodes involved	≥4	<4

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

Supplementary Table 3b – Definition of fitness categories. 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	-
APSGA		0-3	4-8	≥9
MMSE	0-30	≥24	20-24	<20

Supplementary Table 4 - Postoperative tumour, patient and treatment characteristics by receipt of radiotherapy.

		No radiotherapy	Radiotherapy	Total
		N = 1058	N = 1753	N = 2811
Age (years)	**70-74**	374 (35.3%)	799 (45.6%)	1173 (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%)	1327 (75.7%)	2111 (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%)	1305 (46.4%)
	Left	571 (54.0%)	935 (53.3%)	1506 (53.6%)
Tumour size (mm)	**≤ 20**	432 (40.8%)	847 (48.3%)	1279 (45.5%)
	21-50	530 (50.1%)	755 (43.1%)	1285 (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%)	1149 (65.5%)	1913 (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%)	1485 (52.8%)
	Grade 3	331 (31.3%)	534 (30.5%)	865 (30.8%)
	Unknown	40 (3.8%)	40 (2.3%)	80 (2.8%)
Histology	**Ductal carcinoma**	685 (64.7%)	1130 (64.5%)	1815 (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%)

		No radiotherapy	Radiotherapy	Total
		N = 1058	N = 1753	N = 2811
	Positive	844 (79.8%)	1510 (86.1%)	2354 (83.7%)
	Unknown	48 (4.5%)	37 (2.1%)	85 (3.0%)
HER2 status	Negative	816 (77.1%)	1456 (83.1%)	2272 (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%)	1275 (72.7%)	2004 (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%)	1330 (75.9%)	2069 (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%)	1587 (90.5%)	2494 (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%)
AGP SGA category	Low	805 (76.1%)	1375 (78.4%)	2180 (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 performance status	0	675 (63.8%)	1269 (72.4%)	1944 (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%)
	n	1021	1686	2707

		No radiotherapy	Radiotherapy	Total
		N = 1058	N = 1753	N = 2811
Charlson comorbidity index (no age)	**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	1520	2446
	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%)	1385 (79.1%)	1669 (59.4%)
	Mastectomy	746 (70.5%)	341 (19.4%)	1087 (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%)	1256 (71.6%)	1980 (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%)	1502 (85.7%)	2414 (85.9%)

Supplementary Table 5 - Postoperative tumour, patient and treatment characteristics by age.

		70-74	75-79	80-84	>=85	Total
		N = 1173	N = 899	N = 506	N = 233	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)	23.07 (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%)	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%)	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%)	1485 (52.8%)
	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 carcinoma**	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%)

		70-74	75-79	80-84	>=85	Total
		N = 1173	N = 899	N = 506	N = 233	N = 2811
	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%)
	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%)	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%)
	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%)
AGP 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%)

		70-74	75-79	80-84	>=85	Total
		N = 1173	N = 899	N = 506	N = 233	N = 2811
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%)
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
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
Surgery type	Mastectomy	342 (29.2%)	356 (39.6%)	253 (50.0%)	136 (58.4%)	1087 (38.7%)
	Breast conservation	813 (69.3%)	521 (58.0%)	243 (48.0%)	92 (39.5%)	1669 (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%)	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%)
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%)	2414 (85.9%)
Radiotherapy use	Yes	799 (68.1%)	581 (64.6%)	281 (55.5%)	92 (39.5%)	1753 (62.4%)

		70-74	75-79	80-84	>=85	Total
		N = 1173	N = 899	N = 506	N = 233	N = 2811
No		374 (31.9%)	318 (35.4%)	225 (44.5%)	141 (60.5%)	1058 (37.6%)

Supplementary Table 6 – Radiotherapy details by treatment side for all women whose primary treatment was breast conserving surgery.

		BREAST CONSERVING SURGERY COHORT	
		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	Ticked	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	
		Left	**Right**
		N = 192	**N = 148**
Breast		48 (25.0%)	43 (29.1%)
Breast fractions*	**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	**Ticked**	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
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

*This category in the mastectomy cohort includes radiotherapy given to contralateral breast for patients with bilateral breast cancer.

Supplementary Table 7 – 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%)

Site ID	Availability of radiotherapy on site	n/N (%)
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%)
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%)

Site ID	Availability of radiotherapy on site	n/N (%)
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%)
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 8 – Completion of the QoL questionnaires at each time point for patients undergoing BCS or mastectomy.

		BREAST CONSERVING SURGERY COHORT		
		No radiotherapy	Radiotherapy	Total
		N = 210	N = 915	N = 1125
				EORTC-QLQ-C30
Baseline	All	181 (86.2%)	823 (89.9%)	1004 (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%)	1042 (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%)

		No radiotherapy	Radiotherapy	Total
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%)	1002 (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
		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 9 - Mean (SD) scores for the EORTC QLQ-BR23 scale at each time point in the radiotherapy versus no radiotherapy cohorts with adjusted mean difference (95% CI) and p-value.

BREAST-CONSERVING SURGERY COHORT (N=1042)*

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
	Sexual enjoyment	53.44 (35.79, 71.10)	59.54 (53.53, 65.56)	6.10 (-12.30, 24.49)	0.510

	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)	0.140
	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)*

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)	0.940
	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)	0.470
	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)	0.300
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)	0.690
	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)	0.800
	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)	0.060
	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)	0.150
	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

patients with questionnaires available at baseline.

Supplementary Table 10 - Mean (SD) scores for the EORTC QLQ-C30 scale at each time point in the radiotherapy versus no radiotherapy cohorts with adjusted mean difference (95% CI) and p-value.

BREAST-CONSERVING SURGERY COHORT

Time point	Domain	No radiotherapy	Radiotherapy	Treatment Effect	P value
6 weeks	Global health status / QoL	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 / QoL	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)	0.050
	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 / QoL	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)	0.980

	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)	0.090
	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)	0.120
	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 / QoL	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)	0.460
	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 / QoL	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

	Domain	No radiotherapy	Radiotherapy	Treatment Effect	P value
	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)	0.160
	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

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Time point	Domain	No radiotherapy	Radiotherapy	Treatment Effect	P value
6 weeks	Global health status / QoL	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)	0.510
	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 / QoL	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 / QoL	71.13 (69.26, 73.00)	71.04 (67.92, 74.15)	-0.09 (-3.72, 3.53)	0.960
	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)	0.220
	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 / QoL	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)	0.900
	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 / QoL	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)	0.380
	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 11 - 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
CCI	1	-	-
	2	-0.876 (-3.531, 1.780)	0.518
MMSE	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	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)	0.120
	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
CCI	**1**	-	-
	2	-1.161 (-4.327, 2.005)	0.473
MMSE	**Normal function**	-	-
	Mild impairment	1.068 (-2.456, 4.591)	0.553
	Moderate impairment	-6.152 (-17.462, 5.159)	0.287
ECOG	**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

Supplementary Table 12 - Mean (SD) scores for the EORTC QLQ-ELD15 scale at each time point in the radiotherapy versus no radiotherapy cohorts with adjusted mean difference (95% CI) and p-value.

Time point	Domain	No radiotherapy	Radiotherapy	Treatment Effect	P value
		BREAST-CONSERVING SURGERY COHORT			
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)	0.010
	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)	0.200
	Joint stiffness	42.31 (37.71, 46.92)	41.70 (39.81, 43.59)	-0.61 (-5.58, 4.37)	0.810
	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)	0.400
	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)	0.180
	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)	0.060
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 13 - Mean scores and 95% confidence intervals (CIs) 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)	0.300
	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)	0.820
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

Supplementary Table 14 - Radiotherapy adverse events for patients receiving radiotherapy after breast-conserving surgery.

|	Events	Individuals
	N = 1385	N = 1385
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%)

Supplementary Table 15 - Radiotherapy adverse events for patients receiving radiotherapy after a mastectomy.

|	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%)

Supplementary Table 16 – Mortality rates in the overall cohort, in the breast-conserving surgery cohort and in the mastectomy cohort.

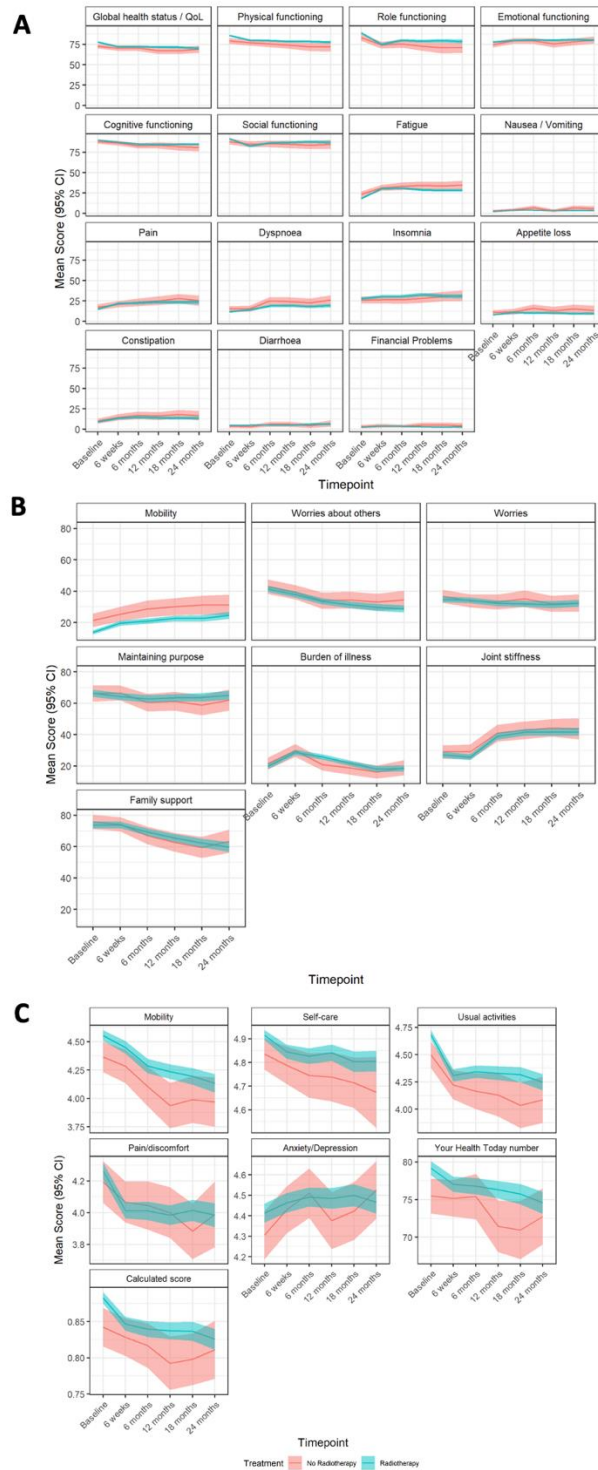|		OVERALL COHORT		
		No radiotherapy	**Radiotherapy**	**Total**
		N = 1058	**N = 1753**	**N = 2811**
Overall death (any cause)	**n**	1041	1716	2757
	No	824 (79.2%)	1469 (85.6%)	2293 (83.2%)
	Yes	217 (20.8%)	247 (14.4%)	464 (16.8%)
Death due to breast cancer-related cause	**n**	1032	1706	2738
	No	955 (92.5%)	1590 (93.2%)	2545 (93.0%)
	Yes	77 (7.5%)	116 (6.8%)	193 (7.0%)
		BREAST-CONSERVING SURGERY COHORT		
		No radiotherapy	**Radiotherapy**	**Total**
		N = 284	**N = 1385**	**N = 1669**
Overall death (any cause)	**n**	277	1354	1631
	No	229 (82.7%)	1205 (89.0%)	1434 (87.9%)
	Yes	48 (17.3%)	149 (11.0%)	197 (12.1%)
Death due to breast cancer-related cause	**n**	276	1348	1624
	No	267 (96.7%)	1297 (96.2%)	1564 (96.3%)
	Yes	9 (3.3%)	51 (3.8%)	60 (3.7%)
		MASTECTOMY COHORT		
		No radiotherapy	**Radiotherapy**	**Total**
		N = 746	**N = 341**	**N = 1087**
Overall death (any cause)	**n**	737	336	1073
	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	1062
	No	665 (91.1%)	269 (81.0%)	934 (87.9%)
	Yes	65 (8.9%)	63 (19.0%)	128 (12.1%)

Supplementary Figure 1 – Completion of the EORTC-QLQ-BR23 at each time point in patient undergoing breast-conserving surgery (top) and in those undergoing a mastectomy (bottom).
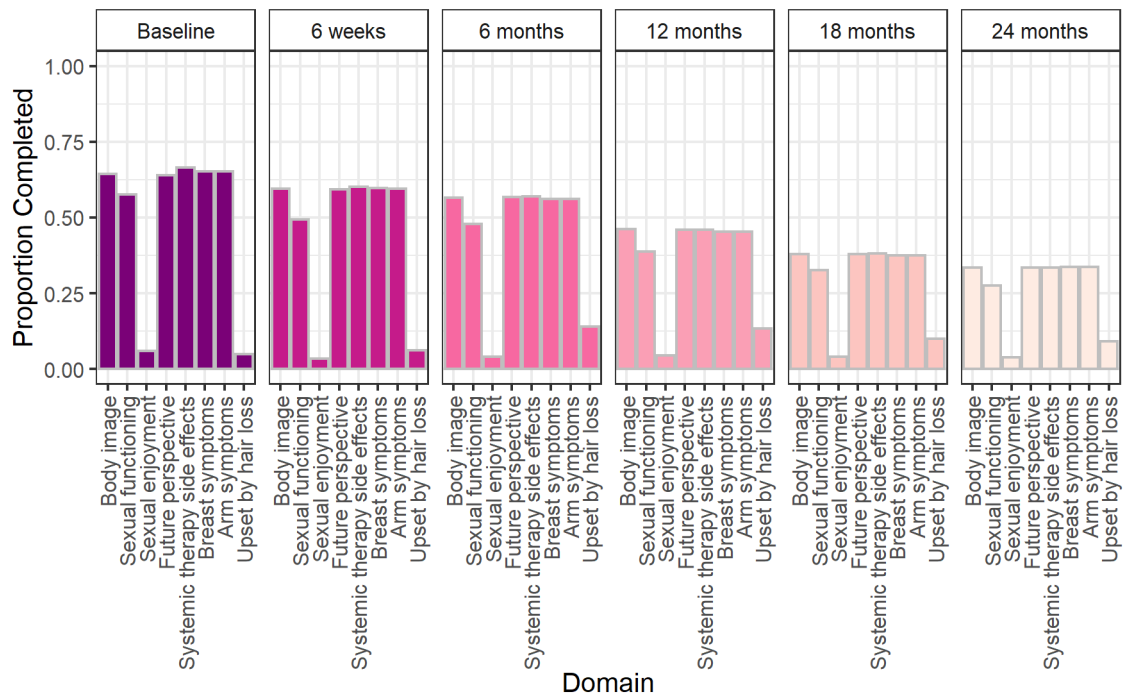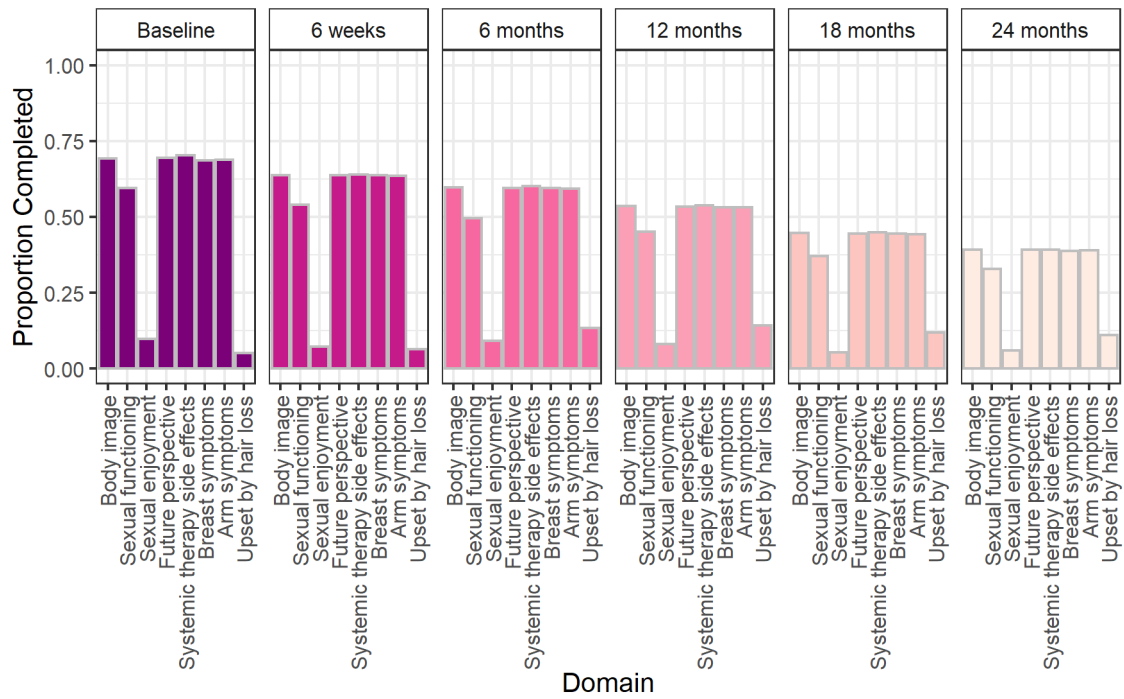
Supplementary Figure 2 – Completion of the EORTC-QLQ-C30 at each time point in patient undergoing breast-conserving surgery (top) and in those undergoing a mastectomy (bottom).

Supplementary Figure 3 – Completion of the EORTC-QLQ-ELD15 at each time point in patient undergoing breast-conserving surgery (top) and in those undergoing a mastectomy (bottom).
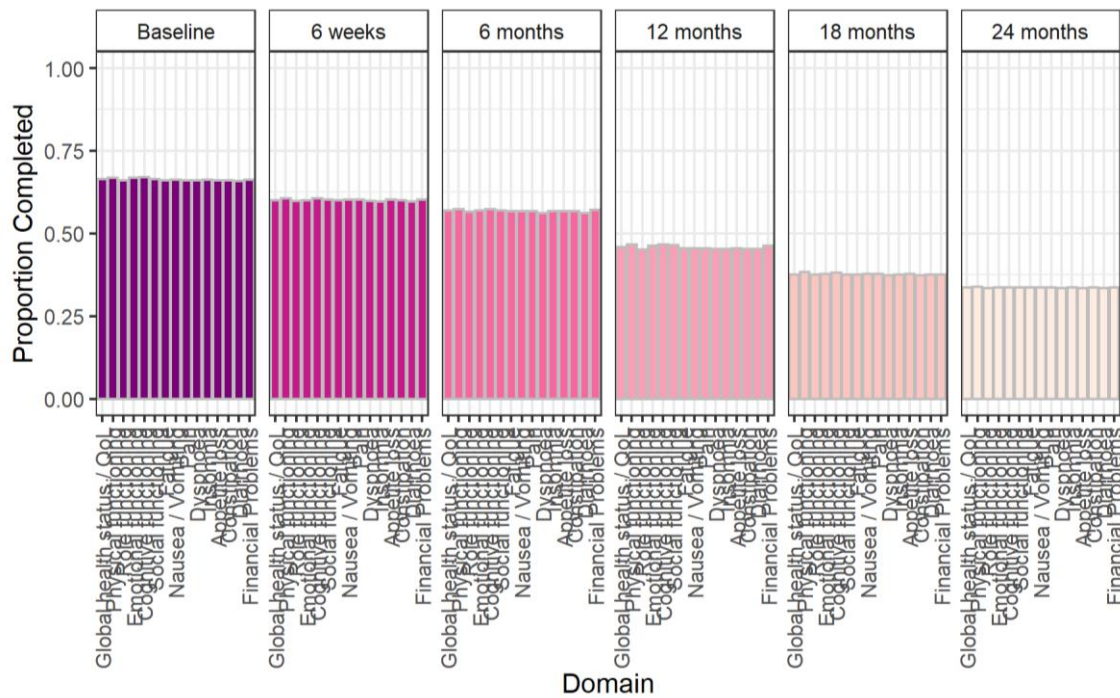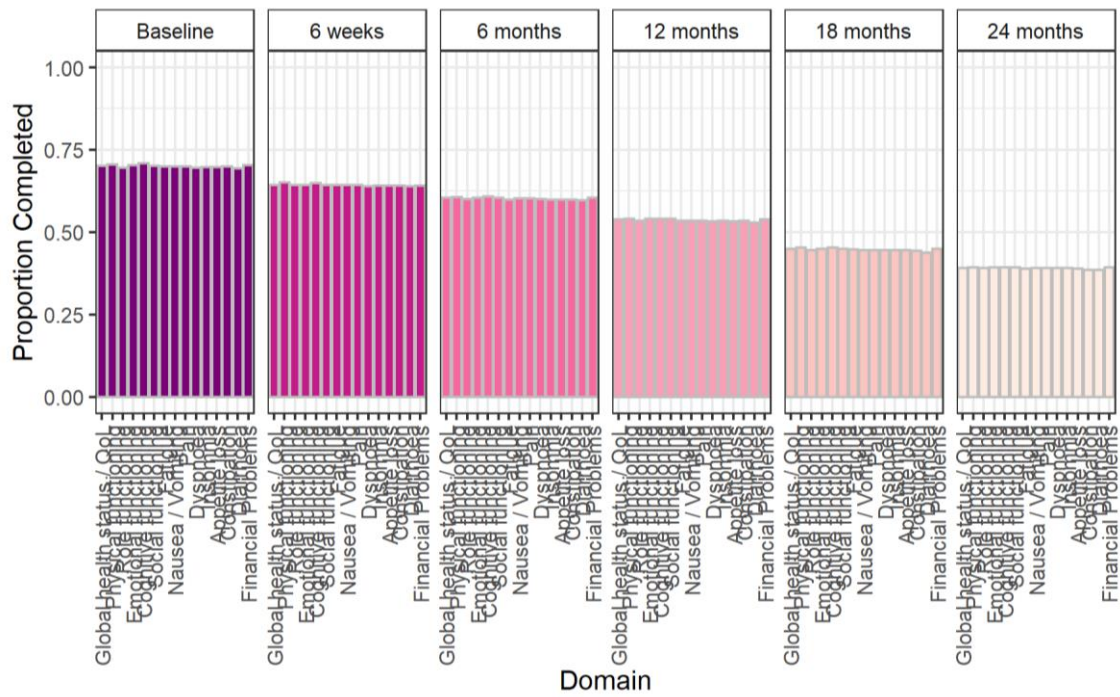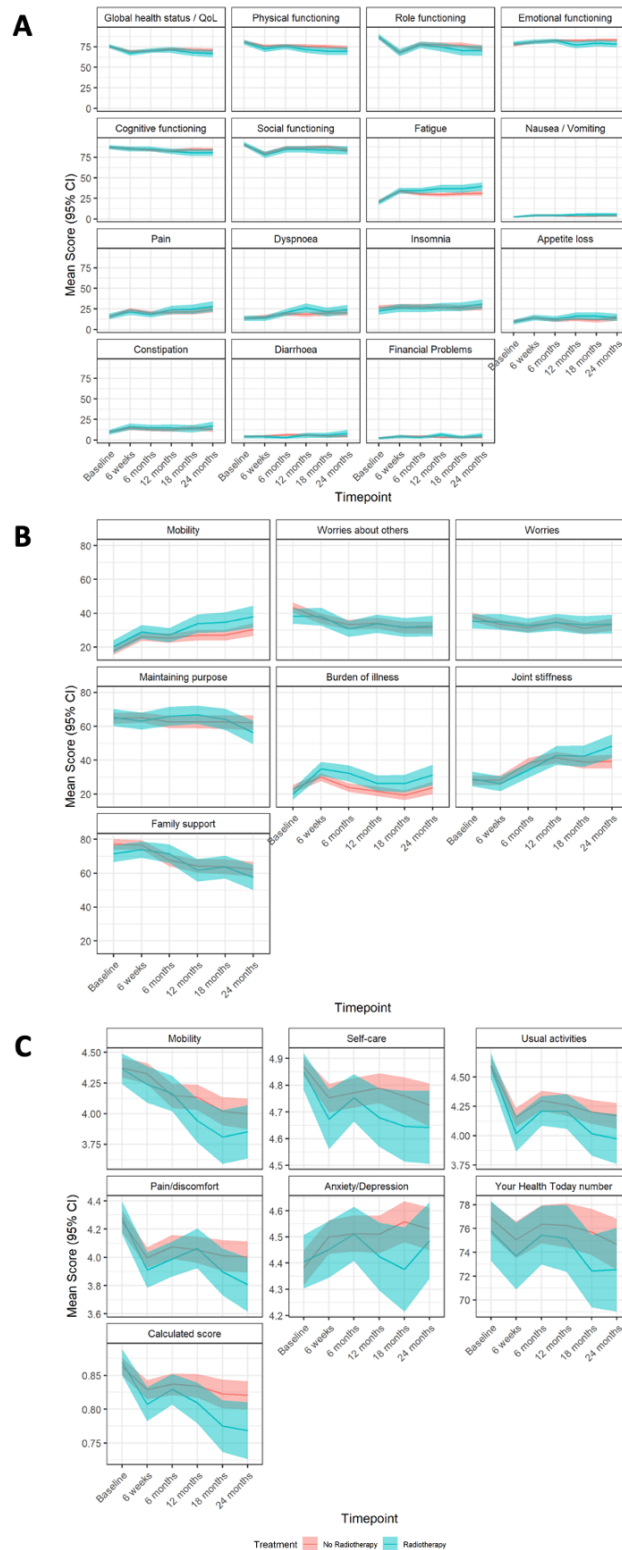
Supplementary Figure 4 – Mean (95% CI) scores over time points for the radiotherapy versus no radiotherapy population measured on the EORTC-QLQ-C30 (A), ELD15 (B) and EQ-5D-5L* scale (C) in patients undergoing breast-conserving surgery.^

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.

^A high score for a functional scale represents a high/healthy level of functioning; a high score for the global health status/QoL represents a high QoL, whilst a high score for a symptom scale represents a high level of symptomology/problems.

Supplementary Figure 5 – Mean (95% CI) scores over time points for the radiotherapy versus no radiotherapy population measured on the EORTC-QLQ-C30 (A), ELD15 (B) and EQ-5D-5L* scale (C) in patients undergoing a mastectomy.^

*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.

^A high score for a functional scale represents a high/healthy level of functioning; a high score for the global health status/QoL represents a high QoL, whilst a high score for a symptom scale represents a high level of symptomology/problems.