# Improving outcomes in older women with ovarian cancer

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## Abstract of thesis:

**Background:** Older women have disproportionately poorer survival outcomes for ovarian cancer. Sarcopenia, the loss of muscle mass and density is of interest as a potential non-invasive biomarker of frailty. Little is documented on decision-making and treatment experience of older women. Given the rising proportion of older patients in oncology clinics, novel approaches to enable oncology teams to deliver a geriatric assessment and crucially, interventions to address deficits identified are required.

**Aims:** To evaluate patient characteristics, treatment patterns, tolerance and survival outcomes in older women treated for ovarian cancer. To assess whether reduced muscle mass and density at baseline and during treatment is associated with poorer treatment tolerance and survival outcomes. To assess the decision-making and treatment experience of older women. To develop and open a clinical trial implementing a GA and protocolled interventions to address deficits identified in the routine oncology clinic.

**Methods:** The chapters of this thesis cover: A literature review of outcomes of older women with ovarian cancer. Outcomes of 280 women aged >65 years treated at two UK cancer centres. The impact of sarcopenia in women over the age of 65 treatment tolerance and outcomes. Treatment experience in women over the age of 65. The development of a novel prospective, interventional clinical trial implementing a GA and algorithms to address deficits identified.

**Results:** Age was not independently associated with poorer survival outcomes once stage and treatment factors are adjusted for. Muscle density but not mass was strongly associated with poorer survival outcomes. Older women with ovarian cancer were overwhelmingly positive about their care experience and desire for anticancer treatment despite logistical burden and toxicities. The FAIR-O study opened in January 2021.

**Conclusions:** Reduced treatment intensity is one of the principal factors in the poorer survival outcomes in the oldest patient**.** Biomarkers such as sarcopenia can be used to help to risk stratify patients. The multi-centre FAIR-O study will assess whether it is feasible for oncology teams to undertake a GA and targeted interventions when indicated.

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## Tables and Figures

## Glossary

ACCI = Age-adjusted charlson comorbidity index

AHP = Allied healthcare professionals

ASA = American Society of Anesthesiologists

ASCO = American Society of Clinical Oncology

CCU = Critical Care Unit

CGA = Comprehensive geriatric assessment

CTCAE = Common terminology criteria for adverse events

DICOM = Digital Imaging and Communications in Medicine

ECOG = Eastern Cooperative Oncology Group

EMA = European Medicines Agency

ES = Erector spinae

FFPE = Formalin-Fixed paraffin-embedded

FIGO = International Federation of Gynecology and Obstetrics

GA = Geriatric Assessment

GFR = Glomerular-filtration rate

GINECO = Group d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens

GVS = Geriatric Vulnerability Score

HADS = Hospital Anxiety and Depression score (HADS)

HCP = healthcare professionals

HRD = homologous recombination deficiency

HRQoL = Health related quality of life

HU = Hounsfield units

IADLS= Instrumental Activities of Daily Living Score (IADLS)

ICBP = International Cancer Benchmarking Partnership

KPS = Karnovsky Performance Status

MDT = multidisclinary team

MMSE = Mini-mental state examination

MNA = Mini-nutritional assessment

NACT = Neoadjuvant Chemotherapy

NCRS = National Cancer Registration Service

OS = Overall survival

PACS = Picture archiving and communication system

PARP = Poly-ADP ribose polymerase

PFS = progression-free survival

PS = Performance status

RMH = Royal Marsden NHS Foundation Trust

RUH = Royal United Hospitals Foundation Trust

SACT = Systemic anticancer treatment

SAT = Subcutaneous adipose tissue

SIOG = International Society of Geriatric Oncology

SMI = Skeletal muscle index

TUGT = Timed up and go test

**Declaration**

I declare that the research contained in this thesis, unless otherwise formally indicated within the text, is the original work of the author. The thesis has not been previously submitted to this or any other university for a degree, and does not incorporate any material already submitted for a degree.

Signed: 

Name: Lucy Emily Dumas

Dated: 28th May 2021

# 1 INTRODUCTION

## 1.2 Poorer outcomes in older women women with epithelial ovarian cancer

Around 7,500 women a year are diagnosed with ovarian cancer[1]. Ovarian cancer is predominantly diagnosed in older women with around half of all diagnoses are in women over the age of 65 in the UK[2]. The median age at diagnosis is 64.7 [3] with the peak rate of incidence occurring between the ages of 75-79[4]. The EUROCARE project [5], which assesses cancer survival across Europe over time, demonstrated that although for almost all cancers there was a continued improvement in outcomes over time, the rate of progress was slower in older patients and in particular for patients with gynaecological malignancies [6]. Interestingly, if older patients with a gynaecological cancer survived the first year after diagnosis, the prognosis for this group was similar to middle-aged patients [6].

Over the past 20 years, significant advances in the management of ovarian cancer have led to the improved survival rates in all groups with the notable exception of those over the age of 80 [1]. For example, in the UK, the mean 1-year survival for stage IV ovarian cancer patients of all ages is 51.0% but this dramatically falls to 35.7% for women over the age of 70 [7].

With an ageing population, although the overall incidence of cancer in the UK is not projected to change, the proportion of patients over the age of 65

is expected to rise: by 2030, 67.5% of all female cancer patients will be over the age of 65 [8]. The UK survival outcomes unfortunately do not compare favourably to those of other developed nations[7, 9] and concerningly this difference is amplified further for older patients [7]. For example, a woman over the age of 70 diagnosed with stage III ovarian cancer in Canada has an expected 1-year survival of 74% compared to just 57% in the UK [7]. Some of the potential reasons for this will be further explored in due course and in further depth within this thesis. There does appear to be an issue with late presentation and a potential delay to diagnosis and therefore treatment within the UK. The ICBP findings demonstrate that two countries with the poorest outcomes were the UK and Denmark, a common feature between both is the gatekeeper function of primary care. Whilst the awareness of ovarian cancer does appear to be improving, symptoms are often insidious and vague. Older patients may take longer to report their symptoms to primary care physicians but unfortunately also experience delays to investigation and referral from first report of symptoms compared to middle-aged women[10]. However, the fundamental issue of worsening outcomes with increasing age is not limited to the UK [11] and factors that are not country-specific such as adverse tumour biology, differential host immune tumour response in older versus younger women and increasing comorbidities that impact on a patient's ability to undergo surgery and/or chemotherapy are likely to all play a role.

### 1.3 Potential causes for poorer outcomes

The reasons for poorer outcomes for older women diagnosed with ovarian cancer both in the UK and internationally are likely multifactorial and incompletely understood. Delayed presentation for a multitude of psychosocial reasons (both patient and system-related) leading to advanced stage at diagnosis, increasing comorbidities, relative under-treatment as well as potentially adverse tumour biology in cancers diagnosed in older women may all play a role.

A 2012 report from the International Cancer Benchmarking Group (ICBP), which reports cancer registry data outcome across seven high-income countries (Australia, Canada, Denmark, Ireland, New Zealand, Norway and the United Kingdom) demonstrated increasing age was associated with a more advanced stage at ovarian cancer[3, 7]. In a recent update that analysed data from patients treated up to the end of 2015, this trend had not changed[12]. One UK based study of the route to diagnosis of ovarian cancer from primary care reported that older women are significantly less likely to be referred for further investigations such as CA125, ultrasound, CT or referral to gynaecology in the year preceding an ovarian cancer diagnosis. A significant delay was also noted in the time to referral for any further investigations after reporting symptoms that could be associated with ovarian cancer with the median time for women aged 75-79 years old to be referred being 20 weeks compared to 9 weeks in a women aged 65-69 years [10]. Older patients are significantly less likely to be referred for investigations such as abdominal ultrasound or to a gynaecologist in the

year preceding a diagnosis of ovarian cancer[10]. Older women are also more likely to be diagnosed following an emergency presentation a factor that has been shown to be associated with poorer survival outcomes[13].

Women over the age of 65 remain underrepresented in phase 3 clinical studies [14-16] and yet form a significant proportion of patients being treated in daily clinical practice. Furthermore, patients with poor performance status or significant medical or functional comorbidities would not be eligible for most clinical trials and therefore evidence for practice is taken from studies involving fit, younger patients and applied to an older more comorbid population. For example, among 28,766 patients enrolled into 55 registration studies in the US involving breast, lung, colorectal, pancreas, CNS, leukaemia, cutaneous T-cell lymphoma and ovary cancer, 35% of the study population were over the age of 65 compared with 60% in the US population in clinical practice[14]. In the pivotal GOG-158 phase trial which contributed to the establishment of carboplatin in combination with paclitaxel as standard of care for first-line treatment in ovarian cancer, 11% of the patients enrolled were over the age of 71 and only 1% over the age of 81 [49]. There is a marked paucity of prospective clinical studies focusing on older, less fit patients with ovarian cancer.

Finally, it has been recognised that there is a need for an alternative assessment method to guide treatment decisions in the older population. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) is the accepted standard for evaluation of a patient's functional status both in

clinical studies and in routine clinical practice. It is widely accepted that this is a limited tool for assessment of older patients and does not accurately represent limitations in functional or cognitive capability [17-19]. American Society of Clinical Oncology (ASCO) [20] and International Society of Geriatric Oncology (SIOG) [21] guidelines have since been published recommending that all older patients being considered for systemic anti-cancer therapy undergo a geriatric assessment.

### 1.4 Surgical outcomes in older women with ovarian cancer

The current gold-standard therapy for advanced ovarian cancer is a combination of complete (no macroscopic residual disease) cytoreductive surgery undertaken by a specialist gynae-oncology surgeon and combination platinum-based chemotherapy[22, 23]. Achieving optimal cytoreduction remains the most significant prognostic factor for ovarian cancer survival [24] and should be considered for all women newly diagnosed with an ovarian malignancy. It has however been consistently shown that increasing age is associated with lower rates of referral to oncology specialists, lower rates of cytoreductive surgery and lower rates of optimal cytoreduction [25-28].

Where disease is considered to be operable at the time of diagnosis, patients are offered primary debulking surgery with the consideration thereafter of adjuvant platinum-based chemotherapy. For those patients with initially inoperable disease or considered to have a high risk of residual disease, neoadjuvant chemotherapy (NACT) is a suitable option. NACT for

3 cycles followed by the remaining cycles post-operatively has been demonstrated to increase the rate of optimal cytoreduction and decreases perioperative morbidity and mortality rates [29, 30]. This approach has not been shown to be inferior to primary debulking surgery followed by chemotherapy as a treatment option for patients with bulky advanced ovarian carcinoma [30-32]. Bearing in mind the improved perioperative morbidity associated with NACT followed by surgery, this may be viewed as an attractive option for older patients who often present with concurrent medical conditions. It also provides a "window of opportunity" to address medical issues and optimise patients for surgery, a practice now gathering interest, often termed as prehabilitation. Many centres have developed prehabilitation programmes and several systematic reviews have recently been published evaluating outcomes. Prehabilitation, despite a wide variety of approaches, has widely been shown to improve length of stay and reduce surgical complication rates[33-36]. Robust prospective studies with patient reported outcome measures and cost-effectiveness analysis are required to further evaluate the role of these programmes and how they should best be utilised within a cancer centre practice.

Post-operative mortality and serious morbidity rates rise significantly over the age of 60 and have been shown to be independently associated with a number of pre and peri-operative factors such as pre-operative weight loss, hypoalbuminaemia, prolonged operative time, need for transfusion or splenectomy and contaminated wound[37]. The age-adjusted charlson comorbidity index (ACCI) incorporates age into the Charlson-Comorbidity

index, a validated score to predict 1 year-mortality comprising of 19 medical comorbidities. In a population of 567 women undergoing primary debulking surgery for epithelial ovarian cancers, taking into consideration stratification for surgical complexity, an ACCI score of 0-1 (low risk) was significantly associated with achieving complete cytoreduction. For example complete cytoreduction was achieved in 44% of women with an ACCI score of 0/1 compared to 32% in those with a score of 2 or higher (p=0.02). The authors suggested that this may relate to a reduced willingness to subject patients with more comorbidity to extensive surgical procedures. The ACCI was predictive for progression-free survival (PFS) and overall survival (OS) but not for rates of minor or major perioperative complications [38]. Identifying those patients at higher risk of post-operative mortality and morbidity potentially improves the risk stratification of older patients and could facilitate more informed patient-centric decision-making. A large retrospective analysis from the U.S. reported a high-risk group comprising of age>75 years, high tumour dissemination or FIGO stage IV disease, high (American Society of Anesthesiologists) ASA score or albumin <3.0g/dl. In this group median overall survival was 17 months (n=38) compared to 40.2 months in the overall study population (n=576) with stage III and IV disease [39]. In a study of 189 women aged 70 years or older undergoing cytoreductive surgery, a pre-operative risk stratification score (GA-GYN) was not shown to be associated with the risk of major perioperative morbidity. In a sub-group analysis of those patients with stage III/IV malignant disease (n=58), an odds ratio of 1.29 (95%CI 1.006 – 1.674, p=0.0456) for every 1 point higher on the GA-GYN score was observed[40].

## 1.5 Systemic anticancer therapy outcomes in older patients

### 1.5.1 Chemotherapy outcomes in older women.

In 2005, a GINECO group study reported the findings of a retrospective pooled analysis of 83 patients over the age of 70 enrolled into a study assessing Carboplatin and Cyclophosphamide (CC) [41] and a further 75 patients over the age of 70 enrolled into a subsequent study evaluating Carboplatin and Paclitaxel (CP). A multivariate analysis of predictive factors for survival in older patients was undertaken [42]. Elements of a geriatric assessment were performed at baseline including Mini-mental state examination (MMSE, regarding a score > 24/30 as normal), polypharmacy (defined in this study as 4 or more daily medications), patient dependence as well as ECOG PS and baseline routine blood tests. In the CP group, a Hospital Anxiety and Depression score (HADS) and Instrumental Activities of Daily Living Score (IADLS) were also performed. 75% of patients in the CC group and 68% in the CP group completed the planned 6 cycles of chemotherapy without severe toxicity. Of all these geriatric assessments undertaken, the only statistically significant prognostic factor for overall survival was the presence of depressive symptoms at baseline. No specific predictive factors for toxicity were identified,

The pivotal phase 3 AGO-OVAR 3 study evaluated adjuvant carboplatin/paclitaxel compared to cisplatin in combination with paclitaxel for advanced ovarian cancer. 103 patients enrolled into this study were over

the age of 70, 80% were ECOG PS 0 or 1. A retrospective analysis of this subgroup demonstrated that combination chemotherapy was tolerable in an older population. Discontinuation rates were double in those over the age of 70 compared to the <70 group [43] despite quality of life or toxicity rates, except fatigue, not differing significantly between younger and older patients. The authors suggested a potential difference in the attitude of investigators when treating older patients with a tendency towards treatment cessation in the event of toxicity rather than treatment delays and instituting supportive care measures in older patients [43]. This will be further explored in Chapter 4.

Most recently, the EWOC-1 study (NCT02001272), presented at ASCO 2019 enrolled patients who were identified as vulnerable according to a baseline geriatric vulnerability score (GVS) in a randomised study evaluating standard 3-weekly carboplatin and paclitaxel against either single-agent 3 weekly carboplatin or weekly dose-dense carboplatin and paclitaxel[44, 45]. The primary endpoint was chemotherapy completion rate. Patients who received standard 3 weekly carboplatin and paclitaxel had significantly improved PFS (12.5 months; 95%CI 10.3-15.3) compared to 3 weekly carboplatin (4.8 months; 95%CI 3.8-15.3) and dose-dense weekly carboplatin and paclitaxel (8.3 months; 95%CI 6.6-15.3), $p<0.0001$ with no worsening of treatment tolerance. Most importantly, this improvement in PFS was achieved with higher treatment completion rates (65% vs. 47% and 60% respectively). Patients in the carboplatin alone arm were most likely to discontinue treatment early due to disease progression ($p=0.004$).

The implications of this practice-changing study will be further discussed in future chapters.

Treatment delays have been demonstrated to be associated with reduced overall survival in older patients [46]. A number of studies have now addressed the question of whether chemotherapy dosing should be reduced in older patients to try and improve tolerance and treatment delivery. Reduced-dose carboplatin and paclitaxel has been demonstrated to be better tolerated in patients over the age of 70 than standard dosing without significantly compromising overall survival (OS 41 months in the lower dose group versus 44 months in the standard dose group p=0.451) [47]. Dose-dense chemotherapy has also been assessed specifically in older women and has been shown to be safe and well-tolerated in older women with 65% of participants completing the planned treatment course[48]. MITO-7 (NCT00660842) subsequently compared weekly Carboplatin (AUC 2) and paclitaxel (60mg/m2 per week) to standard 3 weekly dosing (Carboplatin AUC 6 and Paclitaxel 175mg/m2) in a non-age selected population of women with stage 1C-IV epithelial ovarian cancer [49]. There was no significant difference in overall survival (18.3 months dose-dense arm compared to 17.3 in the standard arm). In MITO-7, the trend towards improved progression-free survival with weekly chemotherapy was greatest in those over the age of 70.

In the recurrent disease setting there is a marked lack of an evidence base to guide clinical practice. Subgroup analysis of women over the age of 70

(n=157) treated within the CALYPSO trial (NCT00538603), comparing carboplatin/liposomal doxorubicin to carboplatin/paclitaxel in platinum-sensitive ovarian cancer was undertaken[50]. Women over age of 70 experienced a higher rate of ≥ grade 2 sensory neuropathy (24.4% versus 15.5%, P = 0.007) compared to younger patients. Rates of haematological toxicities did not differ between the age groups. Interestingly, ≥ grade 2 allergic reactions were less frequent in older patients than those less than 70 years old (13.9% versus 5.8%, P = 0.005). Older patients completed planned treatment as often as younger participants and there was no significant difference in median PFS or quality of life outcomes between older and younger patients. The carboplatin/liposomal doxorubicin combination appeared to have a better toxicity profile in older women with regarding alopecia, sensory neuropathy, arthralgia/myalgia and febrile neutropenia. Consistent with other phase three studies around 95% of patients 70 years old or over had a PS of 0 or 1 and therefore the applicability of these results to older patients in real-world clinical practice who may have a worse performance status are unclear.

## 1.6 Targeted therapy outcomes in older women

### 1.6.1 Bevacizumab

Bevacizumab, an anti-VEGF monoclonal antibody, targeting angiogenesis, has received European Medicines Agency (EMA) approval in combination with chemotherapy as first-line treatment ovarian cancer, for recurrent (platinum-sensitive and platinum-resistant) ovarian cancer. At present in

England however, bevacizumab is not currently funded in the relapse setting. The two studies that established the role of bevacizumab in combination with chemotherapy followed by maintenance treatment in the first line setting were ICON7 [51] and GOG 218 [52]. In ICON7 (NCT00483782), the median age was 57 and recruitment was limited to patients with an ECOG PS of 0 or 1. Currently, there is no published data regarding outcomes and toxicities regarding bevacizumab in the older population within these studies, although of note, increasing age was associated with increased severity of chemotherapy induced peripheral neuropathy[53]. In the GOG 218 trial (NCT00262847), which included patients with ECOG PS 2, the median age was 60 (range 22-89) and 23% of patients were over the age of 70. The improvement in PFS reported in GOG218 with the addition of bevacizumab was not limited to the younger population.

In the relapse setting, OCEANS (NCT00434642), a phase III study which demonstrated that the addition of bevacizumab to carboplatin in combination with gemcitabine followed by maintenance therapy improved PFS for first platinum–sensitive relapse. There was no significant difference in PFS between women aged above (35% of patients, n=85) and below 65 in the bevacizumab arm (12.3 and 12.5 months respectively) [54]. To date, there has been no subset analysis of treatment tolerance according to age. Post-hoc exploratory efficacy and safety analyses were performed in patients ≥65 years (37% of patients, n=133) compared to those <65 in the AURELIA (NCT00976911) trial which assessed the addition of

bevacizumab to investigator's choice of chemotherapy in platinum-resistant ovarian cancer[55] . Similar significant benefits from the addition of bevacizumab in terms of PFS and response rate were seen in older patients compared to the younger group (PFS hazard ratio <65 years 0.49; ≥65 0.47). There were no major differences in toxicities other than hypertension: ≥ grade 2 hypertension was higher in the ≥ 65 years group compared to <65 in the bevacizumab-treated arms (31% vs. 13%). In addition, hypertension at baseline prior to trial therapy was also more frequent in patients ≥ 65 than <65 years (46% vs. 13%)[55]. The OCTAVIA (NCT00937560)[56] trial, a single-arm study which evaluated the addition of bevacizumab to 3 weekly carboplatin and weekly paclitaxel (80mg/m2), included 20% and 9% of patients over the age of 65 and 70 respectively. The median PFS was 20.5 months in the ≥65s (n=37) compared to 24.4 months in the <65 group (n=152)[57]. The incidence of grade ≥3 bleeding was higher in older patients (3% vs. 0%, respectively)[56]. In keeping with the AURELIA subgroup analysis, hypertension at baseline and on treatment was higher in the ≥65s[58].

Bevacizumab, therefore has been demonstrated to be tolerable in an older population and older patients should be offered anti-angiogenic treatment where indicated taking into account the individual risks and benefits. Of note, hypertension is one of the most common medical comorbidities in older patients and bevacizumab-associated hypertension rates are higher in older patients receiving bevacizumab likely due to the higher background rates in this population. This should not necessarily preclude older patients being

considered for this treatment option however careful monitoring and treatment of hypertension prior to commencing and during bevacizumab therapy is required. A meta-analysis of phase 3 studies incorporating bevacizumab in both the first-line and relapse ovarian cancer failed to demonstrate an improvement in PFS in women over 70 (HR: 0.74, CI: 0.54 to 1.02; P = 0.067) [59]. This finding needs to be interpreted with caution given the relatively low numbers and nature of the analysis but clearly further studies, specifically targeting older patients with co-morbidities are required. A study assessing outcomes Bevacizumab in patients over the age of 70 with advanced ovarian cancer completed accrual in 2019, results are awaited (NCT02393898).

### 1.6.2 PARP inhibitors

Approximately 15% of all women with high-grade serous ovarian cancer will harbour a germline *BRCA* 1 or 2 mutation[60]. In addition to this, a proportion of tumours will exhibit “BRCAness” either due to a somatic *BRCA* 1 or 2 mutation or homologous recombination deficiency (HRD). Whilst *BRCA* 1 mutations occur in younger women, *BRCA* 2 mutations in particular have have been identified in patients over the age of 65 [61-63]. Three different poly (ADP-ribose) polymerase inhibitor (PARP) inhibitors are now licensed for treatment of both first-line and relapsed ovarian cancer, Olaparib, Niraparib and Rucaparib. PARP inhibitors have shown significant clinical activity in women with *BRCA* 1/2 mutations[64]. In the pivotal study that led to the approval of olaparib in Europe for women with platinum-sensitive ovarian cancer that harbour a *BRCA* mutation (germline or

somatic), olaparib as maintenance therapy following platinum-based chemotherapy significantly improved PFS compared to placebo (11.2 months vs. 4.2 months; HR 0.18, p< 0.0001 in the *BRCA* mutated cohort). 23% (n=17) of the *BRCA*-mutated cohort and 47% (n=27) of the non-*BRCA* group that received olaparib were ≥ 65 years and the oldest patient in the BRCA-mutated group was 89[62]. Tolerance and outcomes in older women were assessed in a pooled analysis of 8 studies, most were between the age of 65 and 75 and almost all were ECOG PS 0 or 1. No difference was seen in toxicity rates between patients aged over or under[65]. Niraparib, a highly-selective *PARP*-1/2 inhibitor given as a maintenance treatment following a response to platinum-based chemotherapy for relapsed disease has been demonstrated to significantly prolong PFS in patients with a *BRCA* mutation or HRD[66]. In a subsequent subgroup analysis of this study of older versus younger patients[67]. The MONITOR-UK study will further evaluate the real-world experiences of maintenance Niraparib (NCT04295577). Although PARP inhibitors are on the whole, better tolerated than chemotherapy, toxicities such as fatigue, nausea, neutropenia and anaemia if severe or mild but prolonged, may impact significantly on the functional capacity and quality of life of older patients.

### 1.7 The role of geriatric assessment

Comprehensive geriatric assessment (CGA) is a multi-systems review of frailty, comorbidities, geriatric syndromes, mental health, functional difficulties and social circumstances. It has been defined previously as a four-part clinical process of screening, assessment, intervention and follow-

through [68] which has been shown to detect more co-morbidities and functional issues than the standard oncological assessment of performance status [17, 69]. CGA has been the standard of care in care of the elderly practice for many years and in non-oncological settings, has been shown to improve function and quality of life [70-72]. In cancer care, CGA has also been shown to predict treatment tolerance and overall survival in some studies [73] but as yet, there are no interventional studies demonstrating an improvement in survival outcomes although this will be discussed at length in future chapters.

Hitherto, the term CGA has been used in a misleading way in oncology research describing studies that utilised screening or assessment without any management or interventions of deficits identified. The SIOG consensus guidelines [21] better delineate this difference and certainly in more recent years, the focus increasingly has moved beyond assessing the predictive and prognostic role of GA. Despite the wealth of data that now exists, studies remain fairly heterogeneous with no clear agreement on the essential parameters that should be included in a GA to assess older patients with cancer. In 2005, SIOG recommended that a CGA-based approach should be utilised to improve the detection of comorbidities and that follow-up of deficits identified be included in any form of CGA intervention [74]. The SIOG consensus on geriatric assessment states that the key domains in a GA considered to be important are: functional status, fatigue, comorbidities, cognitive impairment and mental health status, social support, nutrition and the presence of geriatric syndromes such as falls.

ASCO recommendations were published in 2018, outlining that all patients aged 65 or over receiving chemotherapy should undergo a geriatric assessment that includes the following domains, function, comorbidity, falls, depression, cognition and nutrition. A number of available tools were evaluated and the recommended tools will be discussed in more depth[20].

### 1.8 Available geriatric assessment tools and scores

Geriatric assessment in the oncological literature has taken a variety of forms including patient-completed questionnaires, healthcare professional-led questionnaires and a combination of both. Biological factors such as hypoalbuminaemia, haemoglobin levels and estimated glomerular filtration rate have sometimes been included. The time it takes to perform a GA in the oncology setting is a practical issue, both from a financial and time perspective and consequently there has been much interest in the development of abbreviated geriatric assessment and screening tools to identify those patients who would benefit from undergoing a full CGA. It has been shown that the questions from the full activities of daily living (ADL) and instrumental activities of daily living (IADL) can be condensed from a total of 18 to 6 and still recognise 98% of those who had a deficit identified from the full questionnaire [75]. The G8 score, one of the most well utilised and thus with the strongest evidence base was evaluated initially as a screening tool to identify older patients who may benefit from a full CGA in a prospective study that included 364 patients with solid malignancies over the age of 70 [76]. G8 consists of a brief questionnaire of 8 questions (7 of which are derived from the mini nutritional assessment (MNA)) with each

individual score ranging from 0 to 2 and a total maximal score of 17. A cut-off value of 14 or less was identified as providing reasonable sensitivity for requiring a full CGA. In the most recent SIOG recommendations, G8 was evaluated as one of the most reliable and sensitive of the screening tools available [77] to predict the need for a full CGA. VES-13, a scoring system based on 13 functional domains that have been validated in the non-oncological geriatric population to predict for mortality [78], has been shown to predict chemotherapy toxicity in older patients with cancer. 59% of older patients, irrespective of the score, experienced severe toxicity and, in keeping with previous findings ECOG PS was not shown to be a good predictor of tolerability s[18]. Both the G8 and the VES-13 screening scores have been recommended in the recent ASCO guidance.

In one of the largest prospective studies undertaken, Hurria et al prospectively assessed the predictive value of a number of geriatric assessment variables for chemotherapy toxicity [73]. 500 patients were assessed with a median age of 73. 17% of the patients included had a gynaecological malignancy. The assessment consisted of the physician evaluated Karnovsky Performance Status (KPS), “Timed up and Go” (a measure of functional status) and a cognitive test. Patients also completed a geriatric-assessment questionnaire evaluating functional status, medical comorbidities, mental state, social activity, social support and nutrition assisted by a healthcare professional when necessary. An 11-point model was derived from evaluation of risk factors associated with severe toxicity combined with factors also considered to be important such as

chemotherapy dosing (summarised in Table 1). A “high-risk” score was associated with 83% grade 3 or 4 toxicity compared to 30% for a “low-risk” score, highlighting a substantial, clinically relevant rate of severe treatment-related toxicity even in a “low-risk” elderly population. Of note, physician-evaluated KPS was not shown to correlate with risk of chemotherapy toxicity.

### 1.9 Studies to date that have incorporated geriatric assessment

The GINECO group reported the first study that prospectively assessed the use of a geriatric assessment, the Geriatric Vulnerability Score (GVS) [42]. Multivariate analysis of overall survival demonstrated a negative prognostic impact from age, emotional disorders as well as stage IV disease and lymphopenia at presentation. 111 patients with a median age of 79 (range 71-93, 41% of whom were over the age of 80) and a diagnosis of advanced epithelial ovarian cancer received single-agent Carboplatin at AUC5. 74% of patients completed the planned 6 cycles; 10 patients stopped treatment early due to toxicity and 5 patients subsequently died from toxicity-related complications. The survival score developed retrospectively is a sum of five covariates (ADL, IADL, Lymphopenia, HADS (Hospital Anxiety and Depression scale) and hypoalbuminaemia)) each assigned a value of one. A deficit in 3 or more covariates resulted in a risk ratio of mortality of 2.94 ($p=0.0006$). This cut–off, also discriminated two groups with significantly different treatment completion, severe adverse events and unplanned hospital admissions rates [79]. There are no clinical studies evaluating the role of GA in endometrial, cervical cancer or recurrent ovarian cancer.

A prospective cohort study, GOG-0273 (NCT01366183) [80], evaluated the role of geriatric assessment to predict toxicity to one of two regimens, single-agent carboplatin or carboplatin/paclitaxel (patient and physician's choice) as first line therapy. In this study, rates of completion of 4 cycles of chemotherapy were higher in the combination cohort (92% combination arm vs. 75% single agent). Overall, the patients in the combination cohort were younger (mean age 73 versus 83) and fitter (PS 2 or 3 11% combination arm versus 37% single agent). In this study, IADL was not found to correlate with tolerance to chemotherapy. However, limitation in social activities was significantly associated with reduced ability to tolerate chemotherapy. A third arm consisting of weekly Paclitaxel has been added and is currently recruiting.

### 1.10 Biological markers of frailty

The development of biological markers of frailty that have the ability to successfully differentiate between older patients who are fit for cancer therapies and those who are more at risk, predict toxicity and survival outcomes has clear and obvious clinical utility. This area remains relatively under studied but some of the potential biomarkers will be discussed in more depth in Chapter 5.

## 1.11 Conclusions and Future work

The evidence base for treating older women with ovarian cancer has improved significantly over the past two decades. It is now clear that geriatric assessment should be considered as standard of care for all older women being considered for systemic anti-cancer therapy in order to highlight issues that would be overlooked in a routine oncological assessment, to better risk-stratify those patients at highest risk of treatment related toxicity and ultimately to enable deficits identified to be addressed in order to facilitate optimal treatment including surgery. The role of prehabilitation in the surgical context needs to be further developed and larger studies assessing both surgical and patient-reported outcome measures as well as cost-efficacy analysis need to be undertaken.

Further understanding of the reasons behind the poorer outcomes seen in older patients can be developed with large retrospective analyses of recent practice. The findings of a retrospective study undertaken across two cancer centres will be presented in Chapter 2. In Chapter 3, the role of a non-invasive prognostic biomarker, sarcopenia, in the context of ovarian cancer will be discussed. Chapter 4 presents the findings of a qualitative study on the treatment expectations and experiences of older women who have received or are receiving systemic anti-cancer therapy for ovarian cancer, an area that has been hitherto under-explored.

Full-geriatrician led CGA with follow-up has yet to be shown to improve outcomes in any cancer setting to date. To address this, two large

prospective interventional studies randomising CGA-led approach compared to standard oncological assessment (PREPARE)[81], GIVE (NCT02785887) are in progress and will be discussed in due course. Full CGA for every cancer patient over the age of 65 has significant practical resource implications. In a recent UK survey, oncologists reported that they do not have ready and available access to specialist geriatric services[82]. An increasingly aged population has led and will continue to lead to a higher proportion of patients in the oncology clinic with multimorbid and socially complex backgrounds and expertise in geriatric oncology will increasingly be required for oncology healthcare professionals. A significant up-skilling in the management of common and pertinent geriatric issues is required. There is a clear need for studies assessing the practical ways in which a geriatric assessment and targeted interventions to address deficits identified could be incorporated into the oncology clinic. One proposed approach to address this is the FAIR-O study, conceptualised by the researcher will be outlined in Chapter 5.

# 2 RETROSPECTIVE REVIEW OF TREATMENT PATTERNS AND OUTCOMES IN TWO UK CANCER CENTRES

## 2.2.1 Background

Ovarian cancer is predominantly diagnosed in older women with around half of all new diagnoses occurring in women over the age of 65. Older patients are less likely to be enrolled in clinical trials[14, 83] that go on to dictate current gold standards. Treatment decisions are usually based on clinical trial results that include a younger, less frail population and applied to an older and often less well group. The efficacy and tolerability of standard of care and novel therapies in an older, potentially frailer population are therefore not clearly understood.

It has long been shown that survival outcomes are disproportionately poorer in older patients[84]. The reasons for this remain incompletely understood but as discussed in the previous introductory chapter, delayed diagnosis/late presentation[10], higher rates of emergency presentation[85], more advanced disease at diagnosis[3, 7, 84], higher rates of unclassified or unclassifiable tumours[84] as well as poorer physical performance status and higher prevalence of medical and functional comorbidities[86] are all likely to play a role.

Developing our understanding of “real-world” experience of treatment for ovarian cancer in an older population is essential to learn how to address

survival outcome discrepancies. Firstly, without contemporaneous data, the scope of the problem regarding survival outcomes cannot be fully appreciated. Secondarily, a clear understanding of the potential risks and hopeful benefits is paramount to directing honest and open patient-centred discussions around potential treatment options. Until the reasons for the difference in survival between older and younger women are more clearly understood, efforts to address the gaps and improve outcomes in our older population will be hampered.

### 2.2.2 Benchmarking data

Institutional outcomes can be benchmarked against national and international registry outcomes. Staging data collected by the National Cancer Registration Service (NCRS) from patients diagnosed in the United Kingdom in 2012 demonstrated that younger patients were more likely to be diagnosed at an earlier stage. Older patients had significantly higher modelled excess mortality rate ratios, 3.53 in patients aged 70-79 vs. 8.98 in patients aged 80-89 years old ($p<0.001$)[87].

Cancer registry data have been assessed on an international scale by two large groups, the EUROCARE[88-91] series and the International Cancer Benchmarking Partnership (ICBP) [3, 7, 9, 12]. It has consistently been shown in both recent series that older women have significantly poorer survival outcomes[12, 92] and notably that an improving trend in 1 and 5-year survival for all age groups is observed excepting those aged over 75 years old[2]. Updated data on breast and gynaecological cancers from the EUROCARE 5 series was presented in 2015. Once again, the gap in

survival between middle-aged and older women was striking. 1-year survival for ovarian cancer for women aged between 55 and 64 was 82.8% compared to 46.4% for those aged over 75[93]. The UK had lower survival outcomes for ovarian cancer than other Western nations; a delay in diagnosis and later stage at diagnosis was postulated as a potential explanation (table 1.).

| Study | Year | Population | 1 year survival | | 5 year survival | |
|---|---|---|---|---|---|---|
| EUROCARE-4 [94] | 2009 | Europe wide cancer registry data | 55-69 years | 78.5 (76.6-80.4) | 55-69 years | 39.8 (37.5-42.2) |
| | | | 70-84 years | 55.5 (53.1-58.1) | 70-84 years | 25.0 (22.6-27.6) |
| Extension of EUROCARE 4 [2] | 2012 | Europe wide cancer registry data<br>72 cancer registries across 29 countries | | | 55-74 years | 58.6 (57.4-59.8) |
| | | | | | 75-99 years | 20.5 (19.1-21.9) |
| EUROCARE 5[5] | 2015 (Data from 2000-2007) | Europe wide cancer registry data<br>80 cancer registries across 29 countries | 55-64 years | 82.8 | 55-64 years | 44.5 |
| | | | 65-74 years | 71.6 | 65-74 years | 33.9 |
| | | | 75+ years | 46.4 | 75+ years | 20.1 |
| ICBP-2[12] | 2019 (2010-2014) | Australia, Canada, Denmark, Ireland, New Zealand, Norway and the United Kingdom | 55-64 years | 82.4 (81.3-83.5) | 55-64 years | 56.6 (55.2-58) |
| | | | 65-74 years | 73.7 (72.5-74.8) | 65-74 years | 45.5 (44.2-46.7) |
| | | | 75+ years | 45.0 (43.7-46.2) | 75+ years | 24.0 (22.9-25.1) |

**Table 1. International Cancer Registry Data.**

**Survival outcomes according to age cohort**

### 2.2.3 Under-treatment

Historically older women have been shown to receive less treatment than their younger counterparts. A large retrospective study in France assessed the impact of age on treatment and survival outcomes whether or not guideline-recommendations for therapy were followed. 1151 patients over a 14-year period (1997-2011) were included in the analysis. Women over the

age of 70 compared to those younger were less likely to undergo surgery (60.9% versus 89.6%, p<0.0001) or receive chemotherapy (57.4% versus 76.4%, p<0.0001). Only 31.9% of patients over the age of 70 underwent both surgery and chemotherapy. 1 and 5-year survival for those over the age of 70 who were treated according to guidelines were 73% and 26% respectively compared to 56% and 18% for those who were not[95]. A prospective study (OVCAD) included 275 women treated for primary ovarian cancer between 2005 and 2008. 17.1% of women were over the age of 70. Older women were less likely to receive optimal therapy, defined as no residual tumour at end of surgery and combination chemotherapy (40.4% versus 70.1%, p<0.001). Older women were less likely to undergo primary debulking surgery (70.2% vs 84.6%, p=0.019) and less likely to receive platinum combination chemotherapy (78.7% versus 97.8%, p<0.001). In this series, median OS for those aged <70 years was 64 months compared to 30 months in those over 70 years old (p<0.001). Age remained an independent risk factor for poorer overall but not progression-free survival after adjusting for FIGO stage, grade, lymph node status, residual tumour, peritoneal carcinomatosis, serous versus non-serous histology and ECOG performance status [25].

The field of geriatric oncology has rapidly developed over the last two decades. The core principles outline the need to holistically assess patients using a comprehensive geriatric assessment rather than basing treatment decisions purely on chronological age and ECOG performance status. This

approach has now been recommended by a number of bodies including the SIOG[21] and ASCO[20].

Although there appears to be a drive to try to address the apparent discrepancy in the treatment of older patients, it is not yet clear whether these principles have filtered down into routine clinical practice. There has not been a recent re-evaluation in the UK of current practice, treatment tolerance and survival outcomes in older women with ovarian cancer. In order to understand where the gaps lie in the treatment of older patients, studies incorporating more detailed assessment of baseline characteristics, in non-selected/real-world populations beyond the scope of most cancer registries are required.

## 2.3 Methods

Local study approvals were received from the Royal Marsden NHS Foundation Trust (RMH) and The Royal United Hospitals Bath NHS Foundation Trust (RUH) (SE386).

### 2.3.1 Study Design

This was a retrospective observational evaluation of all women aged 65 and over treated consecutively for newly diagnosed epithelial ovarian cancer over a five-year period (December 2009 to August 2015). This time period was chosen as the last patient entered, would by the time of data collection have at least one year of follow up and would allow a sufficient number of

eligible patients to provide meaningful statistical analysis. Data were collected using the electronic patient records at both trusts. Standard of care treatment was defined as undergoing debulking surgery at any stage in the primary treatment pathway in combination with platinum-based chemotherapy. Details of treatment received, medical comorbidities, polypharmacy, functional level at baseline (where possible) as well as routinely assessed haematological and biochemical parameters were collected. Where toxicities had not been graded in real-time, according to the description of the event, retrospective grading was applied using the common terminology criteria for adverse events (CTCAE) v4.0 for all grade haematological toxicities. Interpreting the description of low-grade non-haematological toxicities retrospectively from the electronic patient record was considered to be methodologically unreliable and therefore only details of grade 3 or higher non-haematological toxicities were collected.

Following completion of data collection at the Royal Marsden, a collaboration was formed with Dr Rebecca Bowen, consultant medical oncologist at Royal United Hospitals, Bath. These data were subsequently merged with the Royal Marsden data to form a larger, broader dataset.

### 2.3.2 Study primary objectives:

- To assess the proportion of women over the age of 65 who are offered and receive standard of care first-line management

### 2.3.3 Study secondary objectives:

- To assess the progression-free and overall survival from first-line treatment
- To assess the progression-free and overall survival from treatment at first relapse
- To assess the proportion of patients who receive treatment for relapsed disease
- To determine the rate of 30 day peri-operative complications according to the Clavien Dindo classification (RMH only)
- To assess the length of ICU and inpatient stay for cytoreductive surgery (RMH only)
- To assess the time between surgery and next systemic chemotherapy (RMH only)
- To determine the rates of treatment delays and dose reductions in patients in first-line treatment and treatment at relapse
- To assess the proportion of patients who receive targeted agents e.g. bevacizumab
- To assess the proportion of patients offered entry onto a clinical study
- To assess the rate and severity of haematological toxicity to chemotherapy (anaemia, thrombocytopenia and neutropenia)
- To assess the rate and severity of non-haematological toxicities to chemotherapy
- To assess the rate of hospital admissions during chemotherapy

- To assess the rate of 30 day mortality during chemotherapy
- To assess the rate of functional dependence (assistance with one or more ADLs) at baseline
- To assess the rate of hearing or visual impairment at baseline

### 2.3.4 Patient eligibility

Patients were considered eligible if they were aged 65 years or older at the time of their first new patient appointment with a histologically or cytologically confirmed diagnosis of epithelial ovarian, primary peritoneal and fallopian tube carcinoma at either the Royal Marsden NHS Foundation Trust or the Royal United Hospital Trust, Bath.

## 2.4 Statistical analysis plan

Given the retrospective nature of this study the statistical analysis is primarily descriptive with proportions represented as frequencies with 95% confidence intervals. Fishers chi squared test was used to compare proportions across categorical variables. Linear regression analysis was used to assess the relationships between continuous variables. Lengths of time between surgery and discharge from hospital and date of commencement of next cycle of systemic chemotherapy are described as mean and median times along with interquartile range and range. Progression-free survival was measured from start of treatment (both first line and first-relapse) to date of radiological progression (as per local report)

or death from any cause. Overall survival was defined as the time from date of diagnosis or date of relapse (depending on the endpoint) to death. Standard of care treatment was defined as undergoing debulking surgery at any stage in the primary treatment pathway in combination with platinum-based chemotherapy. Details of treatment received, medical comorbidities, polypharmacy, functional level at baseline (where possible) as well as routinely assessed haematological and biochemical parameters were collected. Where toxicities had not been graded in real-time, according to the description of the event, retrospective grading was applied using CTCAE v4.0 for all grade haematological and grade ≥3 non-haematological toxicities.

Death certificate details were not routinely available and therefore precise disease-specific mortality could not be collected. An approximation of this was determined by defining those patients that passed away having been discharged to best supportive care or those who had clear and definite disease progression within 30 days of death were considered to have died as a result of their disease. Where there was any doubt that death was related to disease, this was not considered to be disease-specific. Patients without an event were censored at last follow up. Data were censored on the 1st August 2016.

The Kaplan-Meier method was used to produce survival estimates, median survival is presented with 95% confidence intervals. Hazard ratios for survival, adjusted for factors likely to be significant such as age, stage and

treatment received were calculated using a cox proportional hazards model. All tests are two-sided. A p-value of <0.05 was used to determine statistical significance. All statistical analyses were performed using Stata IC v15.

## 2.5 Results

### 2.5.1 Baseline characteristics

280 patients met the inclusion criteria. Patients were divided into four age cohorts (65-69 years, 70-74 years, 75-79 years and >80 years) to allow for analysis of trends of change in treatment with increasing age. 76% of patients had stage 3 or 4 disease at presentation (table 2.). Stage distribution did not alter with increasing age (p=0.293) (figure 1).

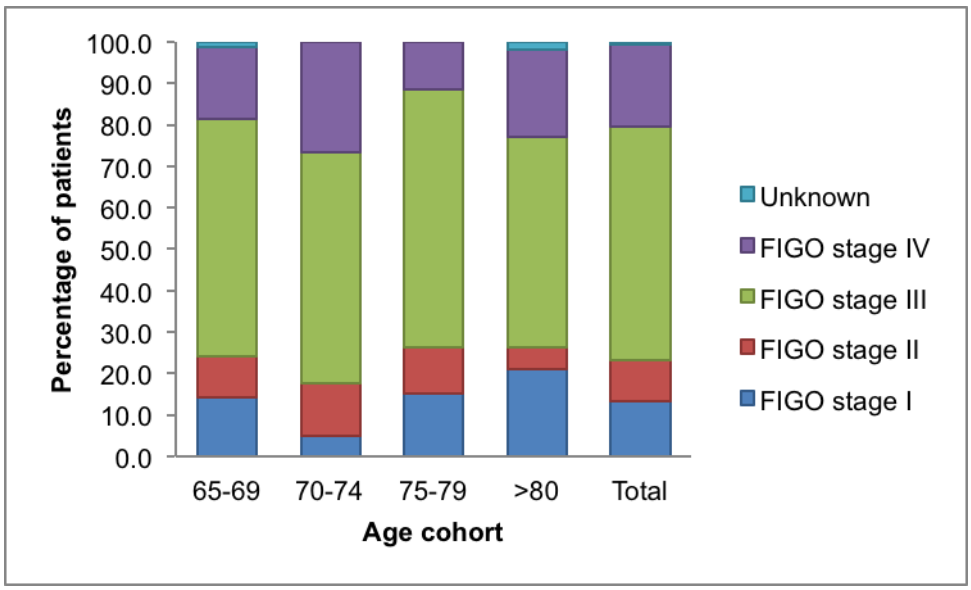



**Figure 1. Stage distribution by age cohort**

64% patients were ECOG performance status 0 or 1, the remainder were stage 2 or 3 (29%), no patients were recorded as performance status 4 and for 21 (7%) patients, ECOG performance status was not recorded. Increasing age was significantly associated with a worsening ECOG

performance status (p=0.008) with for example, 49% of patients over the age of 80 being PS 0 or 1 compared to 71% of patients in the 65-69 years cohort (figure 2.).

| | 65-69 years n=91 | 70-74 years n=79 | 75-79 years n=53 | >80 years n=57 | Total n=280 | p |
|---|---|---|---|---|---|---|
| FIGO stage | | | | | | |
| 1 | 13 (14.3) | 4 (5.1) | 8 (15.1) | 12 (21.1) | 37 (13.2) | 0.293 |
| 2 | 9 (9.9) | 10 (12.7) | 6 (11.3) | 3(5.3) | 28 (10.0) | |
| 3 | 52 (57.1) | 44 (55.7) | 33 (62.3) | 29 (50.9) | 158 (56.4) | |
| 4 | 16 (17.6) | 21 (26.6) | 6 (11.3) | 12 (21.1) | 55 (19.6) | |
| Unknown | 1 (1.1) | 0 | 0 | 1 (1.7) | 2 (0.7) | |
| ECOG Performance status | | | | | | |
| 0 | 30 (33.0) | 12 (15.2) | 9 (17.0) | 5 (8.8) | 56 (20.0) | 0.008 |
| 1 | 34 (37.4) | 38 (48.1) | 27 (50.9) | 23 (40.4) | 122 (43.6) | |
| 2 | 14 (15.4) | 18 (22.8) | 8 (15.1) | 15 (26.3) | 55 (19.6) | |
| 3 | 5 (5.5) | 9 (11.4) | 3 (5.7) | 9 (15.8) | 26 (9.3) | |
| Unknown | 8 (8.8) | 2 (2.5) | 6 (11.3) | 5 (8.8) | 21 (7.5) | |
| Histological subtype | | | | | | |
| High grade serous | 62 (68.1) | 57 (72.2) | 36 (67.9) | 40 (70.2) | 195 (69.6) | 0.547 |
| Low grade serous | 3 (3.3) | 3 (3.8) | 3 (5.7) | 3 (5.3) | 12 (4.3) | |
| Carcinosarcoma | 6 (6.6) | 5 (6.3) | 4 (7.5) | 6 (10.5) | 21 (7.5) | |
| Clear cell | 8 (8.8) | 1 (1.3) | 2 (3.8) | 1 (1.8) | 12 (4.3) | |
| Endometrioid | 7 (7.7) | 3 (3.8) | 2 (3.8) | 2 (3.5) | 14 (5.0) | |
| Mucinous | 1 (1.1) | 2 (2.5) | 0 | 0 | 3 (1.1) | |
| Adenocarcinoma/ Mixed/ Undifferentiated/ Unknown | 4 (4.4) | 8 (10.1) | 6 (11.3) | 5 (8.8) | 23 (8.2) | |
| Medical comorbidities | | | | | | |
| Cardiovascular disease | 26 (28.6) | 21 (26.6) | 16 (30.2) | 14 (24.6) | 77 (27.5) | 0.907 |
| Hypertension | 37 (40.7) | 28 (35.4) | 22 (41.5) | 26 (45.6) | 113 (40.4) | 0.650 |
| Previous malignancy | 5 (5.5) | 4 (5.1) | 6 (11.3) | 1 (1.8) | 16 (5.7) | 0.183 |
| Endocrine disease | 7 (7.7) | 5 (6.3) | 5 (9.4) | 3 (5.3) | 20 (7.1) | 0.834 |
| Osteoarthritis | 4 (4.4) | 5 (6.3) | 7 (13.2) | 4 (7.0) | 20 (7.1) | 0.252 |
| Rheumatological disease | 2 (2.2) | 7 (8.9) | 2 (3.8) | 1 (1.8) | 12 (4.3) | 0.122 |
| CVA/MI/CAD | 7 (7.7) | 4 (5.1) | 6 (11.3) | 3 (5.3) | 20 (7.1) | 0.512 |
| Haematological disease | 0 | 2 (2.5) | 0 | 0 | 2 (0.7) | 0.167 |
| Previous DVT | 15 (16.5) | 8 (10.1) | 8 (15.1) | 4 (7.0) | 35 (12.5) | 0.345 |
| Polypharmacy ( ≥3 meds) | 31 (34.1) | 27 (34.2) | 23 (43.4) | 30 (52.6) | 111 (39.6) | 0.010 |
| Respiratory disease | 6 (6.6) | 15 (19.0) | 6 (11.3) | 1 (1.8) | 28 (10.0) | 0.007 |
| Diabetes | 9 (9.9) | 7 (8.9) | 6 (11.3) | 7 (12.3) | 29 (10.4) | 0.850 |
| Cognitive impairment* | 0 | 2 (2.5) | 0 | 6 (10.5) | 8 (2.9) | 0.001 |
| History of delirium in last 12 months* | 0 | 0 | 0 | 3 (5.3) | 3 (1.1) | 0.007 |
| Depression | 6 (6.6) | 4 (5.1) | 0 | 1 (1.8) | 11 (3.9) | 0.193 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Functional limitations | | | | | | |
| Lives alone | 20 (22.0) | 31 (39.2) | 18 (34.0) | 29 (50.9) | 98 (35.0) | 0.000 |
| Lives in supported accommodation | 0 | 1 (1.3) | 2 (3.8) | 4 (7.0) | 7 (2.5) | 0.032 |
| Use of walking aids | 7 (7.7) | 12 (15.2) | 11 (20.8) | 14 (24.6) | 44 (15.7) | 0.026 |
| Reduced activities of daily living | 16 (17.6) | 22 (27.9) | 13 (24.5) | 19 (33.3) | 70 (25.0) | 0.226 |
| Assistance with activities of daily living | 7 (7.7) | 10 (12.7) | 8 (15.1) | 10 (17.5) | 35 (12.5) | 0.441 |
| Weight loss in last 3 months | 22 (24.2) | 22 (27.9) | 11 (20.8) | 11 (19.3) | 66 (23.6) | 0.799 |
| Visual impairment | 3 (3.3) | 1 (1.3) | 2 (3.8) | 9 (15.8) | 15 (5.4) | 0.016 |
| Hearing impairment | 1 (1.1) | 0 | 2 (3.8) | 3 (5.3) | 6 (2.1) | 0.242 |
| History of falls in last 12 months | 1 (1.1) | 0 | 1 (1.9) | 3 (5.3) | 5 (1.8) | 0.106 |

**Table 2. Patient characteristics according to age cohort**

* as documented in the first new patient letter on the electronic patient record

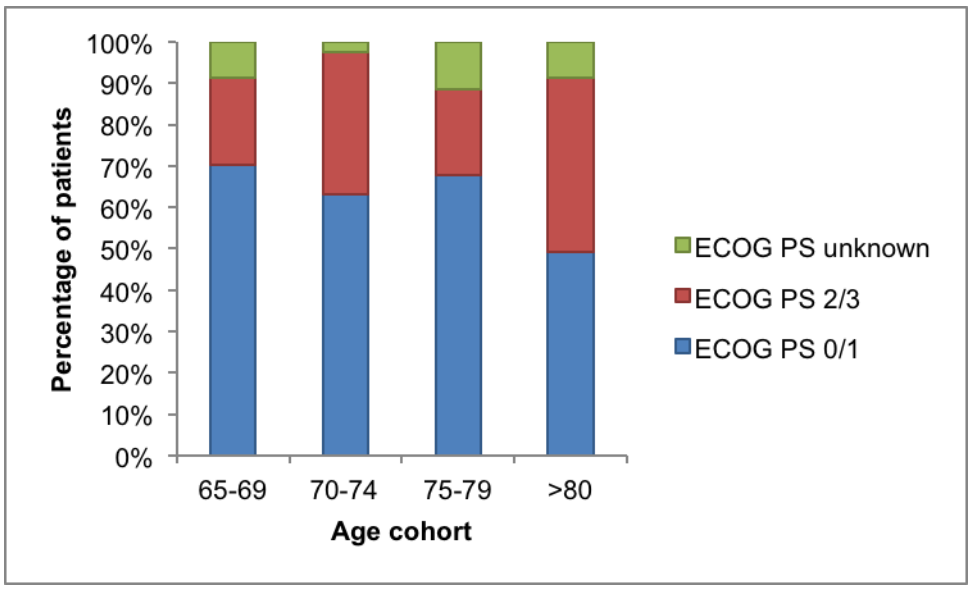



**Figure 2. Association between age and ECOG performance status**

Anaemia at all degrees of severity was common, 49% women were anaemic (any grade) at baseline with 11% patients having a Grade 2 or higher anaemia. Impaired renal function at the start of treatment was also common with 37% of all patients having a mild-moderate reduction of glomerular-filtration rate (GFR) of 60ml/min or less. 41% patients had an

albumin below 35g/l at baseline and 23% of patients had an albumin less than 30g/l. Linear regression analysis demonstrated that hypoalbuminaemia was not significantly associated with increasing age (p=0.36) (table 3.)

| Baseline Laboratory values | Proportion of patients | 95% Confidence interval |
|---|---|---|
| Albumin ≤ 30 g/l | 22.5% | (17.7-27.8) |
| Albumin ≤ 35 g/ | 40.7% | (35.9- 46.7) |
| GFR < 60ml/min | 37.1% | (34.4-43.1) |
| Haemoglobin < 120 g/l | 48.9% | (42.9-54.9) |
| Haemoglobin < 110 g/l | 27.5% | (22.4-33.1) |
| Haemoglobin <100 g/l | 11.4% | (79.5-15.7) |

**Table 3. Baseline laboratory values**

Medical comorbidities were collected as documented at the first new patient clinic appointment. The most commonly documented comorbidities were cardiovascular disease (28%), hypertension (40%), respiratory disease (10%) and diabetes (10.4%). Polypharmacy at the initial consultation, defined as taking 3 or more daily medications was present in 40% of patients. Neither cardiovascular disease nor hypertension was associated with increasing age. Factors and comorbidities significantly associated with age were polypharmacy (p=0.01), respiratory disease (p=0.007) and cognitive impairment (p=0.001) (table 2.).

Increasing age was associated with a higher proportion of women living alone (51% in those over the age of 80 compared to 22% in those aged 65-69 years, p=0.000). Older women were also significantly more likely to live in supported accommodation (p=0.032), use a walking aid (p=0.026) or have a degree of visual impairment (p=0.016). A quarter of all patients reported reduced activities of daily living in the weeks and months

preceding their diagnosis. Self-reported weight loss was also prevalent with 24% of patients reporting weight loss over the 3 months prior to their diagnosis (table 4.). Overall 22% of patients presented as an emergency. The proportion of patients who presented as an emergency did not vary with increasing age (p=0.755) (table 2.)

### 2.5.2 First-line treatment received

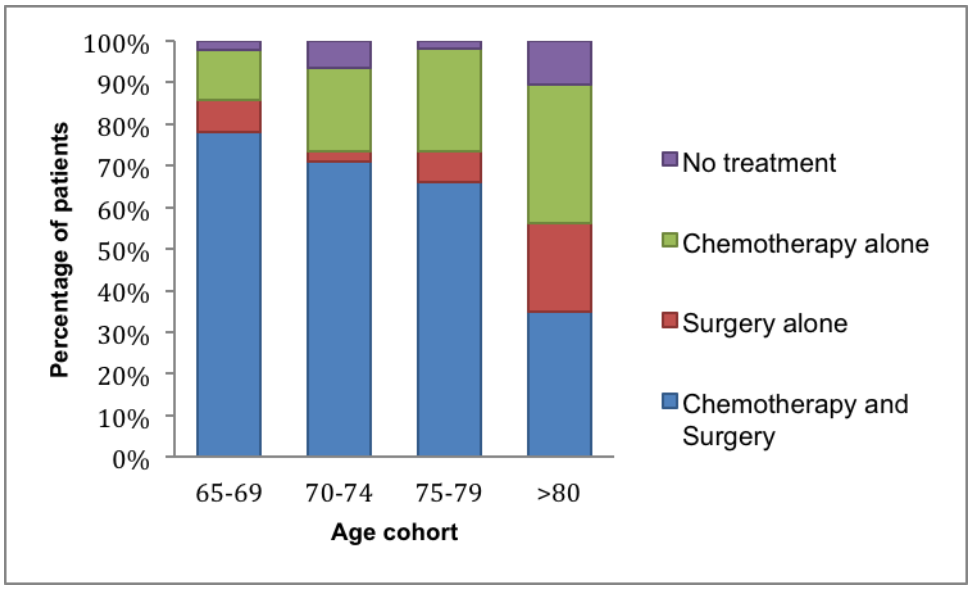



**Figure 3. Primary treatment received according to age cohort**

65% of patients received standard of care cytoreductive surgery and platinum-based chemotherapy. Increasing age was associated with lower rates of receiving standard of care therapy with 35% of those over the age of 80 receiving both chemotherapy and surgery compared to 78% in those aged 65-69 years (p=0.000). 10% of patients over the age of 80 received no active anti-cancer treatment (figure 3.). Six (2%) patients declined surgery and three (1%) declined chemotherapy.

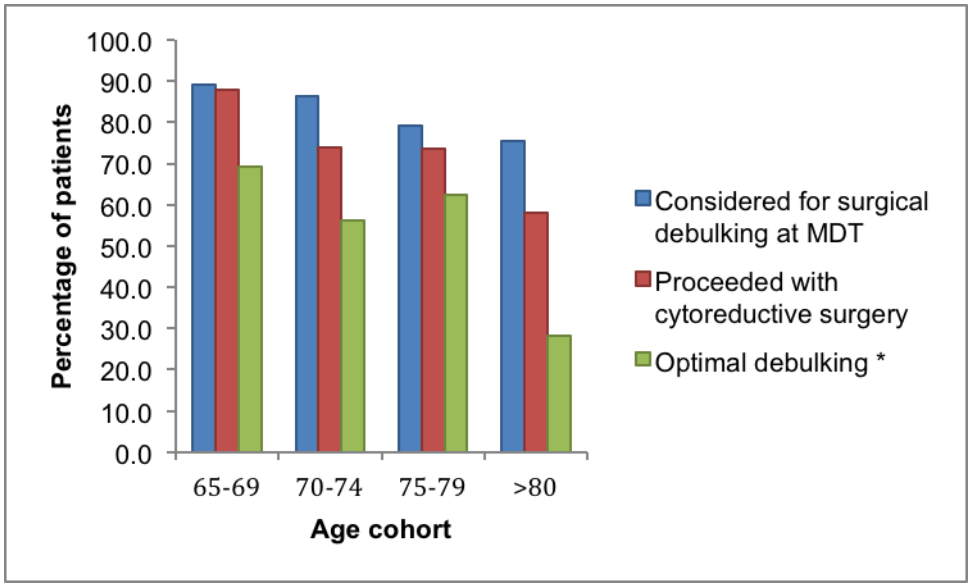



**Figure 4. Surgical status according to age**

* Defined according to the operative report, at least <1cm macroscopic residual disease

Increasing age was also associated with lower rates of undergoing cytoreductive surgery (p=0.001) as well as complete cytoreduction (defined according to the post-operative surgical report) (p=0.006) with only 28% those in the oldest group both proceeding with cytoreductive surgery and having complete cytoreduction compared to 69% in those aged 65-69. When optimal cytoreduction is expressed as a proportion of those who underwent surgery, the rates of optimal cytoreduction are above 76% in all age cohorts apart from those over 80 where this dropped to 49% (figure 4.). There was a trend towards clear documentation of surgery being considered as an option at multidisciplinary team meetings being less common with increasing age (p=0.088).

### 2.5.3 Surgical outcomes (RMH patients only)

Surgical outcome data including complication rates, length of surgery was only available from Royal Marsden Hospital patients (n=208). Median length of surgery was 219 minutes (range 60-625). A lower mean duration of surgery was noted in those women over the age of 80 although this did not reach statistical significance (p=0.133) (fig 6). Median length of stay was 11 days (range 2-111). A trend was observed between increasing length of stay and age; this did not reach statistical significance (p=0.06). The longest admission of 111 days was in an 82 year-old patient. In those patients who had primary or interval debulking surgery, the median time between surgery and next cycle of chemotherapy was 36 days (range 14-120) (table 4.). There was no statistically significant relationship between age and time to next chemotherapy (p=0.842). Rates of post-operative complications were recorded and graded according to the Clavien Dindo classification. 47% of patients experienced a surgical complication of any grade. 43% of all complications were grade 1. Complication rates did not vary with age (p=0.189).

| | Median | Mean | IQR | Range |
|---|---|---|---|---|
| Length of surgery (minutes) | 219 | 244 | 180; 300 | (60-625) |
| CCU admission (hours) | 45 | 55 | 26; 56 | (3-600) |
| Interval from surgery to next chemotherapy (days) | 36 | 38 | 29; 47 | (14-120) |
| Inpatient length of stay (days) | 9 | 11 | 6; 37 | (2-111) |

**Table 4. Duration of surgery, Critical Care Unit (CCU) admission, Length of stay and interval from surgery to next chemotherapy**

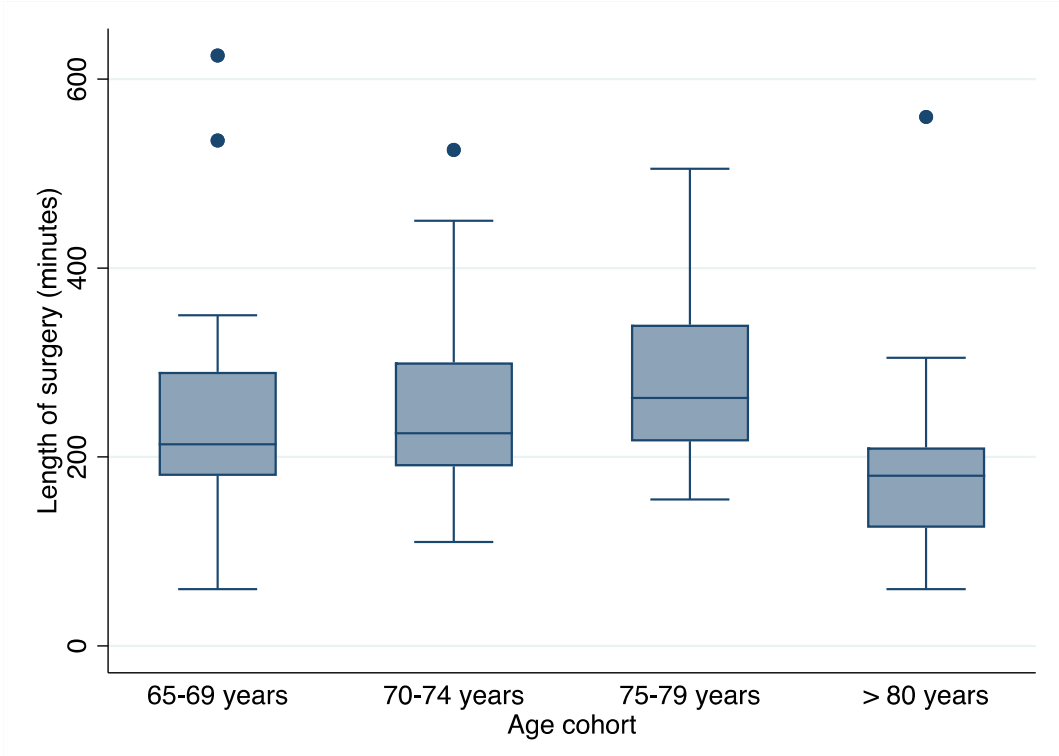



**Figure 5. Box plot displaying length of surgery according to age cohort (median, IQR, range and outliers)**

### 2.5.4 First-line chemotherapy

53.7% of women underwent doublet, platinum-based chemotherapy as first-line treatment. 6% patients did not receive chemotherapy due to this not being indicated in the opinion of the oncology team. Three patients (1%) declined to receive chemotherapy. Older women were significantly less likely to undergo doublet chemotherapy (19% in those over the age of 80 compared to 74% in those aged 65-69 years, p=0.000) (table 5, figure.6).

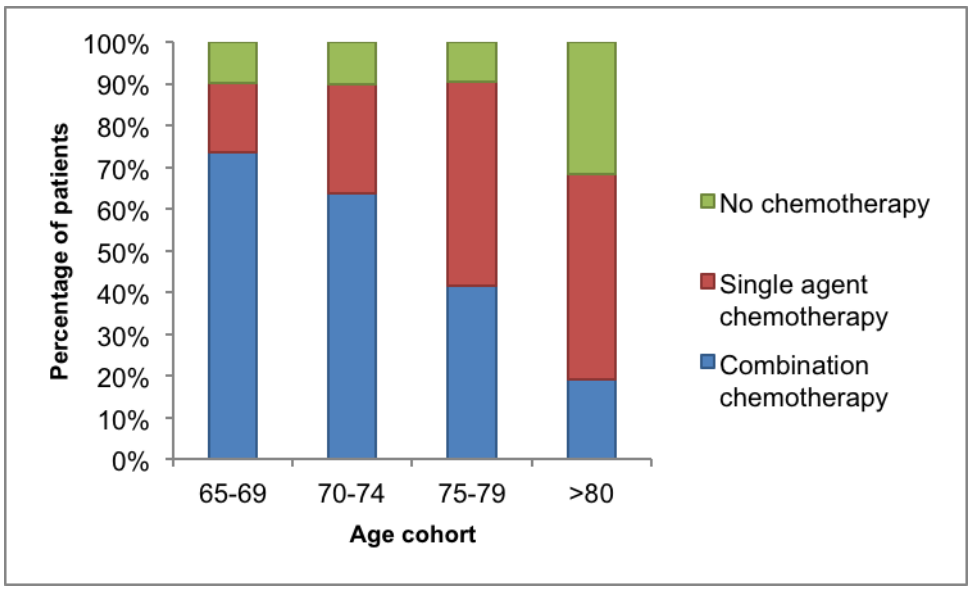



**Figure 6. First-line chemotherapy received according to age**

Overall, 8% women over the age of 65 received any form of targeted therapy during first-line treatment however this proportion decreased with advancing age. 2.3% of women over the age of 80 compared to 12.36% women between the ages of 65-69 received some form of targeted therapy during first-line treatment (p=0.05).

### 2.5.5 Primary treatment in women with advanced (FIGO Stage III/IV disease only)

| | 65-69 years n=68 (31.9%) | 70-74 years n=65 (30.5%) | 75-79 years n=39 (18.3%) | >80 years n=41 (19.3%) | Total n=213 | p-value |
|---|---|---|---|---|---|---|
| Underwent cytoreductive surgery | 56 (17.7%) | 44 (67.7%) | 25 (65.1%) | 19 (46.3%) | 144 (67.7%) | 0.001 |
| Complete cytoreduction * | 39 (70.9%) | 30 (68.2%) | 20 (76.9%) | 6 (33.3%) | 95 (66.4%) | 0.014 |
| Platinum doublet | 54 (79.4%) | 43 (66.2%) | 16 (41.0%) | 11 (26.8%) | 124 (58.2%) | |
| Single agent carboplatin | 8 (11.8%) | 17 (26.2%) | 21 (53.9%) | 22 (53.7%) | 68 (31.9%) | 0.000 |
| No chemotherapy | 6 (8.8%) | 5 (7.7%) | 2 (5.1%) | 8 (19.5%) | 21 (9.9%) | |
| Optimal treatment | 52 (76.5%) | 44 (67.9%) | 24 (61.5%) | 14 (34.2%) | 134 (62.9%) | 0.000 |

**Table 5. Primary treatment received in patients with FIGO stage III/IV disease at diagnosis. * (of those who underwent surgery)**

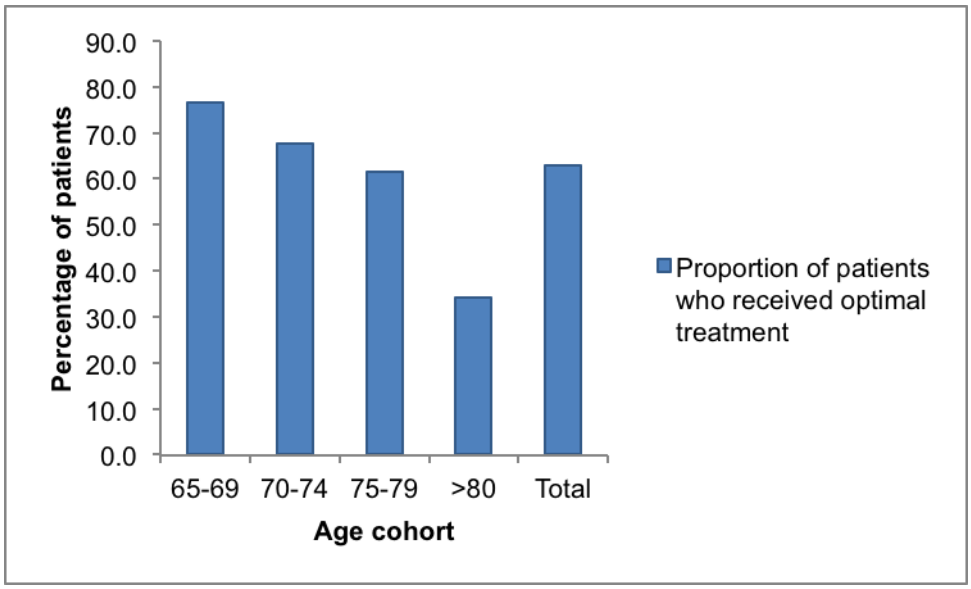



**Figure 7. Proportion of patients with FIGO stage III/IV disease who received standard of care first-line treatment (defined as cytoreductive surgery and commencing platinum-based chemotherapy)**

### 2.5.6 Tolerance of first-line chemotherapy

Increasing age was significantly associated with a lower likelihood of completing 6 cycles (p=0.008). Grade 2 or higher haematological toxicities were reported in 24% of patients with older patients no more likely than younger patients to experience a severe haematological toxicity.

Neutropenia was more common in younger patients (69.6% in those aged 65-69 years vs. 18.8% in those aged 75-79, p=0.007). However, increasing age was associated with a trend towards a higher rate of severe (grade 3 or 4) non-haematological toxicity (23% vs. 12% in those aged >80 years compared to those aged 65-69 years) although this did not reach statistical significance (p=0.082). The most common grade 3 or 4 non-haematological toxicities reported were fatigue (16 patients), diarrhoea (5 patients) and vomiting (5 patients) (table 6).

Increasing age was also significantly associated with a lower likelihood of completing six cycles of chemotherapy (p=0.034). Of the 38 (15.8%) women who discontinued treatment early, 21 (55%) did so because of toxicity.

| | **65-69 years n=82** | **70-74 years n=72** | **75-70 years n=48** | **>80 years n=39** | **Total n=241** | **p-value** |
|---|---|---|---|---|---|---|
| | % | % | % | % | **%** | |
| Dose modification at baseline | 9.8 | 12.5 | 6.3 | 17.5 | **11.6** | 0.365 |
| Dose modification during chemotherapy | 29.3 | 30.6 | 52.1 | 37.5 | **35.5** | 0.193 |
| Completed 6 cycles of chemotherapy | 86.6 | 86.1 | 77.1 | 65.0 | **82.2** | 0.034 |
| ≥ G2 Haematological toxicity | 29.3 | 19.4 | 33.3 | 30.0 | **27.3** | 0.554 |
| ≥ G3 Non-haematological toxicity | 13.4 | 19.4 | 27.1 | 32.5 | **21.1** | 0.082 |
| Febrile neutropenia | 4.9 | 2.8 | 2.1 | 0.00 | **2.9** | 0.540 |
| Hospital admission during chemotherapy | 20.7 | 34.7 | 25.0 | 37.5 | **28.5** | 0.135 |
| Death within 30 days of chemotherapy | 1.2 | 0.00 | 4.2 | 0.00 | **1.2** | 0.184 |

**Table 6. Dose modifications and tolerance of first-line chemotherapy**

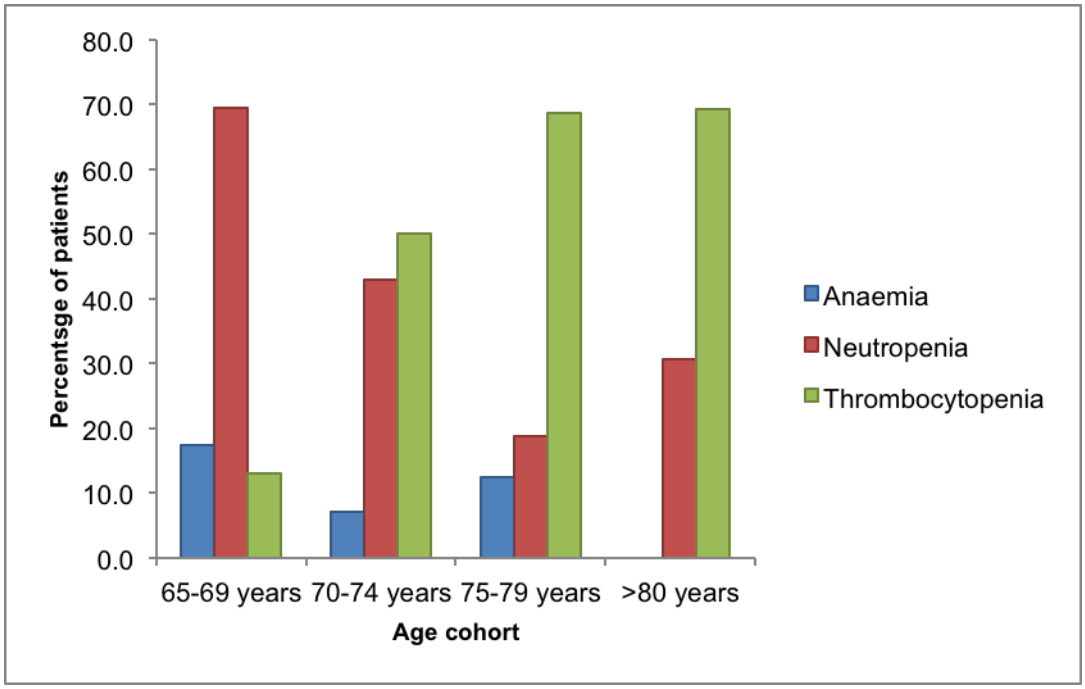



**Figure 8. Highest graded haematological toxicity reported according to age**

Discontinuation of chemotherapy due to toxicity was higher in older patients, for example 54.5% of 75-79 year olds compared to 36.4% of those aged 65-69 years, although this did not reach statistical significance (p=0.15) (table 7). 28.5% of all patients were admitted to hospital as an emergency at some stage during their primary treatment with no variation due to age (p=0.135) 30-day mortality was 1.24% across the whole cohort and did not vary according to age (p=0.184).

| **Of those who stopped chemotherapy early (n=44)** | **65-69 years n=82** | **70-74 years n=72** | **75-70 years n=48** | **>80 years n=40** | **Total** | **p** |
|---|---|---|---|---|---|---|
| | % | % | % | % | **%** | |
| Disease progression/death | 54.6% | 55.6 | 27.3 | 15.4 | **36.4** | |
| Toxicity | 36.4 | 22.2 | 54.5 | 69.2 | **47.7** | **0.15** |
| Reason not known | 9.1 | 22.2 | 18.2 | 15.4 | **15.9** | |

**Table 7. Reasons for early discontinuation of chemotherapy**

### 2.5.7 Treatment at relapse

169 patients relapsed and were alive to potentially receive further treatment. Of these, 124 (73.4%) went on to receive second line chemotherapy, 2 patients underwent radiotherapy and 1 patient (aged 75 years) underwent secondary cytoreductive surgery. Overall 50% of women received chemotherapy at first relapse however older women were significantly less likely to receive chemotherapy than younger women with 91% of those aged 65-69 receiving second line chemotherapy compared to 55% of those aged 75-79 and 52% of those aged over 80 years (p=0.021) (figure. 10) (table 8.). 75 women (59% of those who had treatment for relapsed disease) received carboplatin-based chemotherapy at first relapse. Of the patients who received chemotherapy, there was no association between age and the proportion of women receiving platinum-based chemotherapy (p=0.315) (table 8).

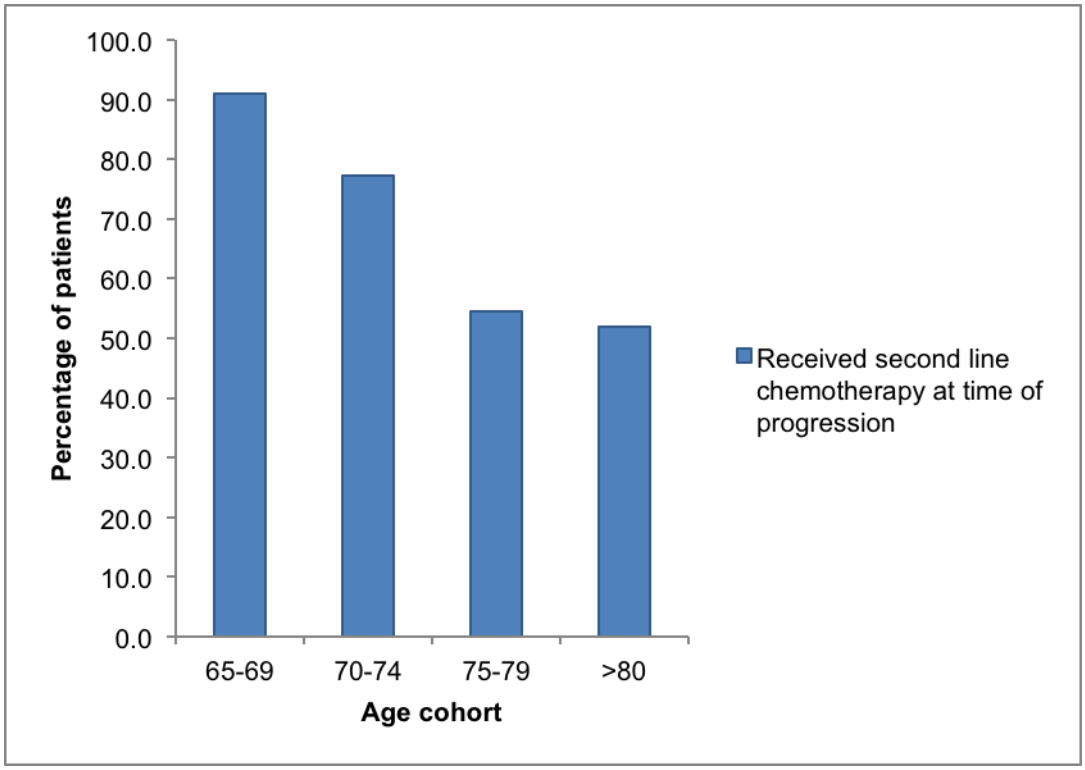



**Figure 9. Proportion of women who receive second-line chemotherapy at relapse according to age**

| Second line treatment received | 65-69 years (n=51) | 70-74 years (n=42) | 75-79 years (n=20) | >80 years (n=14) | Total |
|---|---|---|---|---|---|
| Carboplatin doublet | 29 (56.9%) | 21 (50%) | 6 (30%) | 0 | 56 (44.1%) |
| Single-agent carboplatin | 5 (9.8%) | 4 (9.5%) | 2 (10%) | 8 (57.1%) | 19 (15%) |
| Weekly paclitaxel | 6 (11.8%) | 6 (14.3%) | 6 (30%) | 3 (21.4%) | 21 (16.5%) |
| PLD*/doxorubicin | 6 (11.8%) | 10 (23.8%) | 5 (25%) | 2 (14.3%) | 23 (18.1) |
| Clinical Trial | 5 (9.8%) | 0 | 0 | 0 | 5 (3.9%) |
| Surgery | 0 | 0 | 1 (5%) | 0 | 1 (0.8%) |
| Radiotherapy | 0 | 1 (2.4%) | 0 | 1 (7.4%) | 2 (1.6%) |

**Table 8. Second line treatment received according to age. * pegylated liposomal doxorubicin**

| Second-line therapy | n | CR | R | SD | PD | NE/NK | Median PFS (months) (95% CI) | Clinical benefit rate (CR, PR, SD) |
|---|---|---|---|---|---|---|---|---|
| Carboplatin | 19 | 3 | 10 | 3 | 2 | 1 | 7.8 (1.9-9.8) | 84% |
| Carboplatin doublet | 56 | 2 | 34 | 15 | 5 | 0 | 9.6 (8.6-10.7) | 91% |
| Weekly paclitaxel | 21 | 0 | 7 | 4 | 8 | 2 | 3.6 (2.0-5.0) | 52% |
| Pegylated liposomal doxorubicin/doxorubicin | 23 | 0 | 0 | 6 | 16 | 1 | 2.7 (1.8-4.0) | 26.0% |
| Clinical trial | 5 | 0 | 2 | 1 | 2 | 0 | 6.7 (1.4-nr) | 60% |
| Radiotherapy | 2 | - | - | - | - | - | - | n/a |
| Surgery | 1 | - | - | - | - | - | - | n/a |

**Table 9. Best response to second-line therapy according to local radiological report**

**Response rates were determined according to the description of the clinically reported scans (non-RECIST reporting).**

**CR=complete response, R= response according to local radiological report, SD = stable disease (no significant growth or reduction in tumour volume at first response assessment or end of treatment imaging), PD= progressive disease, NE/NK= not evaluable or not known.**

**NB. PFS data missing from n=27**

Of those who received chemotherapy at first relapse, 56 (45%) received a carboplatin doublet regimen (carboplatin with paclitaxel, pegylated liposomal doxorubicin or gemcitabine with or without a targeted agent for example, bevacizumab) (table 8). Of the 75 women who received platinum at first relapse, 65% achieved some degree of tumour shrinkage as their best response according to the local radiological report with 89% achieving at least stable disease. In those patients who received non-platinum containing regimens, 21 patients (15%) received weekly paclitaxel resulting in a (33.3% radiological response rate and a 52% clinical benefit rate (defined as patients who achieved at least stable disease as their best response documented). 23 (18.9%) patients received either pegylated liposomal doxorubicin or doxorubicin. No responses were observed in this group although 6 (26%) patients had stabilisation of their disease (table 9).

### 2.5.8 Survival Outcomes

Median overall survival (OS) for all patients was 31.5 months. For patients diagnosed with stage III and stage IV disease, median OS was 28.3 and 14 months respectively. 1-year and 5-year survival was 78.1% (95%CI 72.7-82.5) and 28.7% (22.5-35.2%) respectively. For patients aged over 80 years, 1 and 5-year survival were 63.2 and 10.1% respectively compared to 83.5% and 37.8% in those aged 65-69 years. Considering only those patients of International Federation of Gynecology and Obstetrics (FIGO) stage 3 or higher, 1 and 5 year survival for those aged 65-69 years was 78.3% and 25.7% respectively compared to 59.5% and 7.4% in the oldest patients. Stage-specific and age-cohort specific 1 and 5 year survival is

detailed in table 10. Overall survival was broadly equivalent over the first three age cohorts however patients over the age of 80 had a significantly lower survival than those aged 65-69 years (median OS 20.02 months vs. 44.91 months, p=0.000) (figure 10).

| FIGO Stage | 1 year survival | 95% CI | 5 year survival | 95% CI |
|---|---|---|---|---|
| 1 | 86.1% | (69.8-94.0) | 67.9% | (47.2-81.9) |
| 2 | 92.9% | (74.4-98.2) | 54.5% | (27.5-75.2) |
| 3 | 79.1% | (71.9-84.7) | 19.6% | (12.6-27.8) |
| 4 | 61.1% | (46.8-72.6) | 14.5% | (6.0-26.5) |
| Age Cohort | | | | |
| 65-69 years | 83.5% | (74.2-89.7) | 37.8% | (26.5-49.1) |
| 70-74 years | 75.9% | (64.9-83.9) | 25.4% | (14.9-37.3) |
| 75-79 years | 88.2% | (75.7-94.5) | 37.2% | (21.0-53.4) |
| >80 years | 63.2% | (49.3-74.2) | 10.1% | (3.3-23.4) |
| FIGO Stage 3 and 4 only | | | | |
| 65-69 years | 78.3% | (66.6-86.3) | 25.7% | (14.8-38.1) |
| 70-74 years | 73.9% | (61.3-82.9) | 17.0% | (7.4-29.8) |
| 75-79 years | 86.8% | (71.2-94.3) | 20.2% | (6.2-40.0) |
| >80 years | 59.5% | (43.2-72.6) | 7.4% | (1.6-19.6) |
| **Total cohort** | **78.1%** | **(72.1-82.5)** | **28.7%** | **(22.5-35.2)** |

**Table 10. 1 and 5 year survival by FIGO stage and age**

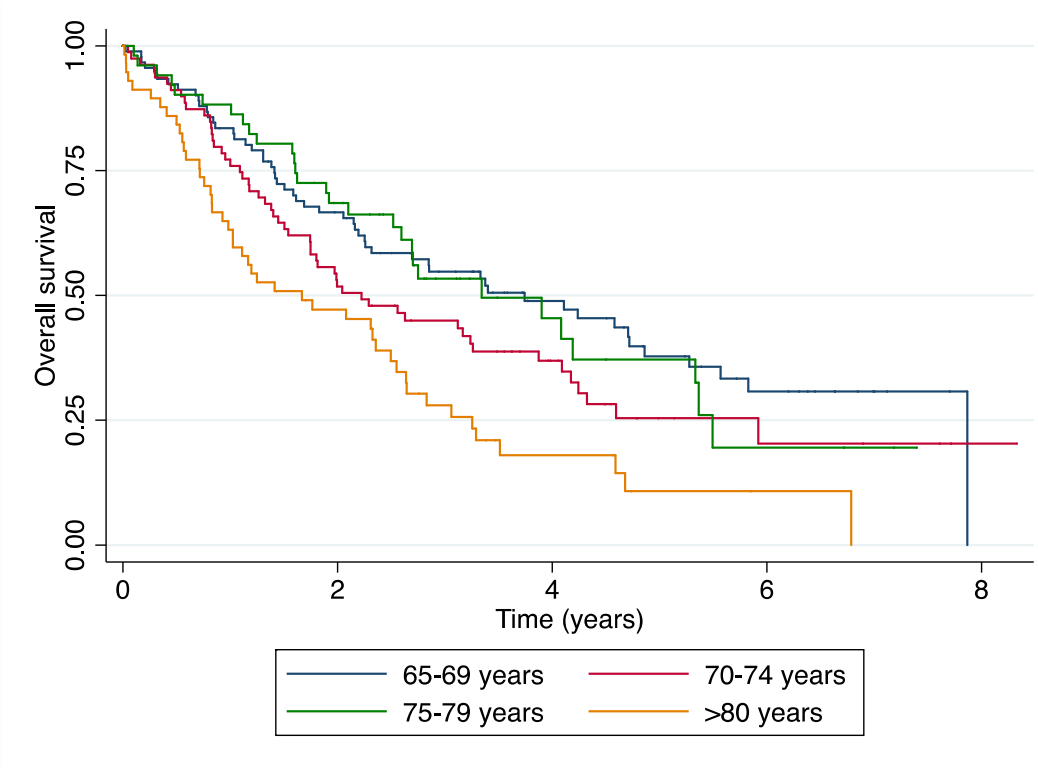



**Figure 10. Kaplan-Meier Overall Survival according to age cohort**

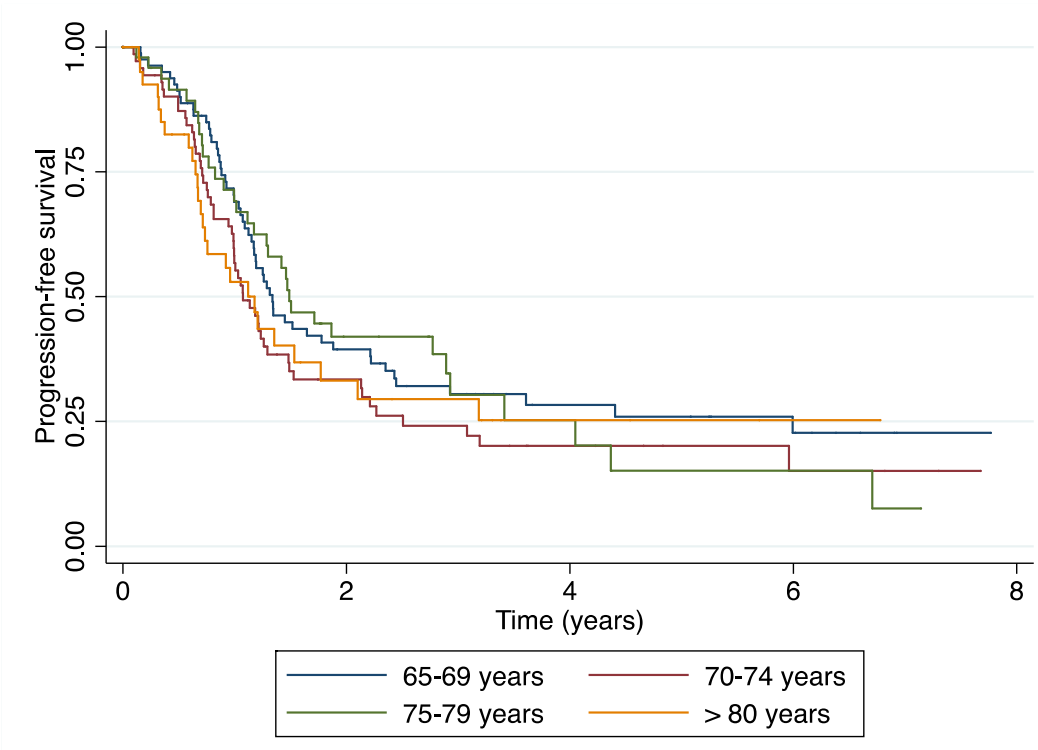



**Figure 11. Kaplan-Meier Progression-free survival according to age cohort**

| | Median OS (months) | HR | p-value | Median PFS (months) | HR | p-value |
|---|---|---|---|---|---|---|
| 65-69 years | 44.9 (27.1-58.3) | *ref.* | - | 16.4 (13.2-19.3) | *ref.* | - |
| 70-74 years | 24.5 (19.3-39.1) | 1.44 | 0.058 | 13.5 (10.9-15.8) | 1.38 | 0.06 |
| 75-79 years | 40.1 (30.2-64.0) | 1.12 | 0.618 | 18.6 (13.0-34.8) | 1.17 | 0.45 |
| >80 years | 20.0 (12.3-30.6) | 2.19 | 0.000 | 12.3 (9.1-15.6) | 2.06 | 0.00 |

**Table 11. Overall and progression-free survival according to age cohort. 95% confidence interval given in brackets.**

Progression-free survival (PFS) was similar across all age groups up to the age of 80 but patients aged 80 years and over had a median PFS of 12.3 months compared to 16.4 in those aged 65-69 years (HR 2.0 p=0.00) (figure 11). First line Carboplatin with paclitaxel combination chemotherapy was associated with improved survival outcomes compared to single-agent carboplatin (OS 39.5 vs. 30.6 months) however this was not statistically significant (p=0.123). Those patients who received no chemotherapy had an OS of 9.7 months (p=0.003) (table 12.)

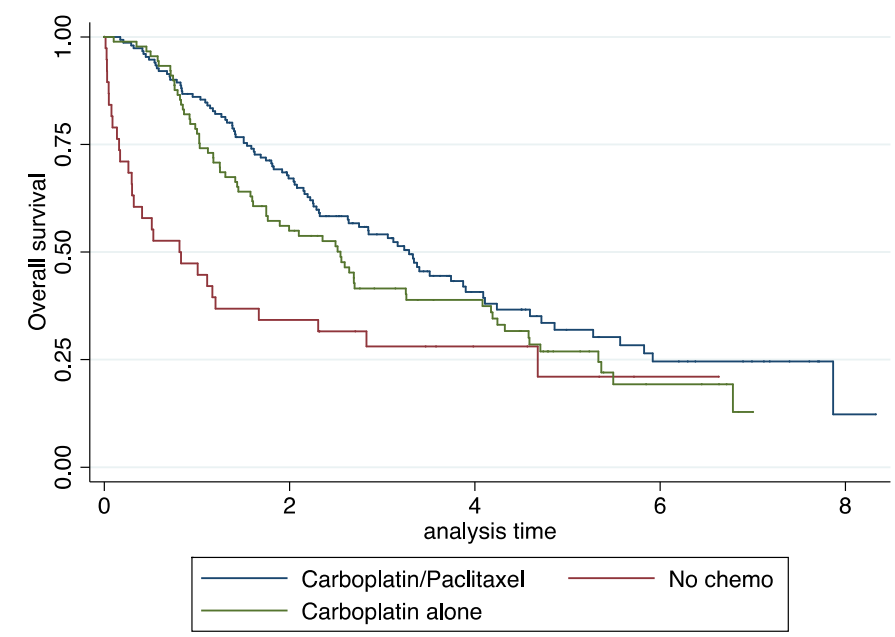



**Figure 12 Overall survival according to combination versus single-agent chemotherapy**

| | Median survival (years) | Median survival (months) | 95% CI |
|---|---|---|---|
| Carboplatin/Paclitaxel | 3.3 | 39.5 | (27.8-46.8) |
| Carboplatin | 2.6 | 30.6 | (19.3-39.1) |
| No chemotherapy | 0.8 | 9.7 | (3.6-20.0) |

**Table 12 Overall survival according to combination versus single-agent chemotherapy**

### 2.5.9 Predictive factors for survival outcomes

Age over 80 years at diagnosis, FIGO stage III/IV disease, incomplete cytoreduction and an ECOG PS of greater than 1 were all associated by univariate analysis with poorer survival outcomes. Of the baseline factors and comorbidities collected, only the presence of cardiovascular disease (p=0.043), polypharmacy (0.011) or having a current or past history of smoking (p=0.008) was associated with poorer survival outcomes. Regarding functional baseline, requiring assistance with instrumental activities of daily lADL (p=0.000), reporting reduced ADLS (p=0.000) and weight loss at diagnosis (p=0.015) was all associated with poorer survival outcomes.

Of the biochemical parameters collected, having any degree of hypoalbuminaemia (p=0.000) or a baseline haemoglobin of less than 110g/l (p=0.000) was associated with poorer survival outcomes. Glomerular-filtration rate (GFR) was associated with poorer survival as a continuous variable (p=0.036) however using a threshold of a GFR of 60ml/min (CKD 3) was not associated with poorer survival outcomes (p=0.064) (table 13).

A multivariate cox proportional hazards model was then constructed incorporating those covariates with a p-value of <0.1 and with sufficient prevalence (n>10). Factor pairs were tested for collinearity using Pearsons correlation, of pairs with r<0.5, one factor was rejected based on clinical appropriateness. Age over 80 years old remained significantly associated with poorer survival outcomes (p=0.04) along with FIGO stage 3 or higher (p=0.012) and ECOG performance status of 2 or higher (p=0.015) (table 13).

| | | n | HR | 95% CI | p | HR | 95% CI | p |
|---|---|---|---|---|---|---|---|---|
| Age Cohort | 65-69 | 91 | *Ref* | - | - | *Ref* | - | - |
| | 70-74 | 79 | 1.40 | (0.96-2.05) | 0.081 | 0.95 | (0.60-1.52) | 0.833 |
| | 75-79 | 53 | 1.07 | (0.68-1.68) | 0.772 | 0.79 | (0.44-1.43) | 0.441 |
| | >80 | 57 | 2.20 | (1.47-3.27) | 0.000 | **1.76** | **(1.03-3.02)** | **0.04** |
| FIGO Stage | 1 | 37 | *Ref* | | | *Ref* | - | - |
| | 2 | 28 | 1.30 | (0.55-3.07) | 0.553 | 7.91 | (0.98-63.61) | 0.052 |
| | 3 | 158 | 3.69 | (1.98-6.89) | 0.000 | **12.99** | **(1.77-95.20)** | **0.012** |
| | 4 | 55 | 6.00 | (3.08-11.68) | 0.000 | **16.16** | **(2.11-123.61)** | **0.007** |
| ECOG PS | 0 | 56 | *Ref* | - | - | *Ref* | - | - |
| | 1 | 122 | 1.86 | (1.18-2.93) | 0.007 | 2.14 | (1.21-3.79) | 0.009 |
| | 2 | 55 | 4.02 | (2.47-6.53) | 0.000 | **2.53** | **(1.20-5.35)** | **0.015** |
| | 3 | 26 | 7.36 | (4.13-13.13) | 0.000 | **3.51** | **(1.37-8.99)** | **0.009** |
| Cardiovascular disease | | 77 | 1.38 | (1.01-1.90) | 0.043 | 0.99 | (0.62-1.57) | 0.95 |
| Taking 3 or more medications | | 111 | 0.07 | (0.01-0.55) | 0.011 | 1.12 | (0.72-1.74) | 0.62 |
| Osteoarthritis | | 16 | 1.70 | (0.96-3.01) | 0.070 | 1.62 | (0.76-3.44) | 0.209 |
| Reduced activities of daily living | | 70 | 2.89 | (2.10-3.98) | 0.000 | 1.53 | (0.90-2.62) | 0.118 |
| History of depression | | 11 | 1.86 | (0.95-3.65) | 0.071 | 1.89 | (0.83-4.30) | 0.128 |
| History of weight loss | | 66 | 1.51 | (1.09-2.11) | 0.015 | 0.93 | (0.59-1.47) | 0.754 |
| Albumin <35 g/l | | 114 | 2.09 | (1.56-2.81) | 0.000 | 1.52 | (0.97-2.38) | 0.065 |
| Haemoglobin <120g/l | | 141 | 1.28 | (0.9601.72) | 0.093 | 0.80 | (0.53-1.23) | 0.311 |
| GFR <60 ml/min | | 104 | 1.33 | (0.98-1.79) | 0.064 | 1.11 | (0.74-1.68) | 0.607 |

**Table 13. Univariate and multivariate analysis of factors associated with overall survival**

A cox proportional hazards multivariate model was built to assess treatment-related factors that were predictive, by univariate analysis for

overall survival. When adjusted for FIGO stage at baseline, surgical outcome and nature of baseline and completion of chemotherapy, age over 80 years old was no longer an independent risk factor for poorer overall survival (table 14). Completion of chemotherapy remained an independently associated with overall survival where as single-agent versus platinum-doublet chemotherapy was not associated with a significantly different in overall survival in either univariate or multivariate analysis.

After adjusting for FIGO stage, ECOG performance status, surgical outcome and chemotherapy regimen, age was no longer significantly associated with poorer survival outcomes (HR 0.95, p=0.913). Looking at these factors individually, age greater than 80 years old remains associated with poorer survival outcomes when adjusted for not receiving platinum combination chemotherapy (HR 1.84, p=0.006) but not when adjusted only for surgical outcome alone (HR 1.30, p=0.362) (table 14).

| | | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|---|
| | | HR | 95% CI | P | HR | 95% CI | p |
| Age Cohort | 65-69 years | *ref.* | - | - | - | - | - |
| | 70-74 years | 1.40 | (0.96-2.05) | 0.081 | 1.22 | (0.77-1.95) | 0.386 |
| | 75-79 years | 1.07 | (0.68-1.68) | 0.772 | 0.85 | (0.46-1.54) | 0.582 |
| | >80 years | 2.20 | (1.47-3.27) | 0.000 | 0.81 | (0.40-1.61) | 0.541 |
| FIGO stage | 1 | *ref.* | - | - | - | - | - |
| | 2 | 1.30 | (0.55-3.07) | 0.553 | 2.39 | (0.86-6.64) | 0.094 |
| | 3 | 3.69 | (1.98-6.89) | **0.000** | 4.38 | (2.02-9.52) | **0.000** |
| | 4 | 6.00 | (3.08-11.68) | **0.000** | 6.96 | (2.81-17.24) | **0.000** |
| Surgical outcome | Residual disease | 2.71 | (1.82-4.03) | **0.000** | 2.09 | (1.32-3.30) | **0.002** |
| Chemotherapy | Platinum-combination | *ref.* | - | - | - | - | - |
| | Single-agent carboplatin | 1.29 | (0.93-1.77) | 0.123 | 1.34 | (0.85-2.17) | 0.203 |
| | No chemotherapy | 2.19 | (1.43-3.35) | **0.000** | 4.49 | (1.99-10.13) | **0.000** |
| | Completed 6 cycles | 0.34 | (0.23-0.49) | **0.000** | 0.33 | (0.19-0.59) | **0.000** |

**Table 14. Cox proportional hazards univariate and multivariate analysis.** Associations between age, FIGO stage and treatment received and overall survival

## 2.6 Discussion

This study provides a useful insight into the current real-world treatment of older women diagnosed with epithelial ovarian cancer across two UK cancer centres. There were very low rates of unclassifiable tumours in this series compared to previously published national cancer registry data where over 50% of women over the age of 80 had an unclassified epithelial or miscellaneous tumour[84]. This may suggest an improvement in the approach and attitudes to older patients with more women having a true histological diagnosis being pursued. Delayed time to diagnosis and therefore later stage at diagnosis has also been postulated as a cause for poorer survival rates however, stage distribution also did not vary with age in this population with the majority of women of all ages being diagnosed with stage 3 and 4 disease. Older patients were more likely to have a poorer ECOG performance status, an independent risk factor for poorer survival, however it is well recognised that ECOG performance status alone is a crude measure in an elderly population that does not accurately reflect the functional and comorbid status of older patients[17, 19]. It has also been previously shown that poor performance status should not necessarily preclude first-line treatment in epithelial ovarian cancer due to the high response rates observed to platinum-based chemotherapy[96].

The higher treatment discontinuation rates seen with increasing age are of interest when it is considered that haematological toxicity rates were comparable across the age groups and although a trend towards a higher

rate of non-haematological toxicities was observed, this was not statistically significant. This is in keeping with post-hoc analysis from the first-line phase 3 AGO-OVAR3 study, which also showed that women over the age of 70 experienced comparable rates of toxicity but were more likely to discontinue treatment early[43]. The AGO-OVAR authors in 2007 suggested a potential difference in attitude towards the treatment of older adults. It can be postulated that this difference persists today. It was relatively rare for patients to decline treatment with six patients declining surgery and three declining chemotherapy; however the more nuanced decision-making over reducing treatment intensity and early treatment cessation is difficult to reliably elucidate retrospectively. The perspectives of older women and oncology teams on treatment intensity, tolerance and treatment goals should be the focus of future study.

Although many older women maintain fit and active lives into their seventh decade and beyond, a quarter of this study population reported reduced activities of daily living in the preceding weeks and months before their diagnosis with 12.5% of patients already requiring help with activities of daily living. This represents a significant burden of functional decline in a population who are likely to experience a further functional decline during chemotherapy[97]. A significant proportion of women in this study also reported living alone, whilst not a concern in and of itself, living alone without sufficient social network or community support particularly in the context of frailty is a challenge for patients and a concern for oncologists when systemic anti-cancer therapy is being considered.

The most striking difference between the oldest patients and those younger than 80 years was that seen in primary treatment received. Under-treatment has long been postulated as one of the primary reasons for the poorer outcomes in older patients. A large retrospective study in France assessed the impact of age on treatment and survival outcomes whether or not guideline-recommendations for therapy were followed between 1997 and 2011. Women over the age of 70 compared to those younger were less likely to undergo surgery (60.9% versus 89.6%, $p<0.0001$) or receive chemotherapy (57.4% versus 76.4%, $p<0.0001$). Only 31.9% of patients over the age of 70 underwent both surgery and chemotherapy[95]. A prospective study (OVCAD) that included 275 women treated for primary ovarian cancer between 2005 and 2008 also showed that older women were less likely to receive optimal therapy and had poorer progression-free and overall survival. In multivariate analysis, age was an independent risk factor for poorer overall but not progression-free survival[25]. Our findings confirm that older women continue to receive less treatment than their younger and middle-aged counterparts and this is likely to be a significant factor in explaining the poorer outcomes seen in this population.

Older patients were less likely to receive targeted therapy however it should be noted that the only targeted therapy available during the study period was bevacizumab, which received NICE approval in 2013[98] therefore only in the final two years of the study period and thus these rates are likely an underestimate. The difference in survival for the oldest patients becoming

no longer significant once stage, surgical outcome and crucially, chemotherapy received is incorporated into the model provides convincing evidence that if patients, irrespective of age are able to receive optimal therapy, survival outcomes are comparable. In both univariate and multivariate analysis, single versus platinum doublet chemotherapy was not associated with poorer survival outcomes. Completion of the planned six cycles however remained very strongly associated with improved survival outcomes after adjusting for stage, age, surgical outcome and chemotherapy regimen received (HR 0.34, p=0.000).

The difference in treatment intensity was even more evident at relapse, rates of second-line chemotherapy were surprisingly low and this difference being even more striking between those aged 65-74 and over the age of 75 is not sufficiently explained by the comorbidities or ECOG performance status documented at diagnosis although this was not collected at relapse. When patients were treated, the response rates (albeit by clinical report, not RECIST) were impressive with platinum-sensitive patients having an ORR of 57 -100%. Historically, older women have been shown to receive less treatment than their younger counterparts at relapse[99]. An analysis of outcomes from 2369 women over the age of 65 in the U.S with relapsed serous ovarian cancer between the period 1992 and 2009 revealed that 23.6% commenced second line chemotherapy within 3-6 months of completing first line therapy, 30.6% within 7-12 months and 45.8% 12 months or longer. Platinum-free interval remained the most significant

prognostic indicator. Median overall survival after commencing second line chemotherapy was 21 months[100].

Furthermore, only one patient in this study population underwent secondary debulking surgery at relapse. There is now evidence from phase III clinical trials that achieving optimal cytoreduction at secondary relapse may provide a survival benefit[101, 102] and ensuring that older patients are not overlooked when they meet the validated AGO criteria[103-105] should be a focus for routine clinical care.

The EWOC-1 study has provided compelling evidence that even vulnerable patients have significantly improved survival outcomes with no significant increase in toxicity when receiving platinum-doublet chemotherapy in comparison to single-agent carboplatin[44]. Therefore even in the most vulnerable patients, optimisation to facilitate administration of doublet chemotherapy should be seen as a priority. Optimisation of older patients medical and social comorbidities has been demonstrated to improve chemotherapy completion rates[106]. Larger scaled versions of this approach are currently being tested in the French PREPARE (NCT02704832) [81] and Italian GIVE (NCT02785887) studies.

This population remains challenging to manage and the expertise needed to optimise and manage comorbidities such as cardiovascular disease, diabetes mellitus and hypertension is lacking in the current environment[82]. Education on common geriatric issues that may be pertinent to systemic

anti-cancer therapy is not currently part of the medical oncology curriculum and there are only a few centres in the UK with geriatric-liaison services that can support routine oncology care. A UK wide survey of current assessment practice of older patients with cancer across 640 healthcare professionals reported that only 14.1% of respondents often involved a geriatrician in assessment of older patients. Up to 44.3% never used any form of structural assessment method[82]. Whilst the outcomes of the recently completed GIVE study and ongoing PREPARE study are awaited, how these outcomes, if positive, will be translated into practice in the UK remains unclear.

## 2.7 Limitations and future work

This was a study providing a very detailed analysis of an older population being treated for ovarian cancer across two UK cancer centres. It is however acknowledged the inclusion of a younger comparator group would have allowed for improved contextualisation of the data. Furthermore, whilst spanning two cancer centres allows for a broader analysis, it is acknowledged that the populations treated at a tertiary cancer centre in London and affluent UK city do not have a wide ethnic or social demographic and are not representative of the UK as a whole. Social deprivation has been demonstrated to be linked to poorer survival outcomes from ovarian cancer[107]. The survival outcomes presented here may well therefore not be representative of the UK as a whole. The retrospective nature of this study increases the likelihood of under-reporting of baseline comorbidities and functional deficits as well as medical comorbidities that

may be seen as less relevant for either the patient or clinician. Impairment of hearing or sight, unless severe, may not be recorded in a new patient letter and yet can represent a significant increased burden for patients undergoing chemotherapy, particularly regarding communication of complex issues. Whilst I felt it was important to attempt to capture information on cognitive impairment and history of delirium, two factors which can have a significant impact on a patient's ability to tolerate chemotherapy, it is acknowledged that the retrospective collection of this information through the electronic patient record is unlikely to provide an accurate assessment of these particular issues. Cognitive impairment was only documented in eight patients formally however the prevalence of mild cognitive impairment at a population level is far higher[108] and this result is highly likely to be an underestimate as without a structured assessment or focused history, mild cognitive impairment can easily be overlooked in a routine oncological consultation. Furthermore, the retrospective collection of chemotherapy toxicities is reliant on accurate documentation in electronic patient records, which allows for room for under-reporting, particularly of non-haematological events. It was considered methodologically unreliable to include low-grade non-haematological toxicities and these were therefore not collected. The impact of chronic, low-grade toxicities, particularly fatigue on a patient's ability to tolerate chemotherapy and quality of life can be very significant and patient-reported outcome measures in prospective studies are essential to better capture this consequence of anti-cancer treatment.

## 2.8 Conclusions

The oldest women continue to receive lower rates of optimal first-line therapy compared to younger women. Once adjusted for FIGO stage, surgical outcome and first-line treatment received, age was no longer an independent risk factor for poorer overall survival. Sub-standard therapy would therefore appear to be a critical factor for the poorer survival outcomes seen in older women with newly diagnosed ovarian cancer. In the absence of a formal geriatric or frailty assessment, assessing patients on chronological age alone may lead to inappropriate under-treatment, adversely affecting cancer outcomes in these women. A formal frailty or geriatric assessment together with interventions to address issues identified would assist in optimising vulnerable patients. This could improve the rates of treatment delivery and completion in older adults thereby improving outcomes in this key demographic.

There are several avenues of further research and development that this study has illuminated a need for. Qualitative studies evaluating the experience of older women who have been treated for epithelial ovarian cancer are lacking. Whilst it is clear that the oldest patients receive lower rates of optimal treatment, retrospective studies such as this cannot extrapolate whether older patients are not being offered more intensive treatment or whether they are being offered treatment but declining due to concerns over their own ability to tolerate treatment or prioritising quality life without treatment toxicity over prolonging life at any cost.

There is a real and pressing need for better, more holistic and accurate assessments of older women with cancer to better delineate those patients that are at higher risk of treatment toxicity and poorer outcomes to be delivered in real-world and clinical trial settings. A geriatric assessment can provide a holistic view of patients' vulnerabilities; predict risk of chemotherapy toxicity[19, 109] and poorer survival outcomes[17, 110-112]. There is a need for an objective, quantifiable biomarker of frailty that may be added to the outcome of a geriatric assessment. Sarcopenia, the loss of muscle mass and function has gathered interest in recent years and will be the focus of the next chapter.

Whilst it is now recommended by ASCO[20] and SIOG[74] that a geriatric assessment be undertaken, there is a wide variety of practice and opinion regarding who should be undertaking this assessment. In the UK there is no widely available geriatric-oncology clinic or liaison services[82]. It is incumbent upon oncology healthcare professionals to become up-skilled in the assessment and management of a population who are becoming an increasingly large and ever more-relevant proportion[8]. With the assistance of management algorithms designed by an expert multi-disciplinary team, the researcher hypothesises that oncology teams will be able to deliver a geriatric assessment and targeted management of issues identified. Along with my fellow co-applicants, I submitted a successful grant proposal to Wellbeing of Women in 2017 and was awarded funding to run a multicentre feasibility study to evaluate this hypothesis. The prospective UK FAIR-O study (NCT04300699) opened to recruitment in

January 2020 and the development of this study will be the subject of chapter 5.

# 3 SARCOPENIA AS A PREDICTIVE AND PROGNOSTIC BIOMARKER IN OLDER WOMEN WITH EPITHELIAL OVARIAN CANCER

## 3.2 Background

Approximately half of all women diagnosed with ovarian cancer are over the age of 65[84] with this proportion set to rise over the next 20-30 years. Unfortunately, older age is associated with disproportionately poor survival outcomes both in the UK and internationally[12, 84]. The reasons for this are multifactorial but, as discussed in Chapter 1, are thought to include late presentation and therefore more advanced disease at diagnosis, increased burden of medical and social conditions that make standard treatment less likely to be offered and tolerated as well as adverse tumour biology. Treatment decisions in routine clinical practice tend to be based on a patients ECOG performance status, a measure that has been shown to be less reliable in an older population. Comprehensive geriatric assessment and screening frailty assessments have been increasingly used to improve the holistic assessment of older patients but there is a clear need for quantitative biomarkers that may either independently or in association with the outcome of a geriatric assessment predict for those patients who may suffer from severe chemotherapy related toxicities or have poorer survival outcomes.

### 3.2.1 Definition of Sarcopenia

Sarcopenia, the loss of muscle mass, quality and function is increasingly prevalent in older adults[113-115] and even more so in those with confirmed frailty[116]. Research into this as a potential non-invasive biomarker has gathered a significant amount of interest in recent years in the context of cancer treatment. In a number of solid organ malignancies it has been shown to be prognostic for overall survival and predictive for chemotherapy related toxicities[117-128].

Sarcopenia can be evaluated in many ways with varying definitions throughout the literature. The European working Group on Sarcopenia in Older people give three criteria needed to define sarcopenia, 1. Low muscle mass, 2. Low muscle strength, 3. Low physical performance [113]. This retrospective study unfortunately will not include assessment of muscle strength or physical performance (aside from ECOG performance status) as this is not currently routinely assessed and this data is therefore not available in a retrospective analysis but will be the subject of a future prospective research study, FAIR-O (NCT04300699), the details of which will be discussed in a subsequent chapter. The CT definition of low muscle mass for women varies but is generally considered to be <38.5-39 $cm^2/m^2$ [115, 129].

### 3.2.2 CT assessment of body composition

Computed tomography (CT) assessment of low muscle mass is considered, for research purposes to be the gold standard and given all patients who undergo treatment for ovarian cancer undergo CT assessment as part of their care, this carries the advantage that no additional imaging is required. Muscle area at the level of L3 is now widely used, subsequently dividing this value by the square of a patient's height to produce the standardised skeletal muscle index ($cm^2/m^2$). Skeletal muscle area (SMA) ($cm^2$) at this level comprises of psoas, erector spinae, quadratus lumborum, transverse abdominus, external and internal obliques and rectus abdominus. SMA correlates in a linear pattern with total skeletal mass, therefore a height-standardised value of skeletal muscle index $cm^2/m^2$ (SMI) is produced by dividing by height squared ($m^2$). There is a wide variation in the reported prevalence of sarcopenia in the literature owing to the variation in methodologies utilised and threshold cut-offs to define sarcopenia. The radiodensity or muscle attenuation (MA) as assessed by CT is related directly to muscle lipid content[130], myosteatosis, a condition that has been associated with ageing, diabetes, obesity and cancer[131]. CT assessed muscle attenuation has also been shown to directly link to muscle strength and function[132]. Stephens et al demonstrated in a small study that cancer cachexia is linked to increased intromyocellular lipid deposition compared to healthy volunteers[133]. The complex interrelationship between cancer cachexia, sarcopenia and inflammation will be discussed in more depth in due course. There are varying methodologies for quantifying CT

muscle attenuation in the literature[131] and as such, there is no one universally agreed threshold for what is deemed to be an abnormally low muscle attenuation in the context of cancer or otherwise. The majority of studies utilising CT assessment of body composition have focused on skeletal muscle volume or index however in more recent years, muscle attenuation has increasingly been shown to be of prognostic significance.

### 3.2.3 The relationship between cancer cachexia, sarcopenia inflammation and frailty

Cancer cachexia is characterised by weight loss, the 2011 international consensus definition being weight loss >5% in the previous 6 months or 2-5% weight loss with a either a BMI of <20kg/$m^2$ or reduced muscle mass[129]. It is highly prevalent in cancers of the gastrointestinal tract and lung[134] and is less well documented in gynaecological malignancies. Weight loss and specifically loss of lean muscle mass may be more difficult to identify in the context of obesity[135, 136] or the presence of confounding factors such as malignant ascites at diagnosis. Whilst cancer-related cachexia may be a driver for sarcopenia, they are clearly distinct entities with the crucial element of the sarcopenia definition being the loss of muscle strength and function[114]. The pathophysiological mechanisms for both sarcopenia and frailty are complex and incompletely understood but may share similar origins [137, 138]. The role of chronic inflammation is of particular interest with several pro-Inflammatory cytokines, in particular IL-6[139] and TNFα having been implicated in cachexia, sarcopenia and frailty[138]. Higher levels of IL-6

have been shown to predict the development of sarcopenia and loss of strength in a longitudinal study of a non-cancer population[140]. In addition, the association between poorer cancer outcomes (both ovarian and other solid-organ malignancies) and inflammatory markers such as c-reactive protein, albumin[141], lactate dehydrogenase and neutrophil-lymphocyte ratio are well documented[142]. Wilson and Lord published a proposed model for the complex interrelationship between cachexia, sarcopenia and frailty with inflammation as a core central process[138]. It is easy to see how a concurrent malignancy could potentiate both cancer-related cachexia, loss of muscle use due to fatigue and a host systemic inflammatory response which has itself been linked as a prognostic marker[143, 144] worsening the degree of sarcopenia and cachexia already associated with the process of ageing.

### 3.2.4 Association between sarcopenia and functional status

Prado and colleagues assessed the prevalence and impact of sarcopenia in a group of 2115 patients with lung and gastrointestinal malignancies. 15% were defined as obese (BMI ≥30), of whom a further 15% met the investigators cut-off for sarcopenia (CT assessed). Loss of function, self-reported using the validated PG-SGA score was more prevalent in patients with sarcopenic obesity than those with non-sarcopenic obesity (47% vs. 26%, p=0.009). Median survival was also significantly lower (11.3 vs. 21.6 months, log-rank p<0.0001)[136].

### 3.2.5 Impact of sarcopenia on outcomes in non-gynaecological malignancies

Over the last decade, poorer survival outcomes have been shown to be associated with poorer survival outcomes in many solid organ malignancies including biliary tract cancer[120], oesophagogastric cancer[122], hepatocellular cancer[123], pancreatic cancer[126] colorectal cancer[145, 146] and lung cancer[136]. A systematic review reported in 2016, evaluated the impact of sarcopenia on overall survival in solid organ malignancies. 7843 patients recruited across 38 studies were included in the analysis. Sarcopenia was associated with both poorer overall survival (HR 1.44; 95% CI 1.32-1.56, $p<0.001$) and cancer specific survival (HR 1.93; 95% CI 1.38-2.70 $p<0.001$)[128]. Of note is the fact that the poorer survival outcomes were still noted even in those patients with non-metastatic disease (HR 1.54; 95% CI 1.31-1.79, $p<0.001$) suggesting that the mechanism of impact on poorer survival outcomes is not solely due to bulk of disease and resulting cancer cachexia.

An association between sarcopenia and poorer chemotherapy tolerance has also been reported in recent years. Prado et al demonstrated, in a group of breast cancer patients receiving treatment with Capecitabine that sarcopenia at baseline significantly correlated with increased toxicity and shorter time to progression[147]. Antoun et al, evaluating a population receiving tyrosine kinase inhibitor therapy for renal cell cancer demonstrated higher rates of dose-limiting toxicities in patients with a BMI

of ≤ 25 and sarcopenia at baseline[148]. Similar findings have been reported in retrospective studies of patients receiving chemotherapy for colorectal cancer[117, 119], oesophagogastric cancer [149] and in phase 1 studies[121].

Retrospective studies have also addressed whether sarcopenia is associated with higher rates of adverse surgical outcomes. A recent systematic review in gastrointestinal malignancies demonstrated that sarcopenia was prevalent in 38.7% of patients and was associated with higher rates of overall and severe post-operative complications (RR = 1.188, 95% CI = 1.083-1.303, P < 0.001 and RR = 1.228, 95% CI = 1.042-1.448, P = 0.014, respectively)[150]. The majority of surgical studies to date have been in colorectal cancer populations and have not been age-restricted[124, 146, 151, 152]. Lieffers and colleagues demonstrated that sarcopenia was associated with longer length of stay (15.9 vs. 12.3 days) and that this difference was even more marked in patients over the age of 65 (20.2 vs. 13.1 days, p=0.008)[124]. Two studies incorporated some form of functional assessment alongside CT-assessed body composition. Huang et al demonstrated that including a functional assessment of hand-grip strength and gait speed increased the predictive power of sarcopenia to predict for grade 2 or higher Clavien-Dindo post-operative complication rates than low muscle mass alone[152]. Reisinger and colleagues reported that a combination of the Groningen Frailty Index (GFI) as well as a nutritional assessment (Short Nutritional

Assessment Questionnaire) with a CT assessed sarcopenia was a strong predictor of post-operative sepsis (OR 25.1; 95% CI, 5.11-123, p=0.001).

### 3.2.6 Impact of sarcopenia in gynaecological malignancies

A small number of studies have been reported since 2015 evaluating the impact of sarcopenia, both in terms of SMI and MA with both being shown to be associated with survival but the findings have not been consistent across all studies. Most studies have been in non-age restricted, primary debulking cohorts. Aust et al retrospectively evaluated a population of 140 women who had undergone primary debulking surgery for ovarian cancer between 2004 and 2012. Loss of muscle mass (defined as SMI < 41cm$^2$/m$^2$) was not associated with a significant difference in OS. The optimal cut-off point for mean muscle attenuation was derived as 39HU and using this definition, low mean MA was demonstrated to be an independent predictor for poorer OS (HR 2.25; 95% CI 1.09–4.65, p=0.028). Using stored frozen serum samples, these authors were able to assess 25 circulating inflammatory cytokines using a multiplex luminex based assay including but not limited to; IL-2, IL-6, IL-10, Interferon α (IFNα) and CCL11. IL-10 and Eotaxin were the only two cytokines to be shown to be associated with low muscle attenuation (p=0.047 and p=0.021, respectively)[153]. Kumar et al evaluated a cohort of patients with stage 3 or 4 ovarian cancer undergoing primary debulking surgery and showed that overall survival was significantly poorer in patients with low muscle attenuation irrespective of whether they had optimal or suboptimal cytoreduction[154].

Two studies have demonstrated an association between sarcopenia and adverse survival outcomes. Using a cut-off of 38.5cm$^2$/m$^2$, Bronger and colleagues demonstrated a 12% prevalence of sarcopenia in a population of 128 patients with FIGO stage 3 or 4 serous ovarian cancer who received primary chemotherapy and surgery. Sarcopenic patients had significantly poorer PFS (15 vs 22 months, HR 2.65; 95%CI 1.24-5.64, p=0.012) and OS (23 vs 48 months, HR 3.17 95% CI 1,29-7.80, p=0.012)[155]. Rutten and colleagues reported a significantly poorer OS (HR 1.536 (95% CI 1.105-2.134), p=0.011) in sarcopenic compared to non-sarcopenic patients however this was not significant in a multivariate analysis. Interestingly sarcopenic patients were also more likely to have ascites at presentation[156]. No studies have been published to date evaluating sarcopenia in the context of relapsed epithelial ovarian cancer. Furthermore, no studies to date have focused exclusively on older women in whom the prevalence and impact of sarcopenia is likely to be different.

### 3.2.7 Impact of loss of skeletal muscle during chemotherapy on survival

Rutten et al evaluated the change in skeletal muscle in a population of ovarian cancer patients receiving neoadjuvant chemotherapy. Baseline and pre-surgical CT imaging (typically after 3-4 cycles of chemotherapy) were assessed and compared. Loss of skeletal muscle (≥ 2%/100 days) was associated with poorer survival outcomes [157], treatment tolerance

was not evaluated in this study. This finding has not been demonstrated in other malignancies, with for example, one study of 310 breast cancer patients receiving either paclitaxel or anthracycline based chemotherapy showing no difference in survival associated with change in body composition[158].

## 3.3 Methods

A service evaluation proposal was approved by the Royal Marsden NHS Foundation Trust clinical cancer research committee (SE691). A prior service evaluation of treatment outcomes in women over the age of 65 treated for newly diagnosed epithelial ovarian cancer was undertaken in 2016 in which 208 patients were eligible to participate (SE486). Of this population where demographic details as well as treatment and survival outcomes were already collected, 179 patients had contrast-enhanced CT data available prior to first treatment and were included in this analysis. Patients were eligible for inclusion if they were 65 or over at the time of a first new patient appointment at the Royal Marsden NHS Foundation Trust having been diagnosed with a histologically or cytologically confirmed epithelial ovarian, primary peritoneal or fallopian tube carcinoma (figure 13).

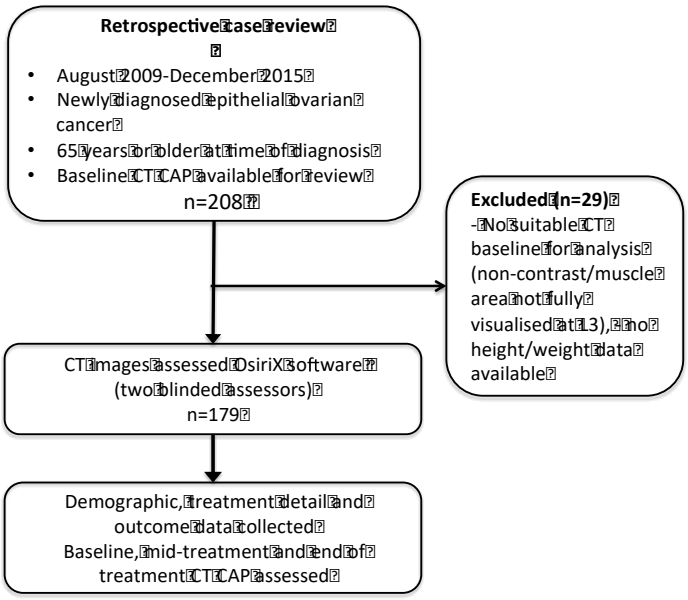



**Figure 13.Study recruitment flowchart**

### 3.3.1 Generation and analysis of regions of interest

CT scans at baseline as well as mid and end of treatment were anonymised and saved to Digital Imaging and Communications in Medicine (DICOM) format to allow for export and analysis using OSIRIX, mac-based software. Hounsfield units (HU) are a quantitative measure of radio-density used in the analysis of CT images. The skeletal muscle attenuation threshold is widely accepted to be -29 to +150HU with adipose tissue taken as measuring between -150 and +50HU [159]. Tumour deposit radiodensity can fall within this range and therefore skeletal muscle and subcutaneous adipose tissue only were assessed as the assessment of visceral smooth muscle and adipose tissue was felt to be methodologically unreliable. In keeping with well-established

methodology, 5mm single-slice CT images at the level of L3 were used for analysis[160].

Skeletal muscle density but not area is affected by whether patients have received intravenous contrast[161] and therefore those patients with non-contrast enhanced CT imaging at baseline were not eligible for inclusion within the study. There is no universally accepted threshold for low muscle attenuation. Martin et al have previously identified a threshold of 41 HU for differentiating patients with poorer survival in a retrospective study in patients with varying solid organ malignancies and for the purposes of the primary analysis; this is the definition that was used[135].

OSIRIX software allowed for manual segmentation of muscle and adipose tissue using the above previously defined HU thresholds[162]. Skeletal muscle (SM) and subcutaneous adipose tissue (SAT), regions of interest (ROI) were generated on the same CT slice. Two assessors (the researcher completing the majority) undertook the generation of all ROIs for 179 patients. ROIs were generated by selecting all pixels within the referenced HU range, muscle and adipose tissue were then further manually segmented out when required. The anonymisation of the imaging ensured complete blinding to the clinical data throughout analysis. To ensure reliability, 20% of the ROIs were repeated and checked by Professor Andrea Rockall, consultant radiologist.

### 3.3.2 Primary objective

- To assess whether loss of muscle mass at baseline and during treatment predicts for progression free and overall survival following first line treatment for epithelial ovarian cancer

### 3.3.3 Secondary objectives

- To assess proportion of patients with sarcopenia at baseline (SMI <39.0 cm2/m2)
- To assess whether baseline sarcopenia predicts for increased rate of ≥ Grade 2 haematological and ≥ Grade 3 non-haematological toxicities
- To assess whether loss of muscle mass during chemotherapy predicts for increased rate of severe toxicities (≥ Grade 2 haematological and ≥ Grade 3 non-haematological toxicities)
- To assess whether baseline sarcopenia and loss of muscle mass during chemotherapy predicts for delays in chemotherapy of ≥ 2 weeks and/or dose reduction.
- To assess whether baseline sarcopenia and loss of muscle mass during chemotherapy predict to reduced likelihood of completing six cycles of chemotherapy

### 3.3.4 Statistical analysis

Progression-free survival (PFS) was measured from the date of diagnosis treatment to the date of radiological progression or death from any cause.

Overall survival (OS) was defined as the time from date of diagnosis or date of relapse (depending on the endpoint) to death from any cause. Patients without an event were censored at last follow up. Data were censored on the 1st August 2016.

The Kaplan-Meier method was used to produce the survival estimates. Demographics, clinical characteristics of the disease along with other data collected are presented as frequencies. Muscle attenuation (measured in Hounsfield units (HU)) and skeletal muscle index (SMI) was assessed using the baseline CT chest, abdomen and pelvis (prior to start of chemotherapy/surgery) and on the first response assessment CT chest, abdomen and pelvis (routinely undertaken after the 3$^{rd}$ cycle of chemotherapy). Percentage change in muscle area was calculated (first response CT SMI-baseline CT SMI)/baseline CT SMI. This was then divided by the number of days between scans and multiplied by 100 to produce a standardised value for percentage muscle loss per 100 days. Loss of muscle mass has been previously determined by Rutter et al as statistically significant when greater than 2% loss/100 days [16]. Sarcopenia in women has been previously defined as <38.5cm$^2$/m$^{2.}$. Mean changes in muscle tissue were analysed with paired t-tests.

Exploratory multivariable analyses for progression-free and overall survival were performed using the Cox proportional hazards model; hazard ratios (HR) and corresponding 95% confidence intervals are presented. Fishers chi squared test was used to test for association

between continuous variables. Statistical significance for all comparative tests was determined at $p < 0.05$.

## 3.4 Results

### 3.4.1 Participant recruitment and population demographics

179 patients met the stated inclusion criteria. Of the original cohort (n=208), two patients had no height data recorded, the remaining 29 patients either had not received intravenous contrast administration or the images were unsuitable for analysis due to poor image quality for example skeletal muscle not fully captured on a single slice at the level of L3 or significant volumes of subcutaneous adipose tissue were not captured or if there was substantial artefact (figure 13). The mean patient age was 73.4 years (range 65 – 94). 82.1% of patients had advanced disease (FIGO stage III/IV) at presentation and high grade serous was the most common histological subtype. Common comorbidities such as cardiovascular disease, diabetes mellitus and respiratory disease were prevalent. 49.4% of all patients received chemotherapy in the neoadjuvant setting, 7 (3.9%) patients received best supportive care. 64.8% of patients received platinum doublet chemotherapy with 27.8% receiving single-agent carboplatin and the remainder not receiving any form of systemic anti-cancer therapy. 129 patients (72.1%) underwent surgical debulking, of whom 94 (71.8%) achieved complete cytoreduction (table 18).

### 3.4.2 Relationship between age and body composition

A Pearson's correlation coefficient was computed to assess the relationship between body composition and age. There was no significant association between age and skeletal muscle index (r=0.05, p=0.397) (figure 14). Increasing age was however strongly negatively correlated with mean skeletal muscle attenuation (r=-0.27, p=0.012) (figure 15). Patients were then divided into four age cohorts, 65-69 years, 70-74 years, 75-79 years and 80 years and over (table 15.).

| | 65-69 years n=63 (35.2%) | 70-74 years n=52 (29.1%) | 75-79 years n=32 (17.9%) | >80 years n=32 (17.9%) | Total n=179 | p |
|---|---|---|---|---|---|---|
| SMI at baseline <38.5cm2/m2 | 26 (41.3%) | 18 (34.6%) | 12 (37.5%) | 9 (28.1%) | 65 (36.3%) | 0.641 |
| Baseline mean muscle attenuation <41HU | 44 (69.8%) | 41 (78.9%) | 27 (84.4%) | 27 (84.4) | 139 (77.6) | 0.27 |

**Table 15. Skeletal muscle index and attenuation according to age cohort**

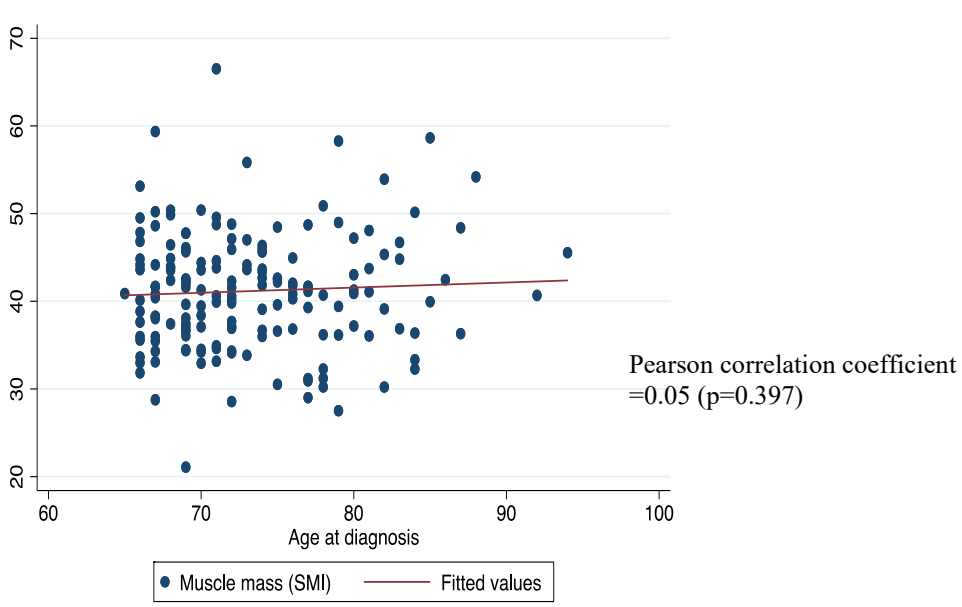



**Figure 14. Association between age and muscle mass (SMI) at baseline**

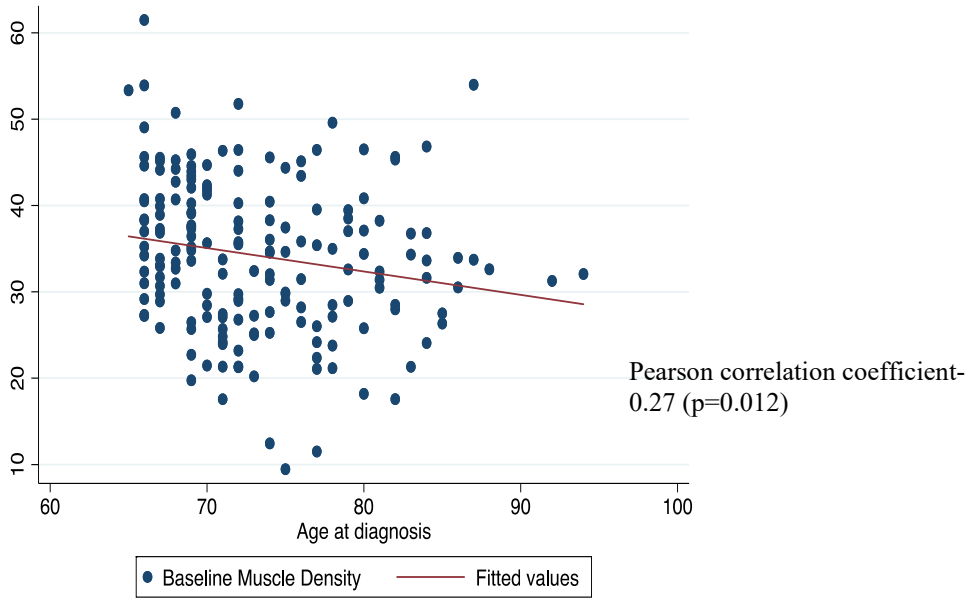



**Figure 15. Association between age and muscle attenuation at baseline**

There was no significant relationship between skeletal muscle index and age with 36.3% of patients meeting the established definition for sarcopenia with an SMI of 38.5cm$^2$/m$^2$ or less. Patients who were sarcopenic at baseline had lower mean weight (59.3kg vs. 68.6kg, p=0.000) BSA (1.63m$^2$ vs. 1.73m$^2$, p=0.001) and BMI (22.8 kg/m$^2$ vs. 27.4kg/m$^2$), p=0.000. Mean age was not significantly different between the two groups (table 16).

| | SMI > 39.5cm$^2$/m$^2$ | SMI <39.5 cm$^2$/m$^2$ | Total (n=179) | t-test p-value |
|---|---|---|---|---|
| Age (mean) | 73.8 (72.6-75.0) | 72.5 (71.1-73.9) | 73.37 (72.4-74.2) | 0.171 |
| Weight (kg) | 68.6 (65.8-71.4) | 59.3 (56.8-61.7) | 65.3 (63.1-67.4) | 0.000 |
| BSA (m$^2$) | 1.73 (1.69-1.77) | 1.63 (1.60-1.66) | 1.7 (1.66-1.72) | 0.001 |
| BMI (kg/m$^2$) | 27.4 (26.3-28.5) | 22.8 (21.8-23.8) | 25.8 (24.0-26.6) | 0.000 |

**Table 16. Body composition according to baseline skeletal muscle index**

### 3.4.3 Patient characteristics according to baseline muscle attenuation

Mean age in patients with low muscle attenuation at baseline was 73.9 (95% CI 72.8-74.9) compared to 71.5 (95% CI 69.8-73.2) in those with normal muscle attenuation (p=0.03). Mean weight, BMI and BSA were all significantly higher in those patients with low muscle attenuation at baseline (table 17).

| | Normal muscle attenuation >HU41 (n=39) | Low muscle attenuation <HU41 (n=140) | Total (n=179) | t-test p-value |
|---|---|---|---|---|
| Age (mean) | 71.5 (69.7-73.3) | 73.9 (72.8-74.9) | 73.37 (72.4-74.2) | 0.03 |
| Weight (kg) | 58.8 (55.3-6232) | 67.0 (64.6-69.5) | 65.3 (63.1-67.4) | 0.001 |
| BSA | 1.6 (1.6-1.7) | 1.7 (1.7-1.7) | 1.7 (1.66-1.72) | 0.007 |
| BMI | 23.6 (22.1-25.0) | 26.4 (25.4-27.3) | 25.8 (24.0-26.6) | 0.007 |

**Table 17. Body composition according to baseline muscle attenuation**

Although a higher proportion of patients with low muscle attenuation were FIGO stage 3 or 4 (84.9% vs. 72.5%), this difference was not statistically significant (p=0.152). Low baseline muscle attenuation at baseline was also associated with poorer ECOG performance status (34% vs. 15.4%, p=0.034). Histological subtype did not vary according to muscle attenuation (p=0.258). Of the documented functional limitations at baseline, only the use of a walking aid was associated with lower muscle attenuation at baseline (14.4% vs. 0, p=0.01) (table 18.)

Patients with low muscle attenuation at baseline were less likely to have received platinum doublet chemotherapy, although this difference was not statistically significant (61.2% vs. 77.5%, p=0.157). Patients with low muscle attenuation had lower rates of debulking surgery (58.6% vs. 65.6%) and complete cytoreduction (70.7% vs. 75%) however these differences were again, not statistically significant (table 18.)

| | Normal muscle attenuation >HU41 (n=40) n(%) | Low muscle attenuation <HU41 (n=139) n(%) | Total (n=179) n(%) | p-value |
|---|---|---|---|---|
| Age (years) (mean) | 71.5 | 73.9 | 73.4 | 0.032* |
| FIGO stage 1/2 | 11 (27.5) | 21 (15.1) | 32 (17.9) | 0.152 |
| FIGO stage 3/4 | 29 (72.5) | 118 (84.9) | 147 (82.1) | |
| ECOG PS 0/1 | 33 (84.6) | 89 (65.9) | 123 (70.3) | 0.034 |
| ECOG PS 2/3 | 6 (15.4) | 46 (34) | 52 (29.3) | |
| **Histological subtype** | | | | |
| High grade serous | 32 (80) | 101 (72.7) | 133 (74.3) | 0.258 |
| Low grade serous | 0 | 6 (4.3) | 6 (3.4) | |
| Endometrioid | 2 (5) | 6 (4.3) | 8 (4.5) | |
| Carcinosarcoma | 3 (7.5) | 9 (6.5) | 12 (6.5) | |
| Clear cell | 0 | 4 (2.9) | 4 (2.2) | |
| Mucinous | 0 | 2 (1.4) | 2 (1.2) | |
| Other | 1 (2.5) | 12 (8.6) | 13 (7.9) | |
| **Comorbidities** | | | | |
| Cardiovascular disease | 7 (17.5) | 50 (36.0) | 57 (31.8) | 0.035 |
| Hypertension | 12 (30) | 58 (41.7) | 70 (39.1) | 0.18 |
| Polypharmacy | 12 (30) | 60 (43.5) | 72 (40.5) | 0.163 |
| Respiratory disease | 3 (7.5) | 17 (12.2) | 20 (11.2) | 0.403 |
| Diabetes | 4 (10) | 16 (11.5) | 20 (11.2) | 0.837 |
| Osteoarthritis | 5 (12.5) | 8 (5.8) | 13 (7.3) | 0.13 |
| **Functional status** | | | | |
| Lives alone | 16 (41.0) | 66 (48.5) | 82 (46.9) | 0.408 |
| Lives in own home | 37 (94.9) | 133 (97.8) | 170 (97.1) | 0.334 |
| Use of walking aid | 0 | 20 (14.4) | 20 (11.2) | 0.011 |
| Assistance with ADLs | 2 (5.0) | 16 (11.6) | 18 (10.1) | 0.223 |
| Patient reported reduced ADLs | 8 (20.0) | 44 (31.9) | 52 (29.2) | 0.146 |
| Cognitive impairment | 0 | 5 (3.6) | 5 (2.8) | 0.224 |
| History of depression | 2 (5.0) | 6 (4.3) | 8 (4.5) | 0.854 |
| Patient reported weight loss | 11 (28.2) | 40 (28.8) | 51 (28.7) | 0.944 |
| Visual impairment | 2 (5.1) | 8(5.8) | 10 (5.7) | 0.873 |
| Hearing impairment | 0 | 3 (2.2) | 3 (1.7) | 0.349 |
| History of falls | 1 (2.6) | 0 | 1 (0.6) | 0.059 |
| **Chemotherapy received** | | | | |
| Platinum doublet | 31 (77.5) | 85 (61.2) | 116 (64.8) | 0.157 |
| Single-agent carboplatin | 8 (20) | 46 (33.1) | 54 (30.2) | |
| No chemotherapy | 1 (2.5) | 8(5.8) | 9 (5) | |
| **Surgical treatment received** | | | | |
| Underwent cytoreductive surgery | 32 (80.0) | 97 (69.8) | 129 (72.1) | 0.204 |
| Complete cytoreduction | 24 (75.0) | 70 (70.7) | 94 (71.8) | 0.639 |

**Table 18. Patient characteristics according to baseline muscle attenuation. Statistical association assessed by chi-squared test**

### 3.4.4 Impact of skeletal muscle volume on survival outcomes

There was no significant relationship between baseline skeletal muscle index and progression-free (HR 0.9, p=0.554, figure 17) or overall survival (HR 0.85, p=0.445, figure 16).

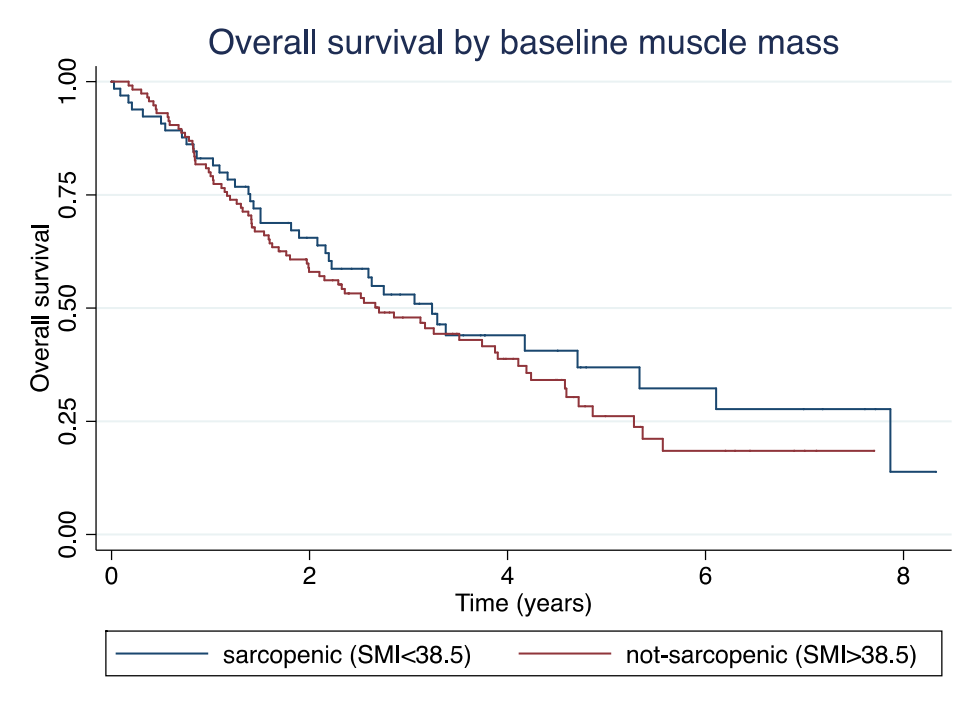



**Figure 16. Overall survival according to baseline skeletal muscle index**

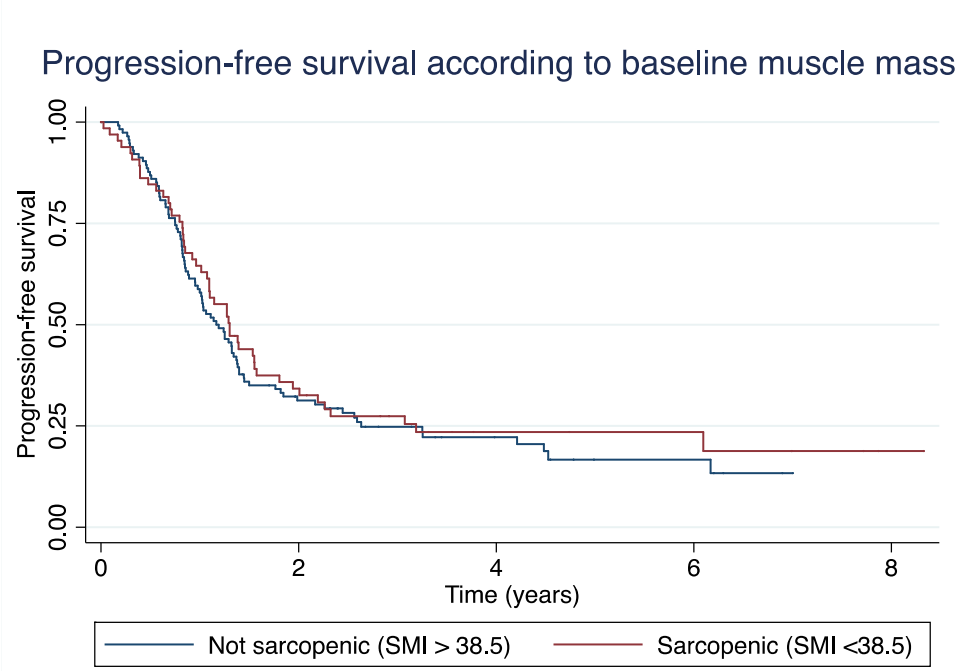



**Figure 17. Progression-free survival according to baseline skeletal muscle index**

### 3.4.5 Impact of skeletal muscle attenuation on survival outcomes

Skeletal muscle attenuation of 41HU or less at baseline was significantly associated with reduced overall survival (median survival 31 vs. 56.6 months, HR 1.85, p=0.013). After adjusting for age, stage at diagnosis and debulking status, the impact remained significant (HR 1.98; 95% CI 1.029-3.835, p=0.04) (figure 18). Progression-free survival in patients with baseline muscle attenuation of 41HU or less was also reduced (median PFS 13.3 vs. 16.6 months, HR 1.57 (p=0.039; 95%CI 1.024-2.306)) (figure 19.) 1-year survival for patients with a baseline MA of > 41 HU compared to lower than 41HU was 92.5% vs. 72.7%, 5-year survival was 43.8%vs 24.5% (p=0.000).

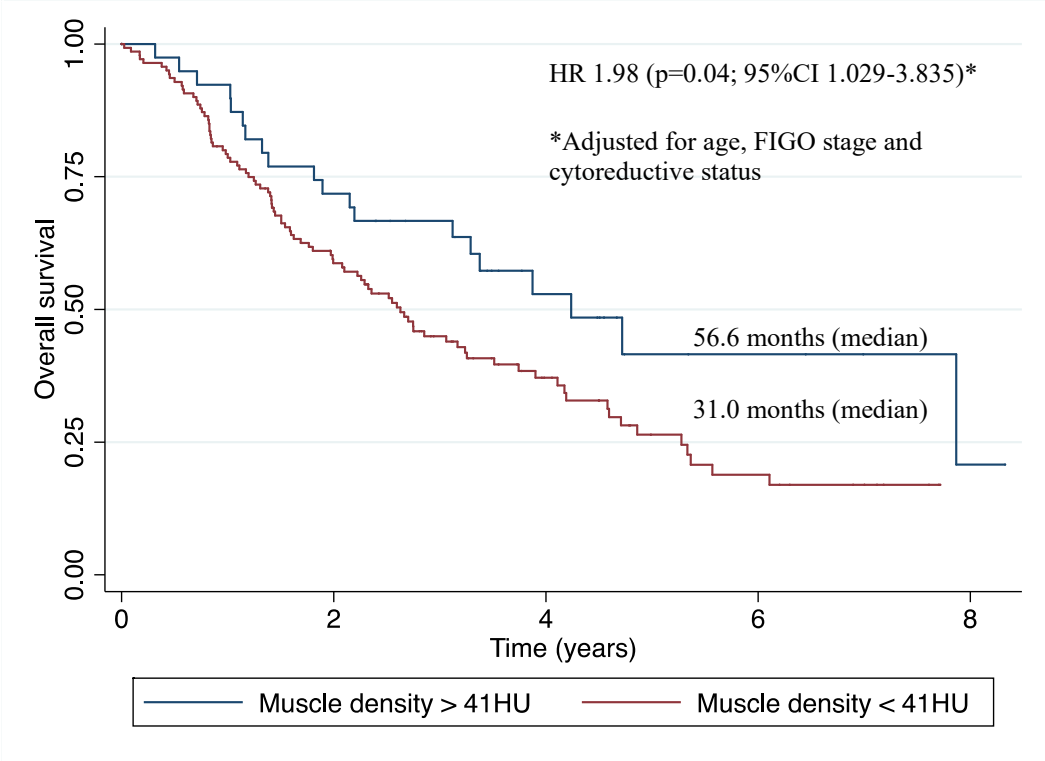



**Figure 18. Overall survival according to baseline muscle attenuation**

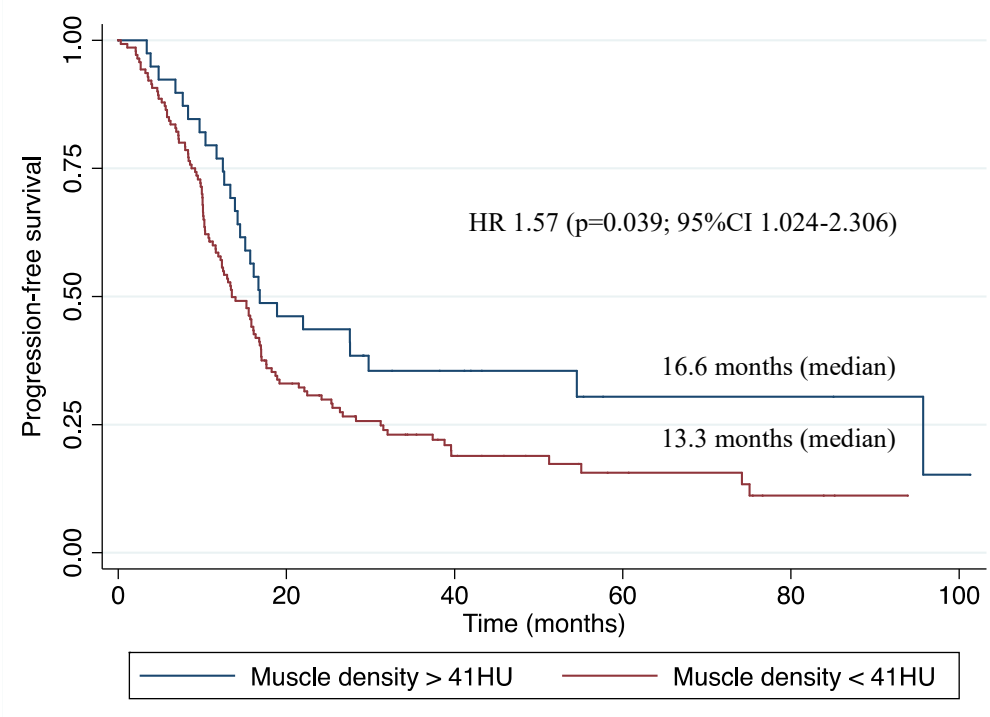



**Figure 19. Progression-free survival according to baseline muscle attenuation**

Other routinely collected assessments of body composition, weight (HR 0.99, p=0.462), BSA (HR 0.84, p=0.716) and BMI (HR 0.98, p=0.2) were not univariably associated with poorer survival outcomes. When patients were dichotomised into ECOG performance status 0/1 versus 2/3, low baseline muscle attenuation remained a significant predictor of poorer overall survival (HR 1.67; 95% CI 1.00-2.79, p=0.05). For example, 1-year survival for a patient with a poor ECOG performance status (2 or 3) and low (<41HU) compared to normal (>41HU) muscle attenuation was 60.8% vs. 86.5%, (log-rank test for equality p-value =0.000) (table 19, figure 20).

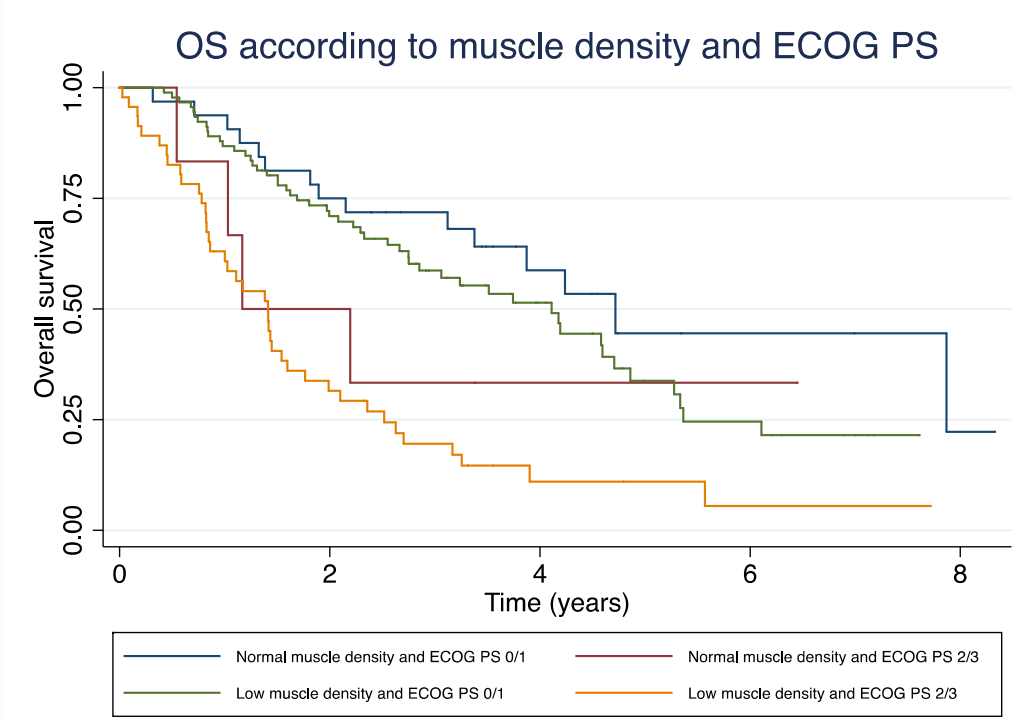



**Figure 20. Overall survival according to baseline muscle attenuation and ECOG Performance status**

| | 1-year survival | 95% CI | 5-year survival | 95% CI |
|---|---|---|---|---|
| Baseline MA > 41HU and ECOG PS 0/1 | 93.9% | (77.9-98.5) | 47.3% | (25.1-66.6) |
| Baseline MA > 41HU and ECOG PS 2/3 | 86.5% | (28.3-97.5) | 33.3% | (4.6-67.6) |
| Baseline MA < 41 HU and EOCG PS 0/1 | 86.5% | (77.5-92.1) | 30.0% | (18.3-44.5) |
| Baseline MA < 41 HU and ECOG PS 2/3 | 60.8% | (45.2-73.2) | 11.0% | (3.5-23.3) |
| Total | 80.1% | (74.4-86.0) | 29.0% | (20.1-37.6) |

**Table 19. 1 and 5-year survival according to baseline muscle attenuation (HU) and ECOG performance status**

| | Observed events | Expected events | Log-rank test, p-value |
|---|---|---|---|
| PS 0/1 and Baseline HU >41 | 21 | 33.09 | |
| PS0/1 and Baseline HU <41 | 64 | 69.92 | |
| PS 2/3 and Baseline HU >41 | 5 | 3.91 | 0.000 |
| PS 2/3 and Baseline HU <41 | 33 | 16.08 | |
| Total | 123 | 123 | |

**Table 20 Log-rank test for equality with ECOG performance status 0/1 and 2/3 with baseline muscle attenuation </> 41 HU**

A similar pattern is seen when patients are dichotomised into those with limited stage disease (FIGO stage 1/2) compared to advanced disease (FIGO stage 3/4) with low baseline muscle attenuation (HR 1.71, 95%CI 1.04-2.81, p=0.034) (figure 21). 1-year survival for patients with advanced disease and low versus normal baseline muscle attenuation was 74.6% vs. 89.7% (table 21). Survival differences were also seen in patients with limited-stage disease however these were more marked with long-term survival with 5-year survival rates of 90.9% vs. 48.3% (table 21), Log-rank test for equality p=0.000, (table 21).

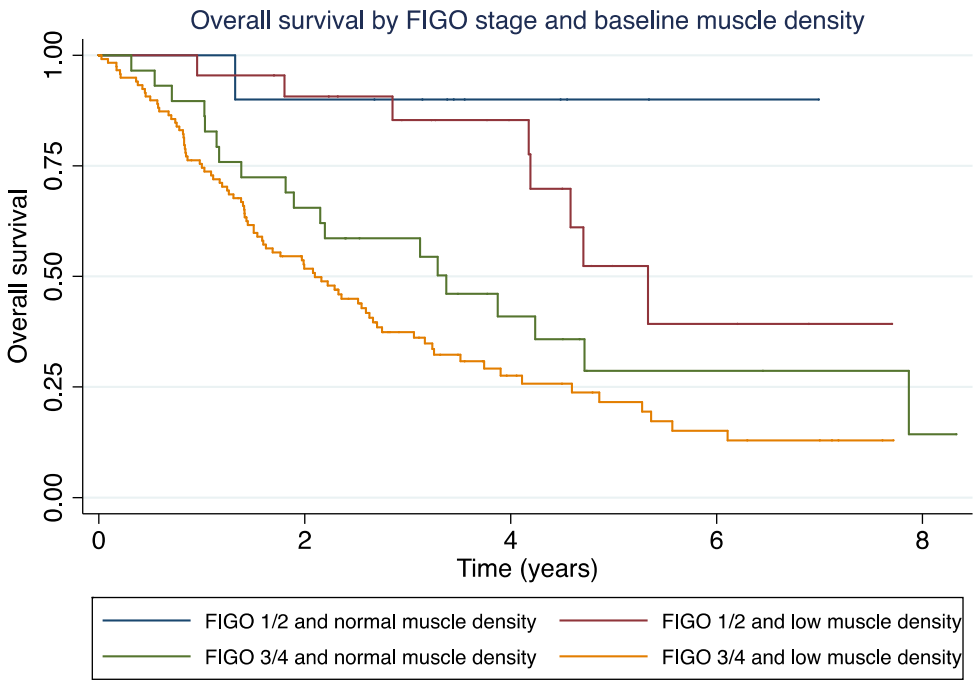



**Figure 21. OS according to FIGO stage and baseline muscle attenuation**

| | Observed | Expected | Log rank test p-value |
|---|---|---|---|
| FIGO stage 1/2 and Baseline HU >41 | 1 | 10.34 | |
| FIGO stage 1/2 and Baseline HU <41 | 8 | 19.28 | 0.000 |
| FIGO stage 3/4 and Baseline HU >41 | 19 | 21.35 | |
| FIGO stage 3/4 and Baseline HU <41 | 85 | 62.03 | |

**Table 21. Log-rank test for equality with FIGO stage 1/2 and 3/4 with baseline muscle attenuation </> 41 HU**

| | 1 year survival | 95% CI | 5 year survival | 95% CI |
|---|---|---|---|---|
| Baseline MA > 41HU and FIGO Stage 1/2 | 100% | n/a | 90.90% | (50.8-98.7) |
| Baseline MA > 41HU and FIGO Stage 3/4 | 89.70% | (71.3-96.5) | 28.70% | (11.3-48.9) |
| Baseline MA < 41 HU and FIGO Stage 1/2 | 95.20% | (70.7-99.3) | 48.30% | (19.3-72.5) |
| Baseline MA < 41 HU and FIGO Stage 3/4 | 74.60% | (65.7-81.5) | 20.20% | (19.3-72.5) |
| Total | 80.10% | (74.4-86.0) | 29.00% | (20.1-37.6) |

**Table 22.1 and 5-year survival according to baseline muscle attenuation (HU) and FIGO stage at diagnosis**

### 3.4.6 Impact of reduced muscle attenuation at baseline on treatment tolerance

With regards to surgery, low muscle attenuation at baseline was associated with significantly longer length of stay (10.8 vs. 7.8 days, p=0.03) post-operatively. 47% patients with low muscle attenuation were reported to have any grade of post-operative complication compared to 39% in those with normal muscle attenuation although this difference was not statistically significant (p=0.503).

Patients with reduced muscle attenuation at baseline were significantly less likely to complete the full six cycles of planned chemotherapy due to toxicity (16 vs. 0 patients, p=0.001). There was a non-significant trend towards worsening chemotherapy tolerance in patients with low muscle attenuation at baseline. 31.3% of patients with low muscle attenuation at baseline experienced a grade or higher non-haematological toxicity vs. 20.5% in patients with a baseline muscle attenuation of greater than 41HU (p=0.192). There was also a non-significant trend towards a higher rate of hospital admissions (35.1 vs. 23.7%, p=0.185) and a higher rate of delays in treatment for two weeks or more (77.1 vs. 66.7%, p=0.188) (table 23).

| | <HU41 (n=131) | | >HU41 (n=39) | | Total (n=170) | | |
|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | (%) | p-value |
| ≥ Grade 3 non-haematological toxicity | 41 | (31.3) | 8 | (20.5) | 49 | (28.8) | 0.192 |
| ≥ Grade 2 haematological toxicity | 39 | (29.8) | 11 | (28.2) | 50 | (29.4) | 0.851 |
| Completed 6 cycles of chemotherapy | 106 | (80.9) | 36 | (92.3) | 142 | (83.5) | 0.092 |
| Early discontinuation of chemotherapy | 25 | (19.1) | 3 | (7.7) | 28 | (16.5) | 0.092 |
| Discontinued chemotherapy due to toxicity | 16 | (12.2) | 0 | 0 | 16 | (9.4) | 0.001 |
| Febrile Neutropenia | 5 | (3.8) | 2 | (5.1) | 7 | (4.1) | 0.717 |
| Hospital admission during chemotherapy | 46 | (35.1) | 9 | (23.7) | 55 | (32.5) | 0.185 |
| Dose delay ≥ 2 weeks | 101 | (77.1) | 26 | (66.7) | 127 | (74.7) | 0.188 |

**Table 23. Treatment tolerance according to baseline muscle attenuation**

A logistic regression model was computed to assess the ability of baseline muscle attenuation to predict for reduced likelihood of completing six cycles of chemotherapy or developing a severe non-haematological toxicity. Increasing muscle attenuation at baseline predicted for a reduced likelihood of developing a severe (grade 3 or 4) non-haematological toxicity (OR 0.96 (p=0.039; 95% CI 0.923-0.998, figure 22). Increasing muscle attenuation at baseline was also associated with an increased likelihood of completing the full course of chemotherapy (OR 1.04 (p=0.049; 95% CI 1.000-1.099, figure 23).

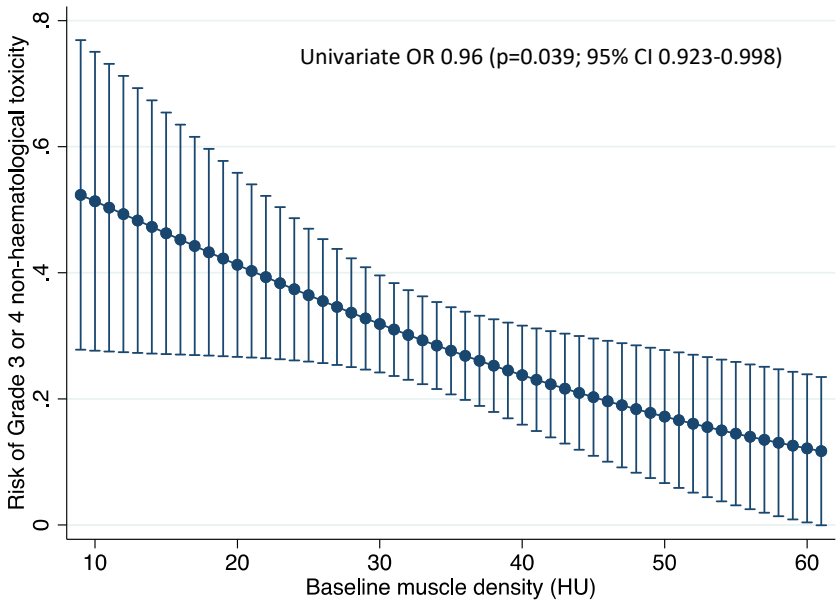



**Figure 22. Predictive margins plot demonstrating association between baseline muscle attenuation and severe non-haematological toxicities.**

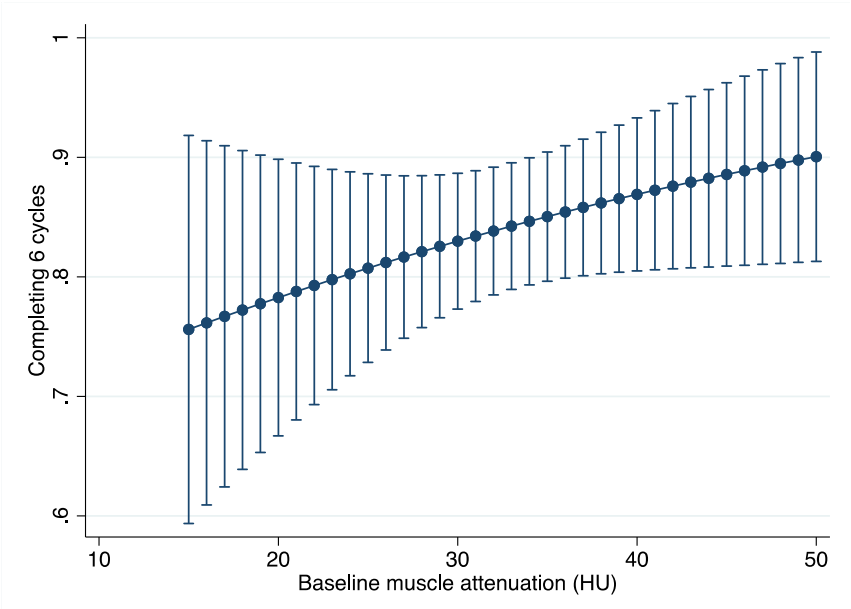



**Figure 23. Association between baseline muscle attenuation and completing 6 cycles of chemotherapy**

Baseline subcutaneous adipose tissue (SAT) area was not related to poorer overall survival (HR 0.99, p=0.531). There was a positive correlation between SAT area and grade 3 or 4 non-haematological toxicities however this was not statistically significant by linear regression (coefficient r=33.9 (95%CI -1.4-69.2), p=0.059). A negative correlation was seen between SAT area and rate of completing six cycles of chemotherapy but this was also not statistically significant (linear regression coefficient -30.0 (95%CI -72.6-12.6), p=0.167). There was no association between baseline SAT area and the development of grade 2 or higher haematological toxicities (linear regression coefficient 1.8 (95% CI -33.7-37.2), p=0.922).

### 3.4.7 Change in body composition during first line chemotherapy

There was a significant reduction in SMI and subcutaneous adipose tissue between baseline imaging and the mid-point imaging (mean reduction -3.48%, p=0.0012 and 4.81%, p=0.0000, respectively). Muscle attenuation did not significantly change between the two imaging time points (table 24).

| | Baseline (mean +/- SE) | Midpoint (mean +/- SE) | Mean percentage change | t-test | p-value |
|---|---|---|---|---|---|
| Skeletal muscle index (SMI) | 40.76 +/- 0.55 | 39.34 +/- 0.59 | -3.48 | 3.31 | 0.001 |
| Muscle attenuation (MA) | 34.12+/- 0.77 | 33.97 +/- 0.71 | -0.44 | 0.25 | 0.800 |
| Subcutaneous adipose tissue (SAT) | 159.81 +/- 8.78 | 141.16 +/- 7.8 | -11.67 | 4.81 | 0.000 |

**Table 24. Changes in body composition between baseline and mid-point imaging**

A regression analysis was undertaken to assess the relationship between change in body composition over time and overall survival. There was no correlation between loss of SAT and overall survival (r=13.04, p=0.618). An outlier was noted (67 year old patient, severely underweight at baseline (34kg), baseline SAT area 0.03cm$^{2,}$ rose to 6.01cm$^{2}$). A sensitivity analysis was performed demonstrating that this potentially anomalous finding did not alter the outcome of the regression analysis. Equally there was also no correlation between loss of muscle attenuation and poor survival (r=1.11, p=0.421) or skeletal muscle index (r=-0.11, p=0.839).

| | Mean | Median | IQR | SD |
|---|---|---|---|---|
| Skeletal muscle index (SMI) (% change/100 days) | -3.4 | -6.55 | (-11.79, 1.94) | 18.61 |
| Muscle attenuation (% change/100 days) | 2.69 | -0.84 | (-8.81, 12.23) | 30.26 |
| Subcutaneous adipose tissue (SAT) (% change/100 days) | 47.07 | -12.6 | (-31.3, 9.08) | 573 |

**Table 25. Changes in body composition standardised /100days**

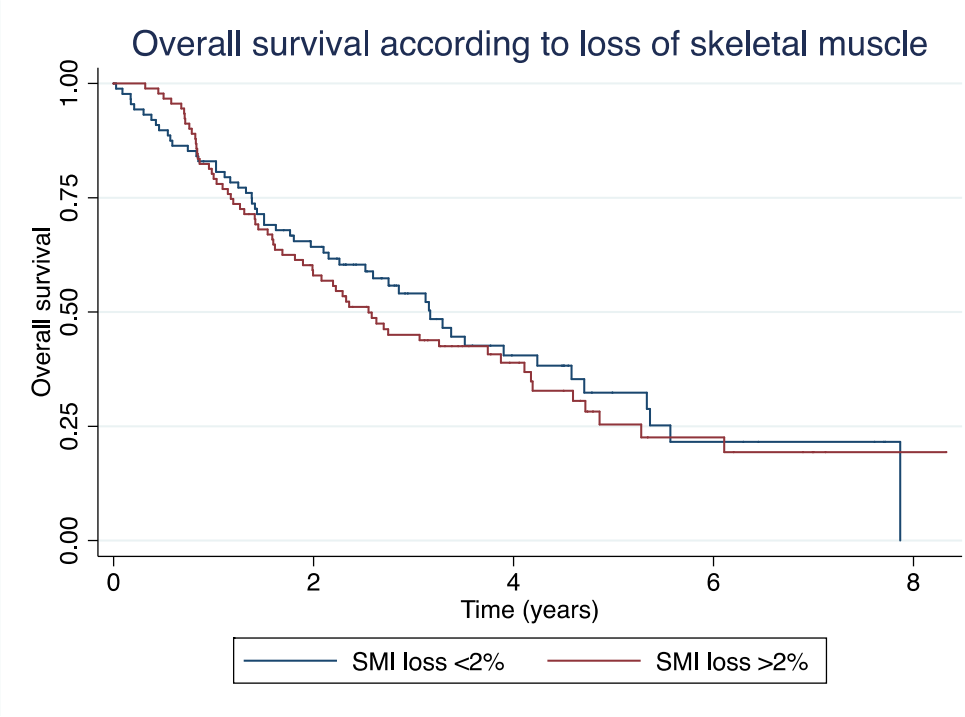



**Figure 24. Overall survival according to whether loss of skeletal muscle </> 2%/100 days**

Further regression analysis revealed that there was no association between the loss of muscle mass and the development of G2 or higher haematological toxicity (r=1.49, p=0.662), G3 or higher non-haematological toxicity (r=0.89, p=0.796) or the early cessation of chemotherapy (r=-7.5, p=0.275).

## 3.5 Analysis of Erector Spinae muscle mass and attenuation alone

During the generation of ROIs for the primary data analysis, I made a visual observation that the main anatomical location where loss of muscle attenuation was most obvious was the erector spinae (ES) muscle group. I therefore proposed to assess on a sample group whether erector spinae alone was a useful surrogate for total SMI. This is a smaller area to

assess and could potentially be readily performed using standard diagnostic (picture archiving and communication system) PACS software i.e. negating the need for anonymisation and export of imaging onto external imaging analysis software. This could potentially be done during the primary evaluation of imaging for example during the preparation for a multidisciplinary team meeting and if confirmed to be an independent prognostic marker or predictive marker for poorer tolerance to systemic anti-cancer therapy could be used as a rapid and easy addition to a frailty assessment tool and performance status evaluation in order to better risk stratify patients.

162 of the original 179 patients were included in this analysis. Given there is no established threshold for what is considered to be low muscle attenuation in this muscle group, the cohort was dichotomised into those above and below the median (27HU) in order to assess whether a clinically meaningful threshold could be established. The mean age was 73.3 (95%CI 72.4-74.2) with no statistically significant difference between those of high versus low ES muscle attenuation as a dichotomised variable however when assessed on a continuum, there was a strongly negative relationship between age and ES muscle attenuation ($r=-0.501$, $p=0.003$) (fig 25). There was a higher proportion of patients with a poorer ECOG PS (2/3) in patients with baseline low ES attenuation (37.8% vs. 15.7%, $p=0.002$). As before, there was no association between stage or histological subtype and total skeletal muscle attenuation. The only comorbidities to be significant associated with low ES muscle attenuation

were cardiovascular disease (p=0.02) and polypharmacy (p=0.048) (table 26).

Both weight and BMI at baseline were higher in those patients with a lower ES muscle attenuation (p=0.016 for both). Baseline weight correlated strongly with baseline SAT index (coefficient 0.73, p=0.000) however there was only a weakly negative, albeit statistically significant relationship between ES muscle attenuation and baseline SAT index (coefficient -0.19, p=0.012). These results raise the possibility that although some of the loss of muscle attenuation could be related to fatty infiltration in a patient with a globally higher adipose content, it cannot solely be attributed to this. There was no statistically significant relationship between ES muscle area and SAT index (pearsons coefficient 0.13, p=0.09).

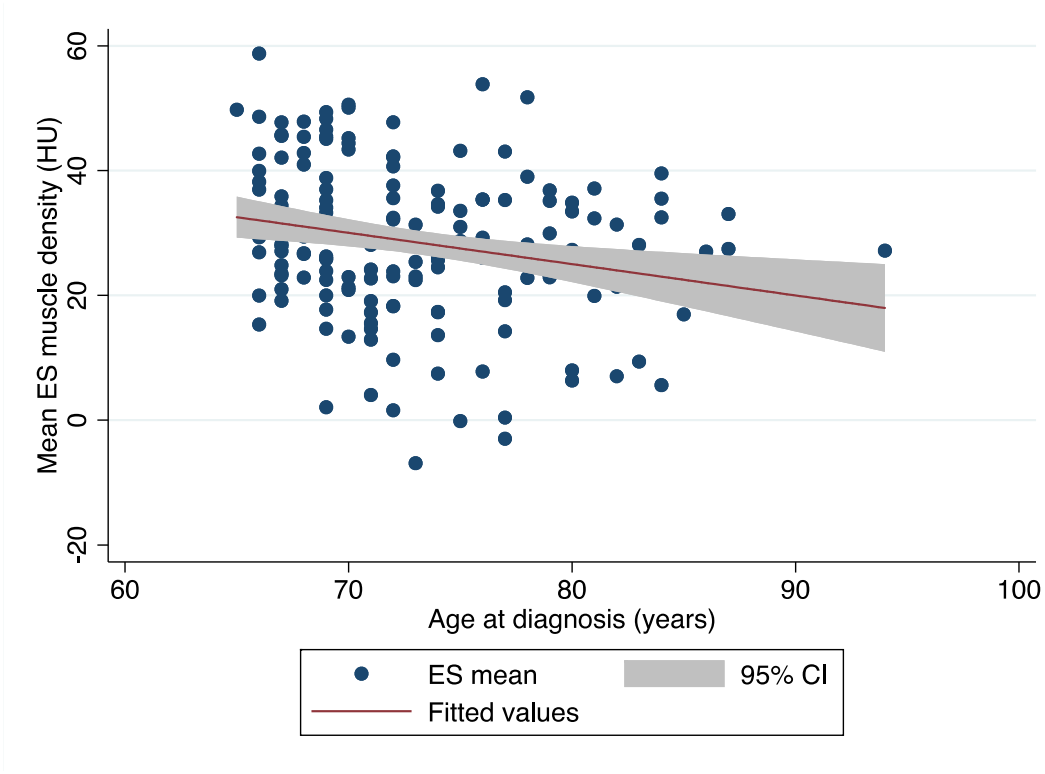



**Figure 25. Association between age and mean erector spinae (ES) muscle attenuation**

| | Erector spinae mean attenuation >27 HU n=86 % (n) | Erector spinae mean attenuation </= 27HU n=76 % (n) | Total % (n) n=162 | p |
|---|---|---|---|---|
| | n = 86 | n=76 | n=162 | |
| 65-69 years | 36 (41.9%) | 20 (26.3%) | 56 (34.6%) | |
| 70-74 years | 19 (22.1%) | 29 (38.2%) | 48 (29.6%) | 0.086 |
| 75-79 years | 17 (19.8%) | 13 (17.1%) | 30 (18.5%) | |
| > 80 years | 14 (16.3%) | 14 (18.4%) | 28 (17.3%) | |
| FIGO Stage I/II | 22 (25.6%) | 10 (13.2%) | 32 (19.7%) | 0.086 |
| FIGO Stage III/IV | 64 (74.4%) | 66 (76.7%) | 130 (80.3%) | |
| ECOG PS 0/1 | 70 (84.3%) | 46 (62.2%) | 116 (73.9%) | 0.002 |
| ECOG PS 2/3 | 13 (15.7%) | 28 (37.8%) | 41 (26.1%) | |
| | | | | |
| High grade Serous | 62 (72.1%) | 57 (75%) | 119 (73.5%) | |
| Low Grade Serous | 1 (1.2%) | 4 (53%) | 5 (3.1%) | |
| Carcinosarcoma | 5 (5.8%) | 6 (7.9%) | 11 (6.8%) | |
| Clear cell | 3 (3.5%) | 1 (1.3%) | 4 (2.5%) | 0.481 |
| Endometrioid | 7 (8.1%) | 1 (1.3%) | 8 (4.9%) | |
| Mucinous | 1 (1.2%) | 1 (1.3%) | 2 (1.2%) | |
| Other | 7 (8.1%) | 6 (79%) | 13 (8.0%) | |
| | | | | |
| BMI (mean) | 24.6 (23.4-25.8) | 26.8 (25.5-28.1) | 25.6 (24.7-26.5) | 0.016* |
| BSA (median, range) | 1.7 (1.6-1.7) | 1.7 (1.7-1.8) | 1.7 (1.3-2.2) | 0.04* |
| Weight | 62.4 (59-65.2) | 68.0 (64.5-71.5) | 74.9 (62.7-67.2) | 0.016* |
| | | | | |
| Serum albumin <35g/dl | 30 (34.9%) | 39 (51.3%) | 69 (42.6%) | 0.035 |
| Cardiovascular disease | 20 (23.3%) | 30 (39.5%) | 50 (30.9%) | 0.02 |
| Hypertension | 30 (34.9%) | 30 (39.5%) | 60 (37.0%) | 0.546 |
| Polypharmacy | 26 (30.2%) | 34 (45.3%) | 60 (37.3%) | 0.048 |
| Respiratory disease | 6 (6.9%) | 10 (13.2%) | 16 (9.9%) | 0.188 |
| Diabetes Mellitus | 10 (11.6%) | 8 (10.5%) | 18 (11.1%) | 0.962 |
| | | | | |
| Neoadjuvant chemotherapy | 40 (47.1%) | 38 (50%) | 78 (48.5%) | |
| Adjuvant chemotherapy | 41 (48.2%) | 26 (34.2%) | 67 (41.6%) | 0.025 |
| Best supportive Care/ Chemotherapy not indicated | 4 (4.7%) | 12 (15.8%) | 16 (9.9%) | |
| Combination chemotherapy | 59 (68.6%) | 51 (67.1%) | 110 (67.9%) | 0.937 |
| Single agent carboplatin | 23 (26.7%) | 3 (3.9%) | 7 (4.3%) | |
| No chemotherapy | 4 (4.7%) | 22 (29.0%) | 45 (27.8%) | |
| Complete cytoreduction | 52 (75.3%) | 35 (66.0%) | 87 (71.3%) | 0.259 |

**Table 26. Patient and treatment characteristics**

* t-test statistic

Consistent with the visual observation that the muscle attenuation in the ES muscle group appeared to be lower than the surrounding skeletal muscle, mean muscle attenuation in the ES muscle group was significantly lower than in the total skeletal muscle area at the level of L3 (28.4HU vs. 34.4HU, p=0.000). ES muscle attenuation was however strongly positively correlated with total skeletal muscle attenuation, (r = 0.71, p=0.000) (fig 26).

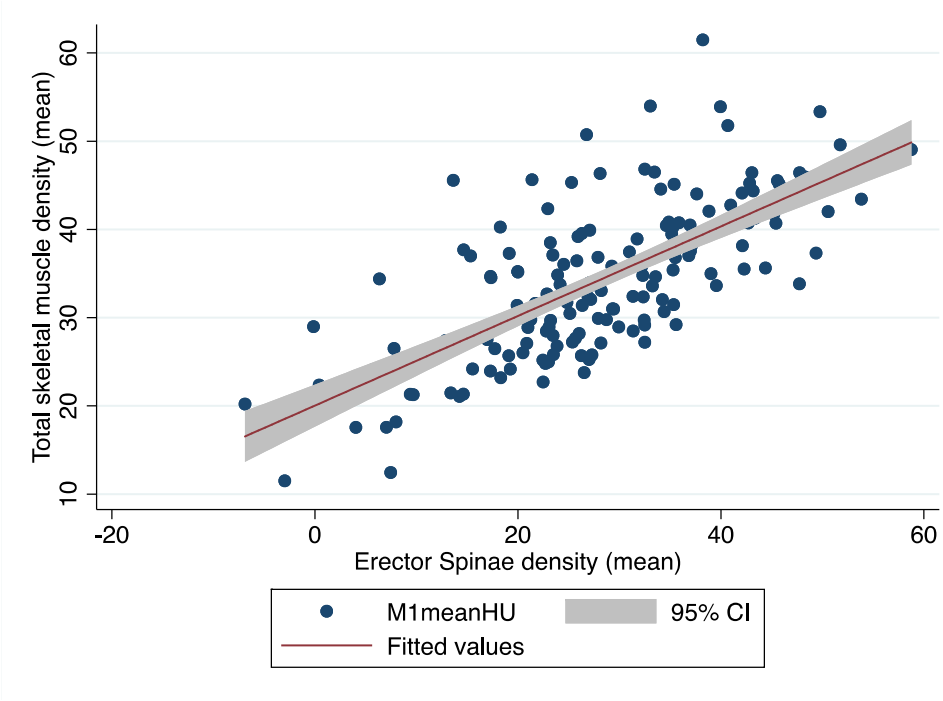



**Figure 26. Relationship between (mean) erector spinae muscle attenuation and total (mean) skeletal muscle attenuation (HU**

Similarly, ES muscle area was proportional to total skeletal muscle area at the level of L3 however the correlation was weaker (r=0.6, p=0.000) (figure 27).

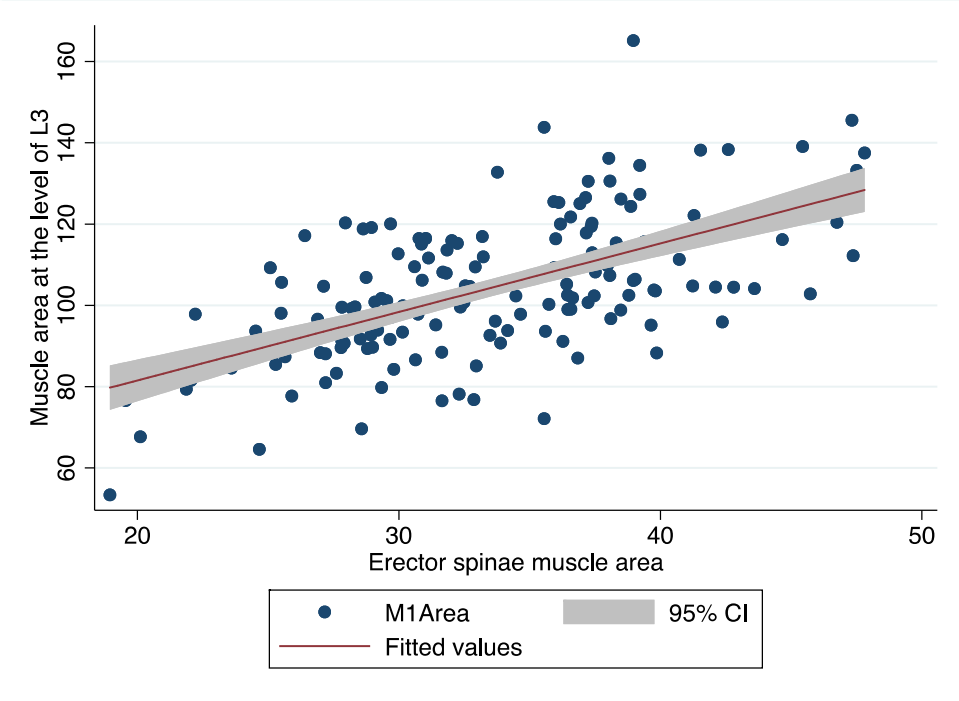



**Figure 27. Relationship between erector spinae muscle area and total skeletal muscle area at the level of L3 (cm2)**

In the overall population, reduced skeletal muscle attenuation but not index was strongly associated with poorer survival outcomes. Using the median as a threshold, Kaplan-Meier curves were generated to assess the impact of lower versus higher ES muscle attenuation on overall survival. Overall survival was significantly lower in those patients with a mean ES HU of 27 or lower (27.5 versus 46.8 months, HR 1.822, p=0.003) (table 27, fig 28). This marked difference remained significant after adjusting for age and stage at diagnosis (HR 1.62, p=0.016). Progression-free survival was also significantly lower in those with low

mean ES muscle attenuation (12.2 months versus 16.6, HR 15.82, p=0.01) (fig 29).

| | ES mean < 27 HU | ES mean > 27 HU | HR | P | 95% CI |
|---|---|---|---|---|---|
| Overall survival (months) | 27.5 | 46.8 | 1.822 | 0.003 | 14.77-32.29 |
| Progression-free survival (months) | 12.2 | 16.6 | 1.582 | 0.01 | 13.37-26.98 |

**Table 27. Survival outcomes according to erector spinae mean muscle attenuation**

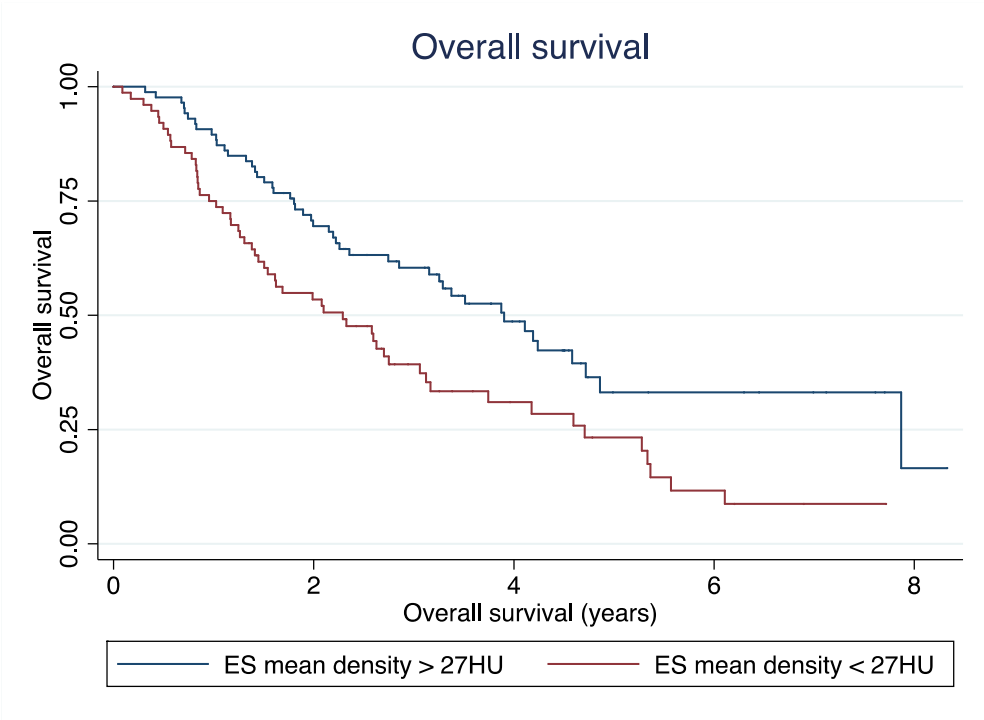



**Figure 28. Overall survival according to baseline erector spinae muscle attenuation (mean)**

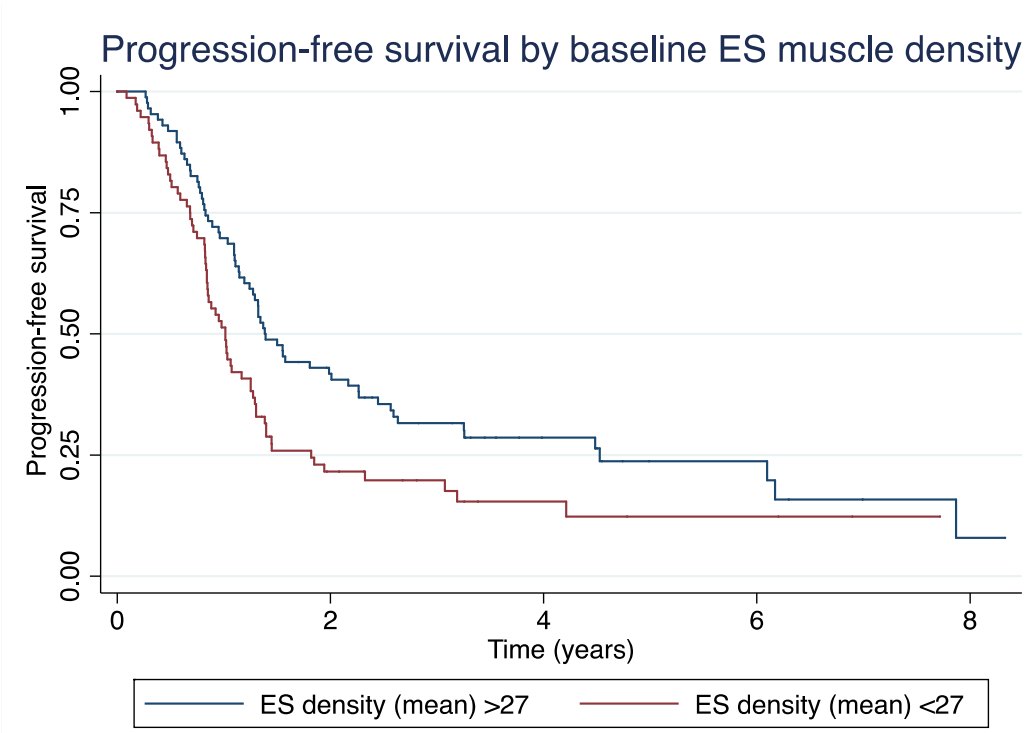



**Figure 29. Progression-free survival according to baseline erector spinae muscle attenuation (mean)**

As a dichotomised group, patients with lower ES muscle attenuation had a trend towards higher rates of dose delays, dose reductions and grade 3 or 4 non-haematological toxicities as well as a lower rate of completing the full six cycles of chemotherapy. These differences were not however statistically significant (table 28).

| | Mean ES attenuation >27HU n=86 | Mean ES attenuation <27 HU n=76 | Total | p-value |
|---|---|---|---|---|
| ≥ G2 Haematological toxicity | 23 (28.1%) | 21 (28.8%) | 44 (28.4%) | 0.921 |
| ≥ G3 non-haematological toxicity | 20 (24.4%) | 25 (34.3%) | 45 (29.0%) | 0.177 |
| ≥ 2 weeks dose delay | 11 (16.4%) | 13 (24.5%) | 24 (20%) | 0.27 |
| Dose reduction during chemotherapy | 27 (33.3%) | 33 (45.8%) | 60 (39.2%) | 0.114 |
| Completed 6 cycles | 76 (88.4%) | 61 (80.3%) | 137 (84.6%) | 0.154 |

**Table 28. Association between chemotherapy tolerance and mean erector spinae muscle attenuation**

Logistic regression analysis was performed to assess the relationship between erector spinae mean muscle attenuation as a continuous variable and the risk of developing a grade 3 or higher non-haematological toxicity (OR 0.97, p=0.05). Likewise, increasing muscle attenuation of ES was significantly associated with a greater chance of completing 6 cycles of chemotherapy (OR 1.04, p=0.02).

### 3.5.1 Inter-rater reliability testing

In order to strengthen the reliability of this finding, a second, independent observer undertook repeated measurements on 160 of the original 179 subjects. The median of the mean erector spinae measurement in HU for the initial analysis of this subset was 27.4HU (IQR 21.3HU-36.3HU) compared to 32.9HU (IQR 26.9-41.4) in the repeat assessment by a

second observer. Concordance correlation was 0.858 (p=0.000). A Bland-Altman plot was then generated to assess the degree of agreement of the erector spinae mean muscle density between the two observers (fig 30).

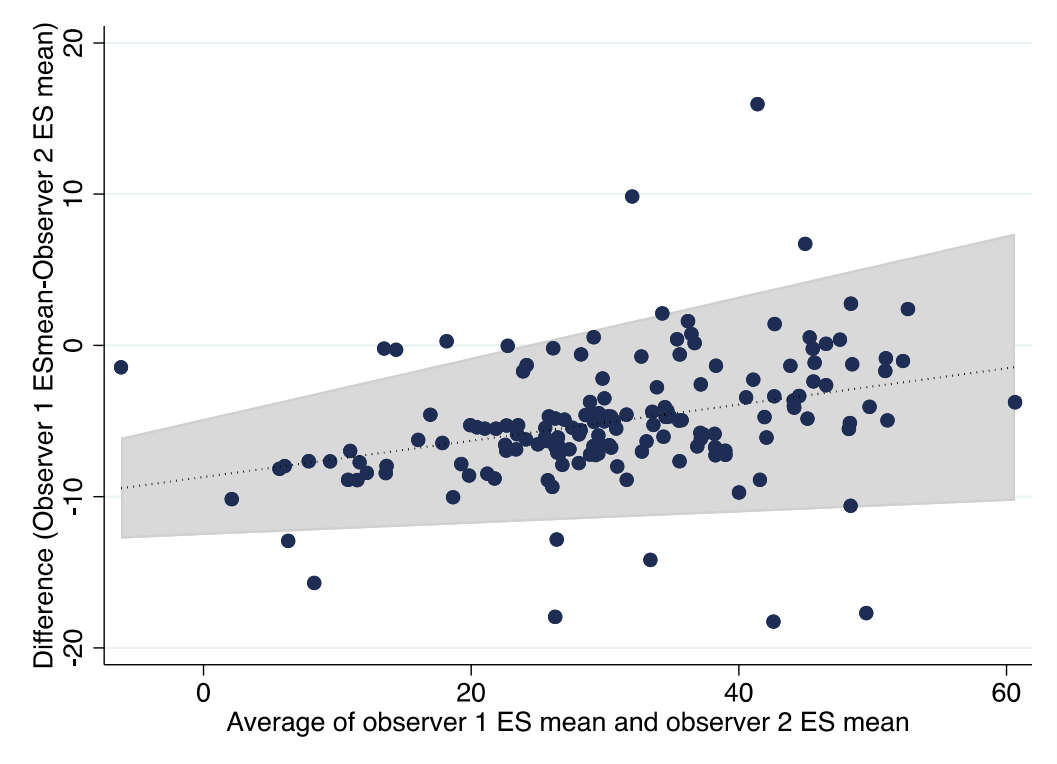



**Figure 30. Bland-Altman plot of agreement between first and second observer mean erector spinae HU**

Likewise for area, the median was 32.9HU (IQR 28.8-37.7HU) and 42.0HU (IQR 27.5-36.3HU). The concordance correlation was 0.895 (p=0.000) and the Bland-Altman plot confirming close agreement between the two measurements is below (figure 31).

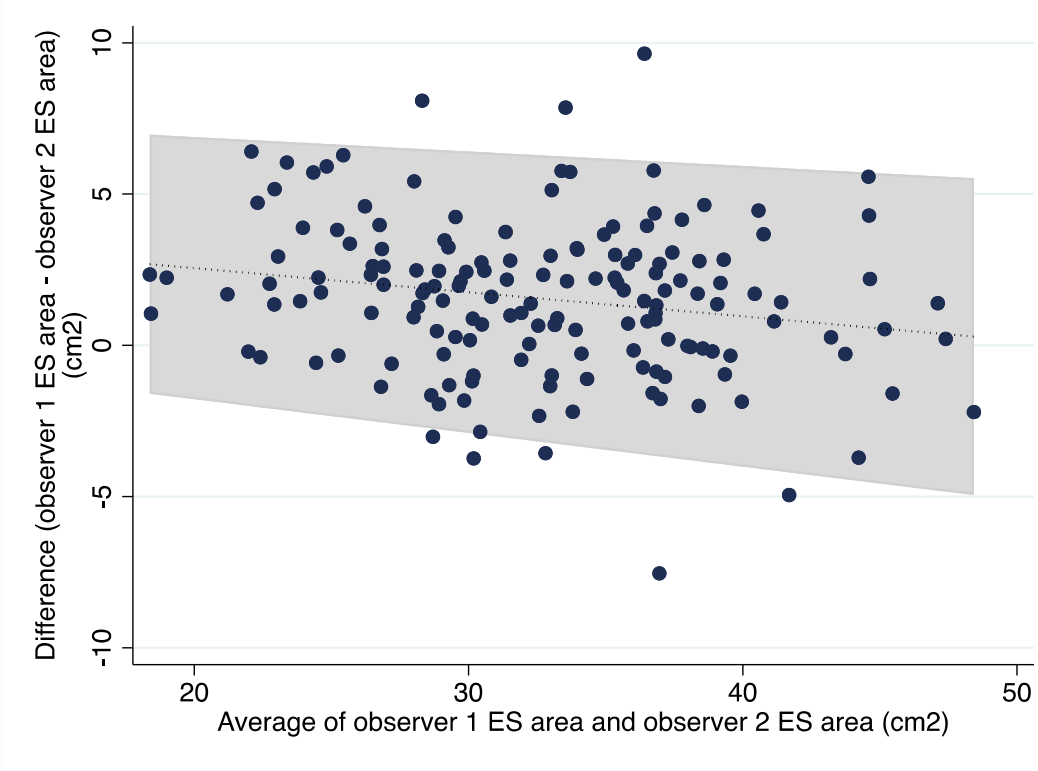



**Figure 31. Bland-Altman plot of agreement between first and second observer mean erector spinae area ($cm^2$)**

### 3.6 Impact of body composition at relapse

92 patients had chemotherapy at relapse and suitable imaging for analysis. 52 (56.5%) received platinum-based chemotherapy (carboplatin single-agent or in combination with pegylated liposomal doxorubicin, paclitaxel or gemcitabine). Mean muscle density did not significantly change between baseline and beginning of second-line therapy (baseline mean HU 32.9 vs. 31.3HU at relapse, t-test p=0.359). Mean SMI did drop between first and second-line therapy (41.3$cm^2/m^2$ vs. 38.7$cm^2/m^2$, t-test p=0.003). However, neither SMI (HR 0.98 (95%CI .095-1.02, p=0.391) or muscle attenuation (HR 0.99 (95%CI 0.96-1.02), p=0.520) was significantly associated with overall survival as continuous variables.

Using the same threshold as for first-line analysis to dichotomise patients into low and normal muscle density (41HU), there remained no significant difference in overall survival between patients of low and normal muscle density at relapse (HR 1.14; 95%CI 0.52-2.49, p=0.751).

## 3.7 Discussion

This is the first study to assess body composition, both muscle mass and attenuation specifically in older ovarian cancer patients receiving first-line therapy. These findings show that sarcopenia defined both as loss of muscle mass and even more so, loss of muscle attenuation are highly prevalent conditions in older women with newly diagnosed ovarian cancer. In contrast to previously reported data, there was no association between skeletal muscle mass and poorer survival outcomes or poorer chemotherapy tolerance. In this cohort, there was also no association between skeletal muscle mass and ECOG performance status, functional level at baseline or any medical comorbidity. Whilst the standard definition of sarcopenia utilises the height-standardised variable SMI, a significant limitation of the use of this measure in an older population is the potential impact of ageing and osteoporosis, a common condition in older women is the loss of vertebral and therefore vertical height. SMI as measured by height is thus potentially less reliable with increasing age and validation of an alternative measure using arm-span would be an important further study.

The major finding of this study is that low muscle attenuation rather than skeletal muscle mass is significantly associated with poorer progression-free survival and overall survival. Furthermore, that loss of muscle attenuation was also associated with increased rates of severe non-haematological toxicities and of even more relevance prognostically, reduced rates of completing the full course of chemotherapy. It is also notable that functional limitation in the form of requiring a walking aid was strongly associated with loss of muscle attenuation but not mass. This further supports the hypothesis that it is muscle quality rather than quantity that is of more relevance functionally.

The closer relationship between muscle attenuation and function rather than muscle mass and function is further explained by the observation that the relationship between production capability and muscle size is not the same in older adults[163]. From the Health Ageing and Body Composition study, Goodpaster et al demonstrated that age-related decline in muscle strength is much more rapid than that of muscle mass[164]. From this same dataset, 515 of 3075 included patients went on to be diagnosed with a malignancy and thus a unique opportunity was provided to assess muscle mass (as assessed by dual-energy radiography absorptiometry) and strength (hand-grip and gait speed). Patients with a cancer diagnosis had a steeper age-related decline in both gait speed and lean muscle mass[165] than those who were cancer-free.

The novel finding that erector spinae muscle attenuation alone is a strong, independent predictor of poorer overall and progression-free survival is clinically, of relevance. It is strongly correlated with ECOG performance status and therefore could provide an objective, quantifiable gauge of a patient's functional capacity, ideally in addition to a formal frailty or comprehensive geriatric assessment. The predictive ability for treatment toxicity was less marked. However it should be noted here that this is a retrospective study, underpowered to assess this outcome and the relationship. These findings may warrant prospective evaluation. It is at present, time-consuming and labour intensive to manually segment and evaluate body composition using external image analysis software. Segmenting one readily identifiable muscle group on the standard clinical PACS could be a relatively quick addition to the preparation a radiologist would normally undertake ahead of the multidisciplinary team meeting. This could theoretically then be incorporated into the clinical and histological information already presented at the team meeting to facilitate individualised decision-making.

Change in body composition, either of loss of muscle mass or attenuation or gain of subcutaneous adipose tissue was not associated with survival outcomes or treatment tolerance. Rutter et al reported that a skeletal muscle mass loss of 2%/100 days was associated with a poorer overall survival in a population of ovarian cancer patients[157]. This was not replicated in this population: no difference was seen in overall survival between those patients who lost more than 2%/100 days of the muscle

mass and those who did not (HR 1.11 (p=0.572; 95%CI 0.76-.61). This finding has not been replicated in other studies. It may be that loss of muscle mass between baseline and the first response assessment is less impactful in ovarian cancer due to, on the whole, an improvement in performance status and functional status during first-line treatment. Patients often present with advanced disease and a high symptomatic burden, ovarian cancer and in particular high grade serous carcinomas are in general chemo-sensitive tumours with high response rates seen with first line chemotherapy[166].

Since this study was commenced, two other groups have corroborated the finding that muscle attenuation rather than muscle mass is predictive of poorer overall survival. Kumar et al reported lower mean muscle attenuation in women over the age of 70. Using a threshold cut-off of 36.4HU, overall survival was poorer in those patients with low muscle attenuation (24.5 vs. 40 months, significance not reported). SMI was not associated with poorer survival outcomes[154]. Subsequently, Ataseven et al presented data on 323 patients with FIGO Stage IIIB or higher ovarian cancer who had undergone primary debulking surgery. 75 (23.1%) of patients were aged 70 years or older. The prevalence of sarcopenia (defined as an SMI < 39$cm^2/m^2$) was 33.7%, there was no association between SMI and overall survival. Using a MA threshold of 32HU, the difference in overall survival was comparable to that seen in this dataset (OS 28 months vs. 57 months, p<0.001)[167]. Both studies

were non-age restricted and the impact of muscle attenuation or mass in relation to chemotherapy tolerance was not assessed in either.

Furthermore, a systematic review that included six studies evaluating the prognostic impact of sarcopenia on ovarian cancer survival reported that sarcopenia was not associated with a significantly different 3 or 5-year survival. Cut-offs for “normal” MA ranged from 32 to 39HU. Low muscle attenuation (defined according to each of the individual study thresholds) was however associated with a significantly poorer 3 and 5 year-survival (OR 3.0, 95% CI 2.0-4.5, $p < 0.001$) and (OR 2.3, 95% CI 1.6-3.4, $p < 0.001$), respectively[168].

### 3.8 Limitations

The retrospective nature of this study allowed for a sufficiently long follow up to enable meaningful survival analysis. Retrospective collection of functional limitations and comorbidities however is likely to result in under-reporting of, in particular, subtle functional limitations. It is not for example, common practice to ask and document falls history although this is now recommended in the recent ASCO guidance[20]. Similarly, whilst collection of haematological toxicities is straightforward and robust methodologically, non-haematological toxicities are more subjective and associated with risk of reporting bias. Although therefore a trend towards poorer chemotherapy tolerance was seen in patients with lower muscle attenuation was seen, given the retrospective nature of toxicity data collection, this association may be underestimated and is worthy of future

prospective evaluation. As previously discussed in Chapter 2, a further limitation of this study relates to choice of patient population. The patient population of a tertiary cancer centre in London is unlikely to represent the wider UK ovarian cancer population. The prevalence of comorbidities, functional loss and indeed sarcopenia/cachexia at baseline reported here may therefore differ from a broader population and further studies to assess this would be beneficial.

A significant limitation of this study is the lack of a physical measure of strength or function at baseline as this is not currently routinely performed at my institution. Although therefore these findings appear to support the conclusion that muscle attenuation could be a surrogate of muscle strength and quality, further studies incorporating at least one physical measure of strength such as grip strength, timed up and go or gait speed test[114, 152] in keeping with the latest consensus definition of sarcopenia should be undertaken to evaluate this hypothesis.

The definition of low muscle attenuation used in this study was taken from a non-age-restricted study. Given that muscle attenuation decreases with advancing age, this may explain the particularly high prevalence of low muscle attenuation in this cohort of older women. As an exploratory analysis, the median value of mean muscle attenuation at baseline (34HU) was taken a cut-off threshold. Using this definition, 93 (52.0%) patients met this definition. Baseline muscle attenuation of <34HU was significantly associated with poorer overall survival even after adjusting

for FIGO stage at baseline and debulking status (HR 2.16; 95%CI 1.30-3.59, p=0.003). Future studies with larger populations across a wider spread of solid organ malignancies may allow the identification of “normal” values for a given age and/or condition to better discriminate between low and normal muscle attenuation and further improve risk stratification and targeted interventions.

## 3.9 Conclusion

Muscle attenuation, as a surrogate measure of muscle quality is a more prognostic and predictive marker of both survival outcomes and treatment tolerance than muscle mass in older women with newly diagnosed ovarian cancer. The lack of a clear relationship between muscle attenuation and outcomes at relapse is of interest and further work is warranted to evaluate this in more depth. The relationship between cancer-related sarcopenia, frailty and inflammation is highly complex and deserving of further study in order to elucidate potential pharmacological and non-pharmacological interventions. Identifying those patients with low muscle attenuation at an early stage in the treatment pathway has therapeutic relevance. Better risk-stratification and prognostic information can only serve to improve the patient decision-making process. Identifying those patients who may specifically require and benefit from multidisciplinary input in the form of a prehabilitation programme, a concept now gaining traction in the field of oncology[169, 170].

### 3.9.1 Future work

The nature of the relationship between low muscle attenuation and poorer survival outcomes remains unclear. Whilst it may simply be that those with low muscle attenuation are more likely to be frail and therefore have poorer survival outcomes, given that inflammation appears to be key driver of both, one could hypothesise that sarcopenia and low muscle attenuation are the result of a more pro-inflammatory, inherently more aggressive tumour phenotype which would thus carry a poorer prognosis. The correlation of low muscle attenuation with poorer chemotherapy tolerance supports the former assertion. In order to better characterise the complex inter-relationship between frailty, sarcopenia and treatment tolerance and outcomes, prospective studies incorporating functional and strength assessment at a minimum and ideally a full geriatric assessment are essential. The prospective study, FAIR-O opened in January 2021 (NCT04300699). This study will include 120 patients being treated in both the first-line setting and at first-relapse. The primary endpoint is the completion of a geriatric assessment by oncology teams in the outpatient clinic, sarcopenia as a predictive and prognostic marker alongside exploratory biomarker analysis are important secondary endpoints.

# 4 QUALITATIVE RESEARCH STUDY: EXPLORING OLDER PATIENT ATTITUDES TO AND EXPERIENCE OF TREATMENT FOR OVARIAN CANCER

## 4.2 Introduction

Although it is known that older patients receive less intensive treatment than younger patients[95, 171, 172], little has been documented regarding the perception of older patients towards anti-cancer treatment. It is therefore currently unclear whether the lower treatment rates are due to older patients declining more intensive therapy or whether clinicians are more reluctant to offer more intensive treatment options owing to concerns over tolerance and burden of treatment in an older patient[173]. Whether older women may have a more negative attitude towards treatment and be more inclined to refuse more intensive options for example significant cytoreductive surgery or chemotherapy with the risk of a higher side-effect profile has not been fully assessed to date.

### 4.2.1 Qualitative studies assessing decision-making process and experience of cancer treatment from patients's perspective

To assess where the discrepancy in treatment decision-making lies, the behaviours and beliefs of older patients about to embark on anticancer treatment need to be examined. A study in Canada[174] consisting of semi-structured interviews with twenty older adults (over 65 years) due to embark on systemic anti-cancer therapy reported that although patients expressed a strong desire to make autonomous decisions regarding their

cancer therapy, the majority accepted their clinicians' recommendation with few patients seeking a second opinion. The desire to prolong life rather than focusing on quality of life was more commonly cited as the primary motivator for treatment. With regards to cytoreductive surgery, a questionnaire-based survey in 2001 demonstrated that there was no difference between older and younger women desiring surgery offering a chance of disease cure (p=0.75) but older women desired cure more if treatment was associated with disfigurement (p=0.029)[175]. Larger studies evaluating the treatment preferences of non-age selected populations have variably reported the importance placed by patients on quality versus quantity of life[176, 177].

In contrast to this, in a secondary analysis of a prospective study, the preferences of patients over the age of 65 about to embark on systemic chemotherapy were examined. In this cohort of 121 patients, just over half of whom were women, using a combination of visual analogue scales (VAS) and an attitude survey, 58% of patients strongly agreed that they would prefer to "I would rather live a shorter life than lose my ability to take care of myself", 81% felt that "It is more important to me to maintain my thinking ability than to live as long as possible"[178]. It is noteworthy that in both studies, the participants had not yet experienced systemic anti-cancer therapy. Whilst this removes the potential for positive or negative recall bias due to response rates and survivorship, the views of participants on a treatment they have not yet experienced needs to be borne in mind when considering these outcomes.

### 4.2.2 Studies assessing decision-making process from the perspective of healthcare professionals

As part of a wider Macmillan funded project across five English healthcare trusts, 22 healthcare professionals were interviewed in a combination of focus groups and telephone interviews to assess their perspective on decision-making in newly diagnosed older patients with breast and colorectal cancer[179]. Clinicians felt time pressure was a significant barrier to decision-making particularly in complex older adults both in the multidisciplinary team (MDT) meeting and in clinic. The focus of multidisciplinary team discussions were felt to be pathology based with the "softer" aspects being left for the clinician to review with the patient as these were often not known by the time of the meeting. Cancer breach targets also posed a problem where the decision-making was more complex, clinicians and oncology nurses felt patients were under pressure to accept a particular treatment line in order not to breach targets. All participants agreed that knowing about a patient's wider health and social care needs was important however it wasn't clear that all participants felt this was the reality in daily clinical practice. Some participants identified a generational difference that older patients were more reticent and reluctant to share information resulting in a further barrier to a more holistic understanding of a patient's fitness. A similar reluctance to share information with healthcare professionals was shown by a retrospective survey where only 54% of patients felt that they would like to talk about their difficulties with cancer[180]. The authors

concluded, “Service targets focusing solely on presenting disease can disadvantage older patients with health and social care needs”.

### 4.2.3 Contrast with attitudes to treatment in younger patients

Where older patients have been shown to receive less treatment and may be more likely to be referred for best supportive care rather than receiving intensive chemotherapy, the opposite can be true in younger populations. The driving factors behind the aggressive treatment of younger versus older patients were examined in a series of interviews at a group of oncology centres in Germany.

A view held by many participating oncologists was that it was easier to discuss stopping chemotherapy with an older patient and their families, as the argument that they were more likely to suffer from side effects than a younger patient and hence worsen pre-existent frailty or quality of life was easier to make and more persuasive. This was felt to be more difficult with younger patients who frequently demanded treatment even when the potential chance of benefit was very small and explicitly explained. A patient dying at a younger age feels unjust compared to an older patient who has had what is sometimes termed as a “good innings”. Furthermore, when clinicians identify with a younger patient who may be of a similar age or stage in life, remaining objective becomes emotionally challenging and making the decision to stop active treatment becomes less likely[181].

### 4.2.4 Studies evaluating decision-making and experience of treatment in ovarian cancer

Most of the qualitative work assessing the impact of age on decision-making regarding cancer treatment has been undertaken in patients with early-stage breast cancer[182-184]. Older patients historically have been shown to be less assertive in consultations and less likely to ask in-depth questions. Previous research has also demonstrated poorer concordance between older patients and their physicians regarding consultation topics and goals compared to younger patients[185]. Patient perception of being involved in treatment decision-making is correlated with quality of life, treatment tolerance and self-rated functional abilities[186]. Few studies specifically relate to gynaecological malignancies. A retrospective survey undertaken in ovarian cancer survivors in the U.S reported that only 55% of respondents felt involved in the decision-making for anticancer treatment and furthermore that age was a significant predictor of perceived involvement in decision-making[187]. The most comprehensive study assessing patient attitudes in gynaecological malignancies in the UK to date was reported in 2001. Nordin and colleagues examined the hypothesis that there was no difference between younger and older patients desire for cure for newly diagnosed gynaecological malignancies[175]. A clinical psychologist undertook structured interviews of 189 patients who had undergone gynaecologic oncological surgery for ovarian, endometrial, cervical or vulval cancer. 95 of the respondents were over the age of 65. The authors reported that older patients desired cure as much as younger

patients with 94.6% of those over the age of 75 agreeing with the statement “No matter how old you are, it is worth putting up with anything to hopefully be cured of cancer”. Interestingly, a lower proportion (82%) of those under the age of 65 agreed with the same statement. Older women were less likely to feel that patients should have the final decision over what treatment is received preferring that the doctors should decide what treatment is given.

### 4.2.5 Gaps in the literature

There are no recent UK based studies exploring older women’s attitudes to treatment decision-making and experience of treatment. Quality of life data that currently exists for treatment tolerance is largely derived from interventional randomised control trials, which, as has been well documented, under-represent older, more comorbid patients[49, 188-190]. There is a consequent lack of information on how older women currently approach decision-making and therefore how to improve the way that information is imparted to allow more patient-centric decision-making. There is also a dearth of information on the real lived experience of older women undergoing systemic anticancer therapy and/or surgery for ovarian cancer and the impact of toxicities on functional capabilities both during and following on from treatment

## 4.3 Aims of study

I aimed to evaluate the experience of older women undergoing chemotherapy both in the first line setting and at relapse. Using a combination of both focus groups and semi-structured interviews I aimed to gain a more complete understanding of the experience and quality of life of older women receiving systemic anti-cancer therapy for ovarian cancer. The study was intended to evaluate their concerns and expectations of treatment and if particular challenges were faced that might have made treatment more difficult, what they were and how well they felt they were supported by both their carers and families as well as by their cancer centre and community support services. The study also aimed to assess whether these patients had felt that there was sufficient information given to them prior to chemotherapy and whether they have any thoughts on how support for older patients might be improved in the future.

## 4.4 Methods

### 4.4.1 Participant recruitment

Study recruitment took place between April and July 2019. Eligible patients were invited to participate using a written patient information sheet. Patients were eligible to participate if they were aged 65 years or over at the time of the first cycle of systemic anti-cancer therapy and had completed at least three cycles of systemic chemotherapy for advanced epithelial ovarian cancer in either the first-line setting or at relapse.

Patients with significant cognitive impairment or mental health problems that would limit their ability to take part in the study as determined by the investigator were not eligible. Patients who could not speak English or were too physically unwell in the opinion of the clinical team were also not able to participate. 36 patients were invited to participate using purposive sampling methods and were posted patient information sheets. For patients who did not respond within one week of the anticipated arrival of the information sheet, one follow-up telephone call was undertaken to ensure the information had been received and to determine the reasons for unwillingness to participate. 15 patients in total agreed to take part in focus groups or semi-structured interviews during April-May 2019. 12 patients attended one of three focus group sessions held at the Royal Marsden NHS Foundation Trust. In total, a further three patients were unable to physically attend but expressed an interest in participating and therefore took part in semi-structured telephone interviews, two of which occurred following the first analysis. 9 patients did not reply to follow up telephone calls. Other reasons for declining to enter the study were predominantly time or logistical constraints, burden of other hospital appointments and having become too unwell.

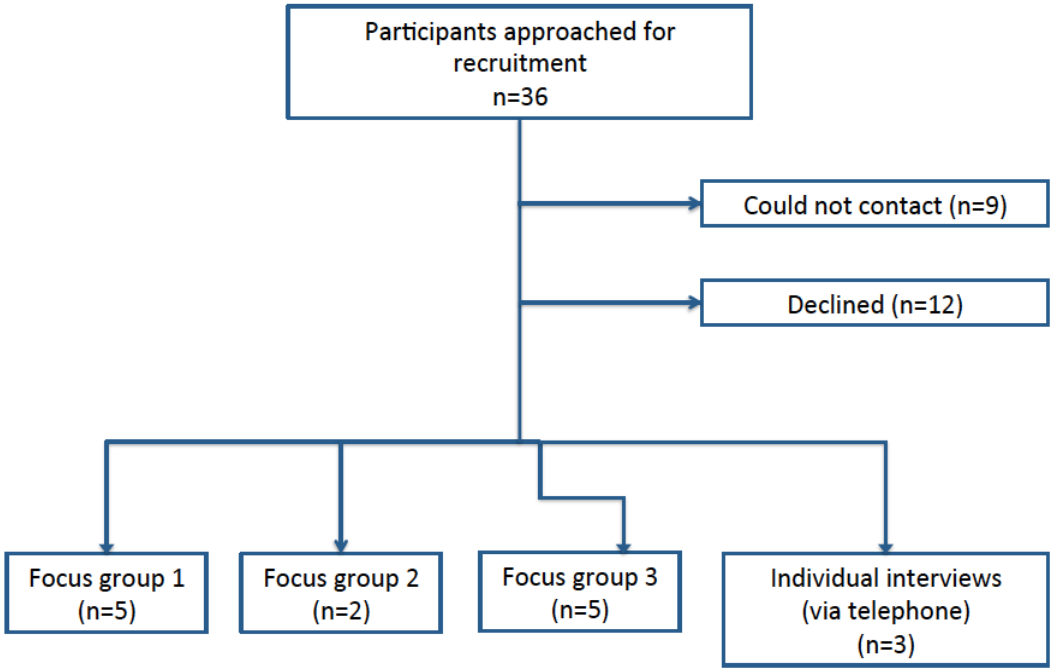



**Figure 32. Flowchart of participant recruitment**

Study approval was granted through the Royal Marsden Clinical Cancer Research Group in October 2018 (SE764). Prior to submission, the proposed questions, patient information sheet and case report forms were presented to the Royal Marsden NHS Foundation Trust Patient Public Involvement panel for review and input.

The first focus group was led by a Clinical Research Assistant (EL). The researcher subsequently led the second and third focus groups and the three semi-structured telephone interviews. EL was a public health researcher with formal training in qualitative data collection and analysis and focus group facilitation. Focus groups were held at either site of the Royal Marsden NHS Foundation Trust in formal meeting rooms. Focus

groups were audio-recorded and written field notes were taken during the group sessions. In addition to the researcher and EL, an advanced nurse practitioner within the Gynaecology Unit also attended.

### 4.4.2 Data analysis

There are five well-documented approaches to qualitative research. Case studies, Narrative analysis, Ethnography, Phenomenology and Grounded Theory[191]. Grounded theory has become a popular method of qualitative analysis in healthcare research, it is based on an inductive process where the raw data are analysed in an iterative process where data collection and analysis can occur concurrently to allow the generation of hypotheses from the data, a so called “bottom-up” approach. Researchers should aim to remain entirely objective and not allow personal perceptions or prior knowledge to influence their findings. The four basic steps in thematic analysis have been well summarised by Guest at al[192]; 1.) Familiarisation with and organisation of transcripts, 2.) Identification of possible themes, 3.) Review and analysis of themes to identify structures and 4.) Construction of theoretical model.

I,along with a colleague (EL) undertook the first level of analysis and coding, known as primary coding. The process for coding has been extensively covered in the literature but most thoroughly described by Saldana[193]. Audio recordings were transcribed verbatim. The primary coding undertaken primarily consisted of process descriptive codes. The primary coding provides the building blocks of the final themes and is

vulnerable to subjective bias due to researchers prior knowledge of the subjects or the subject matter. For this reason, the primary coding was initially performed independently by each researcher before reviewing and combining. The primary coding was generated along with field notes that had been created both during the initial interviews and during the first familiarisation stage where necessary to justify why a particular code had been chosen or to add further insight and potential themes that may already be beginning to emerge at this first early stage of analysis.

At the second-level the initial codes and related excerpts were reviewed using focused coding to combine or split codes and identify the most salient issues. In this phase EL and LD manually analysed codes and associated data to identify potential themes and subthemes. Two further telephone semi-structured interviews were conducted at this stage. The new data was checked against existing data, no new codes emerged from these two interviews and it was therefore concluded that theoretical saturation had been reached[194].

## 4.5 Results

### 4.5.1 Patient population

The summary characteristics of the 15 participants are detailed below (table 29). Mean age at diagnosis was 75 (range 68-89). The mean age at participation was 78.4 years old (range 71-90).

| | n | % |
|---|---|---|
| Lives alone | 6 | (40.0) |
| Lives with spouse | 6 | (40.0) |
| Lives with other family members | 2 | (13.3) |
| Lives in sheltered accommodation | 1 | (6.7) |
| Has caring responsibilities | 4 | (26.7) |
| Retired | 14 | (93.3) |
| Cancer has had no financial impact | 13 | (86.7) |
| Cancer has had a little financial impact | 2 | (13.3) |
| FIGO Stage at diagnosis | | |
| 1 | 0 | (0) |
| 2 | 4 | (26.7) |
| 3 | 9 | (60.0) |
| 4 | 2 | (13.3) |
| Primary treatment | | |
| Platinum doublet chemotherapy | 12 | (80.0) |
| Single-agent carboplatin | 3 | (20.0) |
| Surgery | 11 | (73.3) |
| Primary treatment tolerance | | |
| No delays | 6 | (40.0) |
| Delay 1 week or less | 3 | (20.0) |
| Delay ≥ 2 weeks | 2 | (13.3) |
| Dose reduction at beginning | 0 | (0) |
| Dose reduction during chemotherapy | 4 | (26.7) |
| Has had disease recurrence | 8 | (53.3) |
| Second line treatment | | |
| Chemotherapy (doublet) | 3 | (20.0) |
| Chemotherapy (single-agent) | 2 | (13.3) |
| Clinical Trial | 2 | (13.3) |
| Hormonal therapy | 2 | (13.3) |
| Status at time of study entry | | |
| Receiving primary treatment | 0 | 0 |
| Receiving treatment for recurrence | 6 | (40.0) |
| Follow up | 9 | (60.6) |

**Table 29 Patient characteristics**

Primary coding led to the emergence of 94 individual first-level codes. Second-level coding rationalised these into 18 core codes. From these, three key themes emerged: Multifactorial decision-making, Burden of logistical issues and Coping with side effects.

### 4.5.2 Theme: Multifactorial Decision-making

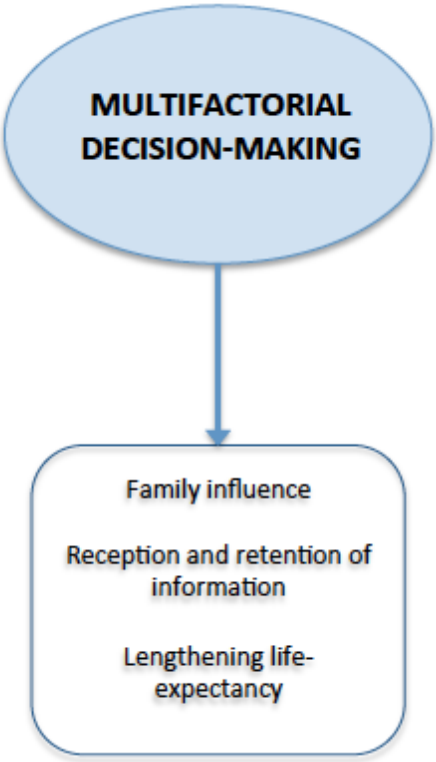



**Figure 33. Theme: Multifactorial decision-making**

#### 4.5.2.1 Reception and retention of information clouds decision-making

Participants frequently felt overwhelmed by the volume of information given to them at the time of first diagnosis. Memories of exactly how the diagnosis was communicated to them including whom by were not always clear. A feeling of shock at the diagnosis, particularly for those patients who had enjoyed a long healthy middle age was apparent.

*"when you're first diagnosed, it's such a shock to you, you don't absorb everything that's being said to you" (Patient 4)*

*"I sort of went into zombie mode" (Patient 12)*

Physical symptoms such as fatigue and for some, being sufficiently unwell to present as an emergency and require hospital admission further inhibited the ability of patients' to absorb large volumes of relatively complex information and voice opinions on treatment related decisions.

*"I was desperately tired at this stage and an awful lot of information is given to you" (Patient 14)*

Participants appreciated the pamphlets given to them at their first appointment but many admitted to not reading them at all and if so, not until many weeks later into treatment, using them as reference material to explain side effects that they had already experienced rather than to prepare themselves ahead of treatment. For some patients, physical symptoms of cancer and in particular, fatigue in the first few weeks of diagnosis were a barrier to reading and absorbing information.

*"pamphlets are really good but there's a lot of reading to do and I wasn't up to it at this stage" (Patient 14)*

For the most part, patients felt that the information given to them on proposed treatment matched their experience however side effects that have a marked effect on functional outcomes during and following on from chemotherapy such as the potential permanency of peripheral neuropathy or myalgia relating to paclitaxel were not always made clear. The time-pressure on making a treatment decision, including clinical trial participation, principally in those patients who were unwell at the time of diagnosis was seen as a stressor by most however two patients viewed it positively;

*"well I had to make the decision on the spot…so there was no time to think about it" (Patient 14)*

For many participants, the Internet played a crucial role as information provider, challenging the long-held notion that older patients may be less adept at managing technology and that complex information cannot be reliably disseminated using this medium. In contrast, some participants felt strongly that the information found on the internet would not be helpful to them, in particular because of a desire not to want to know too much, to protect themselves from information that might not be positive, particularly regarding prognosis:

*"I can't bear looking on the Internet, I just don't want to know". (Patient 8)*

*"I don't want to know what my prognosis is, you know, when your time's up, it's up" (Patient 8)*

#### 4.5.2.2 Lengthening life-expectancy

A striking feature, common to many participants was a clear and absolute determination to be treated with no reference made to age or other medical issues that may or may not be present although participants were conscious that age might be considered as a factor against receiving optimal treatment. A sense of making a decision between life and death was apparent.

*"I was told I could go profoundly deaf…but I had to take that chance" (Patient 7)*

*“I would have done anything to have treatment, gone through anything” (Patient 1)*

Fear of treatment being reduced or discontinued was a clear anxiety for some with one patient, suffering from severe peripheral neuropathy which had already resulted in significant functional limitation admitting to needing some persuasion to allow the team to dose-reduce chemotherapy accordingly due to the fear that this would lead to a shortening of life-expectancy. The potential negative impact of treatment on functional ability and quality of life did not appear to act as a deterrent.

*“I’d still want to be alive because there’s other things I’m sure I’d be able to do” (Patient 1)*

Whilst other medical comorbidities could represent a burden for patients undergoing systemic anti-cancer therapy, for some, the perspective of cancer treatment was positively altered by their prior experience. One participant, who’d been unable to undergo full standard treatment owing to anaesthetic risk expressed disappointment but had rationalised and come to terms with this decision, focusing on the benefits to quality of life instead. All participants, when asked, knowing what they know now would they go ahead with treatment again if required, unanimously stated that they would.

#### 4.5.2.3 Family influence

The interplay between personal preferences for treatment and external influences, in particular from friends and family was complex for many

patients. For those patients who were primary carers for dependent spouses or family members, undergoing treatment represented a challenge in terms of being able to manage their caring responsibilities but was also a driver to receive treatment due to concerns over how their spouse and family may manage after their death.

*"I think the thing that put most pressure on me was my husband being ill"*

*(Patient13)*

Undergoing treatment for others, rather than themselves was a common feature amongst study participants. Adult children or close nieces and nephews played an important role in decision-making at the beginning and during treatment and often played a strong, positively supportive role.

*"be very positive, everything's going to plan"*

For most this was not in the form of direct coercion but participants expressed concern over the ramifications of not having treatment and therefore a potential shorter life expectancy on their family rather than fears for themselves of their own mortality.

*"if I don't, I'll be upsetting them and I don't want to upset my two kids"*

*(Patient 2)*

*"well obviously they didn't want me to have six months or less to live, it's not nice for them knowing one's doing to die so that's why they said yes to chemo, to see how much longer it would give them" (Patient 2)*

### 4.5.3 Theme: Burden of logistical issues

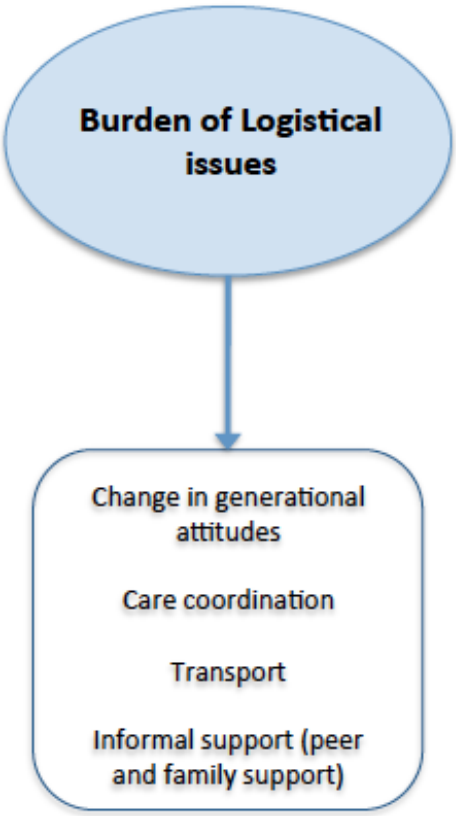



**Figure 34. Theme: Burden of logistical issues**

#### 4.5.3.1 Care coordination

By and large, participants felt well supported at their cancer centre and expressed gratitude for the care received.

*"it's like a blanket around you isn't it" (Patient 1)*

However, particularly for those patients with pre-existent medical conditions, communication between the oncology team and external healthcare providers was a source of concern and anxiety. Some patients waited many months to be seen by a second speciality at the request of the cancer centre. Patients felt that ensuring adequate communication between healthcare professionals was reliant on them.

The navigation of logistical issues surrounding a new diagnosis and treatment plan was a dominant discussion point in all focus groups. Patients felt that the burden of responsibility, predominantly in the early stages of the diagnostic and treatment pathway lay with them and this, in the early stages of their diagnosis and treatment coincided with a time when they were more physically ill than they had been in their lives previously.

*"it's just these things on the ground that you have to do as a patient when you're feeling exhausted" (Patient 14)*

Participants recounted a lack of communication between their primary care and oncology teams and did not perceive primary care as a support or involved during their primary treatment. The perception of the role of primary care in the diagnostic pathway and through treatment was mixed. For some participants, significant delay had been experienced in the lead up to formal diagnosis culminating in an emergency presentation; this

consequently had an impact on the perception of the contact and support with primary care through treatment. Many participants also perceived that primary care was under significant resource strain and viewed the change in model of primary care negatively. Where previously, participants had had one doctor who knew them, dissatisfaction was frequently expressed over the lack of continuity of care from primary care.

*"I don't actually know who my doctor is"*

Participants reported an awareness of the resource limitations of both hospital and community teams and had sometimes been reluctant to seek advice or care during their primary treatment as a result.

*"I was always worried about being a burden as I know how busy you all are"*

#### 4.5.3.2 Transport

Difficulties with sourcing and arranging hospital transport represented a significant source of stress. Many patients reported not knowing hospital transport was available until they had attended many outpatient appointments. When they were informed of this service, it was frequently by members of the reception or clerical team rather than the medical or nursing team. The need to arrive significantly earlier and leave much later for appointments for those utilising hospital transport added to the stress and fatigue associated with hospital visits.

#### 4.5.3.3 Informal support

Friends and family who were willing and able to attend clinic or chemotherapy appointments or be a support on the end of a phone following on from treatment were frequently cited as invaluable.

*"Oh your family back you up don't they" (Patient 2)*

Faith was brought up independently by some participants who reported finding solace in their faith during treatment, as a way of relieving themselves from the responsibility of the future and treatment outcomes.

*"the only thing I can do is put my hand in the hand of god and you, I can't do anything more"*

For some, the regular routine of faith worship and associated community support was of real benefit. Supportive therapies were not widely known of or taken up by participants. Only one subject accessed any form of support from an older patient or elderly specific charity. Peer support was widely acknowledged to be invaluable, usually sought informally via friends and family. Formal tumour-specific support groups had not been accessed by any participants.

### 4.5.4 Theme: Coping with side effects

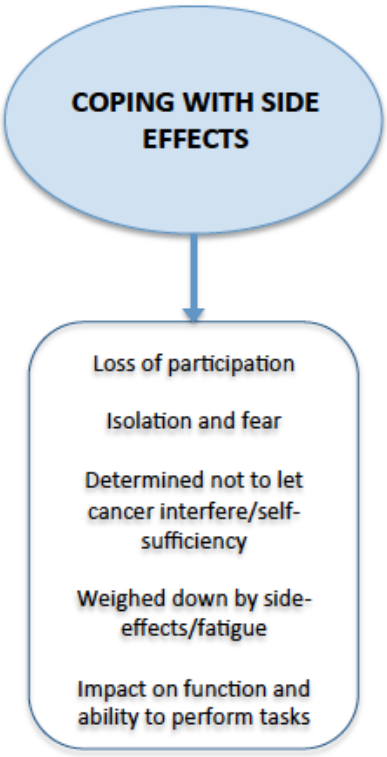



**Figure 35. Theme: Coping with side effects**

#### 4.5.4.1 Weighed down by side-effects

The impact of chemotherapy side effects varied widely with some subjects expressing surprise and gratitude at how little they had suffered compared to their expectations. For many however, toxicities such as myalgia and arthralgia came as a surprise and were very difficult to tolerate, leading to the need for additional analgesia. Peripheral neuropathy and its impact on subsequent functional capabilities particularly for participants who had previously enjoyed recreational walking and other physical activities was a significant and long-term issue

for some participants. Cognitive impairment was only mentioned by one participant as a sequelae of treatment although it is noteworthy that two of the fifteen participants self-reported a degree of memory impairment at the beginning of the study. Overwhelmingly the most frequently reported issue however was the impact of fatigue or “utter exhaustion”.

The physical impact of severe fatigue and weakness during chemotherapy was profound. Participants described being only able to manage the most basic of activities of daily living and managing these would be at the expense of doing anything else.

*“I was incredibly weak and then you still have to do things and you can’t manage it” (Patient 11)*

*“it’s a matter of dragging my body around to keep up with essentials” (Patient 14)*

This level of fatigue for some continued on for many months following on from treatment with some patients still not able to undertake activities that they previously could. Where remedies such as gentle exercise had previously improved fatigue levels prior to their cancer diagnosis, during chemotherapy this was not the case.

*“it just made me more exhausted and you have to do all the day-to-day things just to keep alive” (Patient 14)*

The consequence of severe fatigue had ramifications beyond physical limitations. Many participants reported a sense of loss as a result of their treatment. With the loss of participation of activities that they had previously performed and enjoyed due to fatigue and peripheral

neuropathy, even simple tasks like walking the dog were described as having been *"taken away".*

A resultant loss of confidence in their ability to remain independent, travel on their own and the subsequent loss of independence were all clearly described both during treatment and as a long-term consequence following on from chemotherapy. The effect of this loss on mood was also evident with some participants openly admitting that they *"get very depressed at times".* This was more evident in those participants who lived alone or who were socially isolated, these participants also reported a fear of an accident or fall occurring when they were alone and therefore unable to access help.

#### 4.5.4.2 Determination not to let cancer interfere

Despite the clearly significant impact of cancer treatment, the desire to remain independent and self-sufficient was strongly expressed by many participants. One participant, discharged from hospital following her surgery researched Internet videos to work out how to safely sit up in bed. Others rebuffed well-meaning efforts by family members to ease their recovery refusing aids and implements that would in their view, render them an invalid and refusing to take on the sick role.

Continuing activities that were undertaken and enjoyed preceding their diagnosis took on a greater importance for many participants. Those who were physically active before felt that their current treatment was a

setback from which they would recover and get back to the activities they enjoyed before if they weren't able to currently perform them. An unwillingness to be hampered by a medical diagnosis was clear.

*"I just carry on as normal, I do my Pilates, I go to a club, but I've forgotten what it's like to feel normal" (Patient 1)*

Despite physical limitations, in particular fatigue and a feeling of lack of muscle strength, participants almost universally expressed a desire to continue on to the best of their abilities with a markedly stoic outlook.

*"I live life normally and I will go on like that until it's my time to go" (Patient 11)*

Patients rarely conceded that their age may contribute to difficulties managing and recovering from cancer treatment but one patient did acknowledge that

*"things sort of accumulate; it does take longer to recover when you're older". (Patient 12)*

## 4.6 Discussion

This cohort of patients was treated relatively intensively with 12 (80%) having commenced platinum-doublet chemotherapy and 12 (73.3%) of patients undergoing cytoreductive surgery. Women overwhelmingly desired treatment with the hope of the lengthening life expectancy and would undertake treatment again despite reporting a significant burden of morbidity during and following on from treatment. Despite the exhibited stoicism and determination not to allow a cancer diagnosis and treatment to change the way they live, the reported impact of chemotherapy in this

cohort was clearly significant and for many, long-term ramifications on essential functioning was apparent. When coupled with social isolation and functional limitations at baseline, common in many older adults due to pre-existent medical conditions and frailty, treatment may post a larger burden on older patients.

There is a dearth of information regarding the coping strategies of older adults when faced with a diagnosis of cancer with no clear consensus on general trends. Some studies suggest that older patients are more likely to adopt an avoidant coping strategy[195] as for example seen in a study of older versus younger patients with head and neck cancer[196]. Similarly, a study of older cancer patients coping strategies compared those of 263 older patients with cancer and compared them to older patients without cancer and middle-aged (50-70 years old) patients with cancer. Older cancer patients were less likely to adopt active and avoidant coping strategies and more likely to exhibit a passive reaction[197]. Although a small group of patients in our study were unwilling to seek out information on the Internet for fear of being confronted by their prognosis, reflective of an avoidant coping strategy, most patients in this group approached their diagnosis and treatment openly and exhibited marked resilience. Those patients who exhibited more of an avoidant coping strategy in this study were more frequently being treated for relapsed disease. Kahana et al described a number of behaviour types in a group of older adult cancer survivors, most reflected

in our population were the determined, active, “busy bees” and those who adopted a more passive strategy during treatment “the passers-by”[198].

The primary aim of this study was to assess, in a population of older women who had all experienced systemic anti-cancer therapy and for some, cytoreductive surgery for ovarian cancer, the lived experience of treatment and the impact on patients who are older and who are more likely to have accumulated other medical and social issues. With the increasing evidence that older women are less likely to receive as intensive anti-cancer treatment as their younger counterparts more work is required to understand whether the lower rates of treatment are being driven by patients or their oncology teams. Whilst the decision for older women to not undergo cytoreductive surgery or platinum-doublet chemotherapy may well be based on sound medical concerns owing to pre-existent medical comorbidities, this study provides evidence that older women do not exhibit lower levels of wishing to be less aggressively treated than their younger counterparts and do not consider their age in and of itself to be a barrier to treatment. The desire for full and active treatment and for their age not to be considered was a striking feature from all participants, including those who had suffered and continue to suffer with treatment related toxicities.

This study provides further evidence therefore that it should not be assumed that an older woman is less likely to desire active treatment or be less willing to tolerate side effects. Treatment aims and goals with

likely outcomes should be clearly discussed with all patients irrespective of chronological age.

26% of all new cases of ovarian cancer are diagnosed following an emergency presentation with this proportion rising significantly with increasing age[13]. Older patients are also more likely to have had a delay to diagnosis[10], making them potentially more unwell during the decision-making process for treatment. This study demonstrates that the physical and mental incapacity associated was a significant barrier to patient-centred decision-making. How information could be best disseminated deserves further work, the assumption that older patients may be less able to utilise web-based resources is challenged by the findings of this study. There is however unlikely to be a “one size fits all approach” and a variety of information sources, including peer support and informational videos could be utilised to great effect in older patients who may struggle to take in all the information given to them in the first appointment with their oncology teams. Older women may also benefit from opportunities to re-discuss treatment aims later in the treatment pathway.

The logistical challenges experienced by patients were cited as a major issue by many participants and some are relatively simple to overcome. Asking patients directly regarding any concerns they have regarding transport or the need to communicate with other healthcare providers at a first consultation could immediately improve the experience of the first

stage of the treatment pathway. It is essential to ascertain for all patients and particularly those who are older and more likely to live alone who is around to support them at home. Information on available charitable organisations that may be able to provide additional emotional and physical support should be provided at the initial consultation, particularly to those who are socially isolated.

A striking feature of the older population sampled in these focus groups was the altruism and concern for the impact of their diagnosis on spouses and adult children/family rather than themselves. A few patients in this study had caring responsibilities for spouses and this represented a significant source of anxiety and stress and for some was a reason to continue with palliative chemotherapy. This highlights the need to carefully evaluate the social situation of all patients and be aware of support services that may be available to not only patients but also their families. Primary care physicians are uniquely placed to have a full understanding of patients' wider social set-up and improved communication between primary care and cancer centres could facilitate improved social support for patients and their families. Some older patients in this study had been reticent to seek out support or advice when symptoms or toxicities developed during chemotherapy to avoid being a 'burden", potentially representing a generational attitude. Emphasising the appropriate methods of communication in case of issues arising whilst on treatment and in follow up, during the primary consultation may be of additional benefit in older patients.

### 4.6.1 Strengths and weaknesses

One of the strengths of this study was the use of a mixed methods approach, the dialogue of a focus group, encouraged by others who have lived similar experiences allows for a breadth of experience and views to emerge. By allowing semi-structured interviews as well where patients do need to be physically present to participate, the risk of participation bias is reduced.

The first main limitation is that this study assesses only the experiences of patients at one UK cancer centre and it is well documented that there is significant geographical variability in the UK in cancer care and outcomes[84]. As has been previously discussed, the demographic of a southwest London tertiary cancer centre is not representative of the UK wider population. Furthermore, this study population was not ethnically diverse; both of these factors limit the generalisability of these findings to a broader UK population. Secondly, the small sample size inherent to qualitative research limits generalisability. In hindsight, a comparator group of younger patients would have improved this study. Many of the issues raised by the participants are general cancer-related issues do not appear to be specific to an older population. Whether there are true differences between the perceptions of older versus younger patients regarding decision-making and the impact of cancer treatment could be further assessed by a broader mixed-methods study involving younger and older patient cohorts.

This study is also subject to survivor bias as we were assessing only those patients who had received at least three cycles of systemic therapy meaning those patients who deteriorated early or chose not to receive treatment could not be included.

### 4.6.2 Future work

A prospective, longitudinal study evaluating decision-making, treatment preferences and importantly, patient reported outcome measures specifically evaluating health-related quality of life and functional ability would allow for a broader analysis and exploration of the themes here identified. Larger prospective studies, across different cancer centres would mitigate survivor bias and improve generalisability.

## 4.7 Conclusions

The older women who participated in this study were overwhelmingly positive about their experience of cancer care and although logistical and physical challenges were certainly experienced, a striking feature, almost universally reported was the desire for anticancer treatment without age to be seen as a barrier. Older women may face additional challenges, both in terms of medical comorbidities and social concerns for example, being a primary carer to spouses who are themselves unwell however, despite these, both surgery and chemotherapy were approached with a stoicism and determination that was remarkable. Geriatric assessment

would allow for the more holistic evaluation of older patients and should now be considered standard of care in keeping with recent guidance[20].

# 5 DEVELOPMENT OF THE FAIR-O STUDY. A MULTICENTRE FEASIBILITY STUDY ASSESSING THE IMPLEMENTATION OF A GERIATRIC ASSESSMENT AND PROTOCOL-LED INTERVENTIONS IN OLDER WOMEN BEING TREATED FOR OVARIAN CANCER

## 5.2 Introduction

There is now generalised acceptance, as set out in the ASCO guidelines of 2018 and SIOG consensus statement of 2014 that geriatric assessment should be standard of care for all patients over the age of 65 being considered for systemic chemotherapy. This is however far from being achieved in everyday practice in the UK. A national survey of 640 oncology professionals led by Harari and Kalsi in 2016 demonstrated that only 34% of respondents would use any form of validated geriatric assessment tool. Just 25% had urgent access to a specialist geriatrician and only 14% often or always involved a geriatrician in the care of older oncology patients[82].

Healthcare professionals, when surveyed have mixed views on their ability to detect complex healthcare needs. Clinicians responded that rather than using an assessment tool “we just think we know…we kind of go on a hunch or…our sort of clinical expertise about how a patient is functioning and coping”[179]. Whilst the importance of an experienced clinicians’ judgement cannot be underestimated, it is now widely accepted

that clinical judgement and performance status alone result in over or underestimation of a patient's ability to tolerate and manage systemic anticancer therapy[17, 41, 111]. Furthermore, comorbidities such as mild cognitive impairment, prevalent in the UK older adult population[199], are easily overlooked in routine clinical assessment and can impact on a patients' ability to manage chemotherapy related toxicities and be negatively influenced by chemotherapy administration[200].

Over half of all newly diagnosed patients and around two thirds currently in follow up are aged 65 and over[8], it is therefore not practical to expect highly specialist multidisciplinary teams to manage every older adult cancer patient. A marked lack of training for oncology trainees in the particular needs of older adults with cancer has been previously demonstrated[201]. There is a need to improve training and up-skill oncology teams, providing them with the necessary tools and support to allow them to manage patients in their own clinics. Oncology teams undertaking a geriatric assessment in itself carries the advantage that the team is then engaged in the outcome and invested in the process to address deficits identified. This could potentially overcome one of the limitations of geriatric assessment reported in the literature so far where patients have had a comprehensive geriatric assessment performed by a specialist multidisciplinary team who have then fed back the recommendations to the treating oncology team. These recommendations have been variably taken up[202, 203] which clearly

impacts on the potential utility of performing the geriatric assessment in the first instance.

There seemed a very clear need to move forwards from the realm of studies demonstrating the ability of varying geriatric screening scores to predict the likelihood of chemotherapy related toxicity and overall mortality[17, 74, 110, 204-206]. Survival and patient reported outcome measures such as quality of life and functional independence were unlikely to be impacted whilst no actions were being taken to address any of the issues identified.

This led to the aim of designing an interventional study aimed at introducing an oncology-led geriatric assessment followed by interventions to address deficits identified. Initial thoughts centred on the key question of whether this study should be a randomised controlled study or a single-arm feasibility study. Leaving aside for the moment the ever-present concerns regarding resource, both cost and time, there were concerns over whether randomisation of an intervention and therefore potential withholding of interventions for deficits identified could be considered ethical. Whilst randomisation would have however allowed the crucial question of whether geriatric interventions can impact on treatment-related and patient reported outcome measures to be answered. There was a very valid concern that if a full geriatric assessment was undertaken, whether it would be ethical to not act on any issues identified. Moreover, a risk was perceived of potential dilution

of the observed difference between control and interventional group as clinicians may not feel able to for example, not correct an identified anaemia in a patient in the control group. Methodologies employed in geriatric medicine research where randomisation has long been challenging due to inherent complexity and heterogeneity of the patient populations, for example implementation-based methodologies[207] seemed to be a potential alternative option. These methodologies have historically been less employed in oncological research where randomised controlled trials are often, appropriately the only option. Where the outcome of the study potentially leads to a change in service delivery rather than investigating a novel investigational medicinal product however, implementation-based methodologies, may, unusually for an oncological study be more appropriate. Resource, from a practical perspective is also highly relevant. A randomised study to answer the key question of whether survival or chemotherapy completion or tolerance is affected by comprehensive geriatric assessment and targeted interventions would necessitate and very large sample size. Two such studies are currently underway in Europe as have previously been discussed. The PREPARE (NCT02704832) study[81] aims to accrue 1500 patients across France and is currently recruiting and the Italian GIVE (NCT02785887) study has now completed accrual of over 300 patients with results pending. There seemed little need to replicate these studies in the UK gynaecology oncology population. Perhaps of more relevance was the question, assuming both studies demonstrate a benefit

to older patients from full CGA with interventions, can this be reliably implemented in the UK routine oncology practice?

## 5.3 Scoping Sub-study: Quality improvement project, the CRANE questionnaire

### 5.3.1 Introduction

In order to assess the current rate of common geriatric issues in the oncology clinic, a validated geriatric assessment tool was introduced into the gynaecology chemotherapy clinics in February 2018. The Macmillan/Guys and St Thomas's CRANE assessment tool was utilised as a practical tool already in routine clinical use together with the Royal Marsden Nutrition Screening Tool and Instrumental activities of daily living (IADL).

### 5.3.2 Methods

During the 6 month study period (16/04/2018 to 16/10/2018), patients were invited to complete the CRANE questionnaire (figure 40-42) when they were attending chemotherapy clinic appointments. Approval was granted by the Royal Marsden NHS Foundation Trust CCR (SE873).

### 5.3.3 CRANE Study aims and objectives

#### 5.3.3.1 Primary objectives

1) To assess the prevalence of risk areas and needs as identified by the CRANE score in patients over the age of 65 receiving SACT for ovarian cancer in the following domains:
    a) Physical health
    b) Psychological needs
    c) Practical needs
    d) Social-well-being
    e) Environmental needs
    f) Comorbidities

#### 5.3.3.2 Secondary objectives

1) To assess the proportion of patients at medium or high risk of malnutrition
2) To assess the proportion of women who have a deficit in one of more domain of the Instrumental activity of daily living score
3) To assess the rate of full completion of all aspects of the gynaecology pre-treatment assessment (CRANE, RMNST and IADL)

#### 5.3.3.3 Inclusion criteria

1) Over the age of 65 and received at least one cycle of systemic anti-cancer treatment (SACT) for ovarian cancer for any treatment intent
2) Ability to self-complete questionnaires in English

### 5.3.4 Results

- 70 patient eligible patients in total were identified during the study period. 57 patients agreed to take part however 11 were found to be ineligible, either due to age <65 years or not currently receiving SACT. This resulted in a 65.7% recruitment rate.

| Patient Characteristics | n=46 |
|---|---|
| Age at diagnosis (median, IQR) | 74 (69-80) |
| Age at completion (median, IQR) | 76 (71-81) |
| Histology | |
| High grade serous | 39 (84%) |
| Low grade serous | 1 (2%) |
| Mixed | 2 (4%) |
| Carcinosarcoma | 2 (4%) |
| Clear cell | 1 (2%) |
| Endometrioid | 1 (2%) |
| FIGO stage at diagnosis | |
| 1 | 3 (7%) |
| 2 | 4 (9%) |
| 3 | 25 (54%) |
| 4 | 14 (30%) |
| Current treatment | |
| First-line treatment | 23 (50%) |
| Second-line treatment | 8 (17%) |
| Third-line or beyond treatment | 13 (28%) |
| Not known | 2 (4%) |
| Treatment intent | |
| Neoadjuvant treatment | 16 (35%) |
| Adjuvant treatment | 4 (9%) |
| Palliative treatment | 26 (56%) |

**Table 30. CRANE study: Patient characteristics**

The median age at diagnosis was 74 (range 49-88). At study entry, median age was 76 (range 65-89). The majority (84%) of patients had high-grade serous tumours and in keeping with data presented previously, most (84%) patients had presented with advanced (FIGO Stage III/IV) disease at diagnosis. 50% of patients were receiving first line treatment. 44% of patients were receiving treatment with curative intent.

| Medical Comorbidities | N=37 (data fields not completed for n=9) |
|---|---|
| Cardiac | 11 (30%) |
| Respiratory | 5 (14%) |
| Liver | 0 |
| Renal | 3 (8%) |
| Neurological | 6 (16%) |
| Diabetes | 2 (5%) |
| Hypertension | 25 (68%) |
| Thrombosis | 6 (16%) |
| Dementia | 0 |
| Low mood | 3 (8%) |
| Hearing loss | 0 |
| Taking > 3 daily medications (n=38) | 30 (79%) |
| Taking > 5 daily medications (n=38) | 18 (47%) |

**Table 31. CRANE study: Medical comorbidities at the time of study participation**

The medical comorbidity questionnaire (clinician completed) was the most inconsistently completed section of the geriatric assessment with 37 of 46 completed questionnaires submitted leading to an 80% completion rate. The most frequently reported comorbidities were hypertension (68%), cardiac (30%), neurological (which included prior CVA/TIA) (16%) and VTE/PE (16%). Polypharmacy defined as either taking 3 or more daily medications (79%) or 5 or more daily medications (47%) was also highly prevalent.

| Functional/geriatric assessment | N=44 |
|---|---|
| Weight loss in last 6 months | 24 (56%) |
| Memory problems | 6 (14%) |
| Urinary symptoms | 19 (43%) |
| Stool urgency | 11 (26%) |
| Ongoing pain limiting activities | 10 (23%) |
| Fatigue limiting activities | 25 (57%) |
| Low mood | 8 (19%) |
| Low interest in usual activities | 9 (20%) |
| Falls in last 6 months | 3 (7%) |
| Needed help with walking | 13 (30%) |
| Needed help with food shopping | 6 (14%) |
| Needed help with using the telephone | 1 (2%) |
| Needed help with standing from sitting | 10 (23%) |
| Needed help with climbing stairs | 9 (20%) |
| Needed help with public transport | 5 (12%) |
| Needed help going to the toilet | 2 (5%) |
| Use of walking aid | 11 (25%) |
| Lives alone | 20 (45%) |
| Has a friend or carer to look after if necessary | 36 (86%) |
| Has a carer | 8 (19%) |
| Is a caregiver | 5 (12%) |
| Admitted to hospital in the last 3 months | 12 (27%) |
| Help with finances | 2 (5%) |
| Feels safe at home | 37 (84%) |

**Table 32. CRANE study: Functional/geriatric assessment**

44 (95.6%) of patients completed the CRANE functional assessment. 56% of patients reported weight loss in the last 6 months. Bowel and urinary symptoms were common with 43% of women reporting urinary concerns and 26% patients reporting problematic stool urgency. 57% patients reported a level of fatigue that interfered with activity levels. Low mood was a concern for 19% of patients and 20% patients reported a loss of interest in usual activities. Overall, 21 (48%) of patients reported needing assistance in any of the categorised basic daily activities. Mobility was the most common concern with 30% of patients needed

assistance walking, 23% standing up from sitting and 20% with climbing stairs. 45% of women lived alone however 86% had a friend or carer to look after them if necessary. 12% of patients were themselves a caregiver. The IADL score was poorly completed with 24 (52%) of respondents completing it in full. 50% of patients had one or more functional deficits according to the IADL (table 34).

| Nutrition | N=38 |
|---|---|
| RMH Nutrition score >5 | 23 (50%) |
| RMH Nutrition score >10 | 18 (39%) |
| BMI (median, IQR) | 26 (24-29) |
| Weight (median, IQR) | 67.4 (61.6-76.1) |

**Table 33. CRANE study: Nutritional assessment.**

RMH Nutrition score > 5= medium risk of malnutrition, RMH Nutrition score >10 = high risk of malnutrition.

The Royal Marsden Nutrition score is a validated, self-completed screening assessment tool. The higher the score the greater the risk of malnutrition with a maximal score of 23. This tool is used clinically to triage the need and urgency for dietetic input. Nutritional issues were highly prevalent with 50% of patients being at medium risk of malnutrition and 39% at high risk of malnutrition despite the majority of patients having a BMI in the normal range (table 35.)

### 5.3.5 Sub-study (CRANE) conclusions

The completion rate overall of the CRANE assessment was 65.7% which represents a reasonable rate of uptake and completion when compared to other studies of a similar nature[208] however clearly there is

significant room for improvement. Of those patients who did not participate, it is not clear whether they declined or were missed in the pre-clinic screening process and therefore not approached regarding the study, as this information was not collected as part of the study. The patient completed CRANE questionnaire had the highest completion rate (96%), which was strikingly high compared to the completion rate of the IADL (52%). The clinician completed comorbidity and polypharmacy section also had a lower rate of completion. This is useful information to take forwards into the FAIR-O study where healthcare professionals will be undertaking the IADL and the comorbidity assessment (CCI) to inform the teams at site initiation visits to hopefully improve the completion of quality data. In keeping with previously reported data[171], most women had high grade serous tumours and had presented with advanced (FIGO stage III/IV disease) at diagnosis. In keeping with the cohort proportional split in the FAIR-O study, 50% of women were receiving first-line treatment. Just over half of all women were receiving treatment with palliative intent.

The spread and prevalence of medical comorbidities was unsurprisingly, similar to that seen in the data presented in chapter 2. Most strikingly was the rate of polypharmacy, 47% defined by the more stringent criteria of 5 or more daily medication. It was not within the scope of this study to assess whether or not these medications were all appropriate however clearly this is a highly prevalent issue, often overlooked in a routine chemotherapy appointment and one that will be actively addressed in the

FAIR-O study. Whilst diarrhoea would routinely be asked about in a chemotherapy consultation, urinary symptoms, unless a concern of an infection was being raised often would not be and yet in this population of post-menopausal women with pelvic malignancy, 43% reported urinary incontinence. Whilst urinary incontinence may not impede chemotherapy delivery or affect performance status, it can have a profound impact on patient's quality of life and in many cases can be improved by relatively simple measures.

It is concerning that while 48% of patients reported needing help with one or more activity of daily living, 45% of women lived alone and only 19% had a carer (formal or informal). This represents a significant unmet need and whilst again this will be formally assessed in the FAIR-O study with more robust reporting and data capture, this data will also be fed back locally via a unit meeting. At present at the Royal Marsden NHS Foundation Trust, all new patients complete the RMH Nutritional screening score. This is used to triage for dietetic referrals with those patients at high risk having an urgent review, those patients are medium risk having a routine review and those at low risk being given an "eating well with cancer" booklet. It is however not routinely undertaken again in the patient pathway routinely unless a concern is raised regarding weight loss by the team or the patient themselves. This cohort is at particular risk of malnutrition being overlooked due to their normal weight and BMI. Given the potential benefits of appropriate dietary interventions[209-211],

this is again an area where improvements can be made with relatively simple measures.

This small prospective service evaluation has provided a very timely and useful insight into the prevalence of medical and functional problems experienced by patients who have been deemed fit enough to be receiving systemic anticancer therapy. It provided an early insight into what are likely to be the most pertinent deficits identified by a formal CGA in the FAIR-O study and will help direct the focus in site initiation visits on the CGA components that are likely to be less well completed.

## 5.4 FAIR-O Study Design

### 5.4.1 Presentation and discussion at NCRI ovarian CSG meetings

In 2017, a subgroup of the National Cancer Research Institute ovarian clinical subgroup, the Older Women Working group was set up. This was formed of five interested and engaged medical oncologists based at different trusts around the UK. I first developed a first presentation of the study proposal envisaged to the group, presented by my supervisor, Dr Susana Banerjee in September 2017. Two study schemas were presented. Both with an interventional and non-interventional group; stratified by risk status as identified by the G8 screening score.

The first consideration was the choice of population to be assessed. Patients being considered for first-line therapy have potentially the most to gain regarding long-term survival outcomes however there are challenges here. Patients receiving first-line therapy may however have already undergone primary debulking surgery prior to referral to the medical oncology team with the potential confounding of peri-operative frailty concerns being addressed prior to study entry and potential peri-operative morbidity influencing accrual. Recruitment was also perceived to be an issue with competing first-line studies and a significant proportion of patients, particularly in the older population are too unwell at the time of diagnosis for consideration of study entry, with the need for commencement of chemotherapy very rapidly, sometimes as an inpatient. The original grant proposal thus outlined a study population only of relapsed patients being considered for further chemotherapy. The original grant submission was not approved but, unusually, was granted a chance to amend and re-submit 6 months later with one of the key conditions being that first-line patients if not the only patient group, were included. It was therefore decided to split the study population in two, half of the patients would be treatment naïve first-line patients and the second at first relapse.

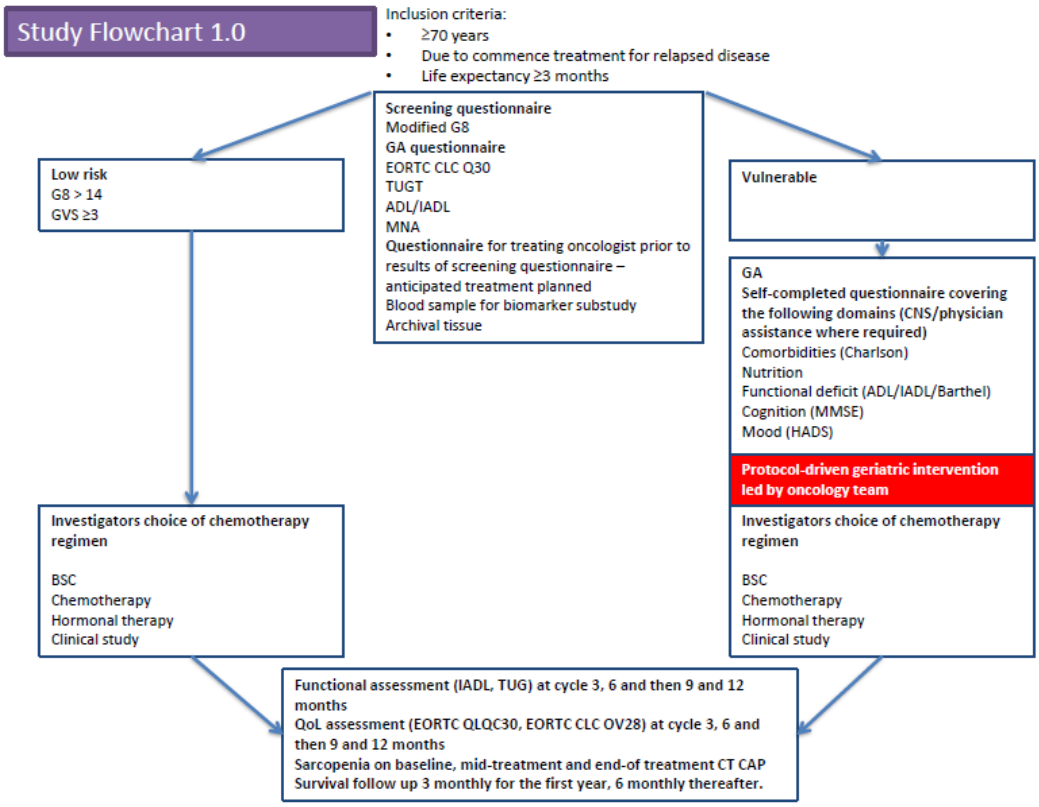



**Figure 36. Study Flowchart version 1**

Version 1 (figure 36) of the study schema allowed for the comparison between interventional and standard of care arm but was rejected for the obvious consideration that a fair comparison could not be made between two different risk populations. A clear study question could not be addressed with this design. Two screening scores were considered as potential candidates, the G8 score or the Geriatric Vulnerability score (GVS).

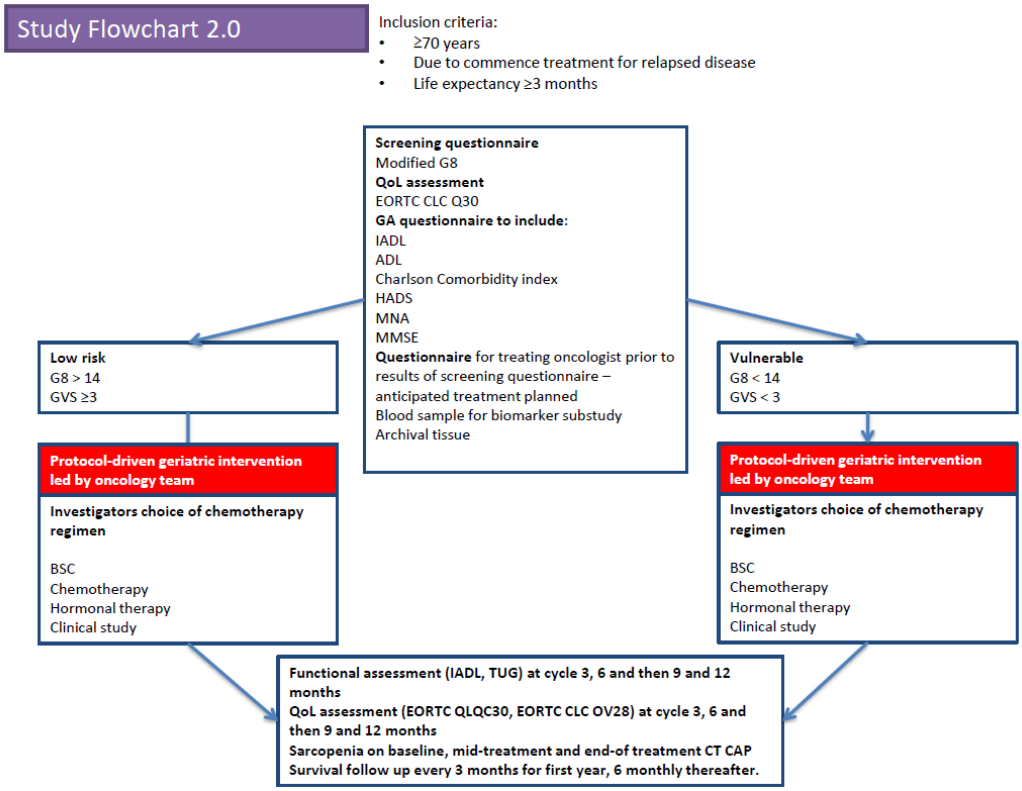



**Figure 37. Study schema version 2.**

The second version of the study schema (figure 37) again stratified patients into two at risk categories but in this version, both groups were in an interventional category. This removed the concern over withholding the intervention from patients in whom it may be considered unethical to not intervene on issues identified however there is once again, no fair comparison that can be brought between these two groups and the benefits of stratification here are unclear. The final study scheme (figure 38) was therefore arrived at with two study populations but all patients undergoing a full CGA and protocol-led interventions to assess the primary endpoint of feasibility of implementing a geriatric assessment into the oncology clinic.

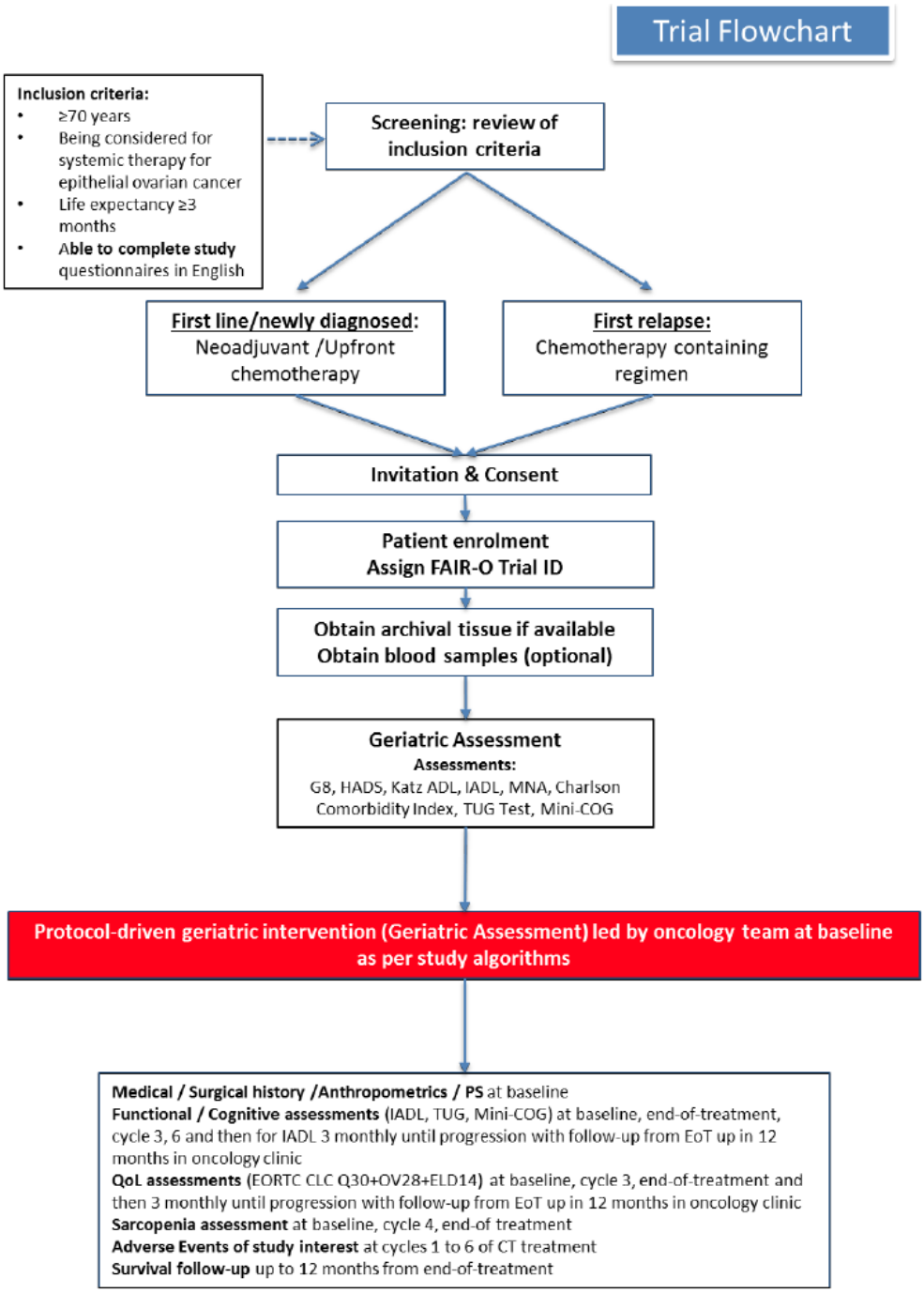



**Figure 38. Final study schema**

### 5.4.2 Development of grant writing team and successful grant application to Wellbeing of Women

The benefits of working with an expert multidisciplinary team early in study design were obvious. Prior to commencing medical oncology training, I worked at Guys and St Thomas's NHS Foundation Trust in the oncology unit where Dr Tania Kalsi and Dr Danielle Harari were setting up the GOLD clinic, a liaison service providing geriatric oncology input to patients due to embark on systemic anti-cancer therapy. Dr Harari and Dr Kalsi kindly agreed to be involved with the study from its first inception and this collaboration has been extremely productive. In addition to Dr Susana Banerjee, chief investigator, Dr Rebecca Bowen, with whom previous work assessing current treatment practice of older women with ovarian cancer in the UK was undertaken (see Chapter 2) was also involved from study inception at the grant application stage. Professor Andrea Rockall is a consultant radiologist with an interest in body composition and radiomics as predictive biomarkers in gynaecological malignancies. She supervised the previously reported project on the impact of sarcopenia and body composition at baseline on treatment outcomes in older women with ovarian cancer (see Chapter 3) and was part of the grant writing team. Crucially, three senior, highly experienced allied healthcare professional researchers agreed to provide support and expertise for this proposed study. Dr Claire Shaw, Consultant Dietician and Lead for Therapy Research, Cathy Sandsund Physiotherapist and Therapies Researcher and Siobhan Cowan-Dickie, Clinical Specialist Physiotherapist at the Royal Marsden agreed to be involved and have a

wealth of experience running studies utilising complex methodologies, mixed methods and implementation based clinical studies. Latterly, as advised by the Wellbeing of Women grant review team, input was also sought from expert psychologists with an interest in patient reported outcome measures. I am indebted to Dr Olga Husson, postdoctoral research fellow and Emma Lidington, PhD student, based at the Netherlands Cancer Institute and the Institute of Cancer Research for their interest, expertise and contributions.

### 5.4.3 Aims, objectives and endpoints

#### 5.4.3.1 Primary Objective

1) To assess whether the implementation of a geriatric assessment and protocol-led geriatric interventions where indicated is feasible within the routine outpatient oncology clinic for patients over the age of 70 with epithelial ovarian cancer being considered for systemic treatment (first line or at first relapse)

#### 5.4.3.2 Secondary Objectives

1) To assess whether sarcopenia and reduced muscle attenuation at baseline, predicts for reduced tolerance to chemotherapy, functional decline and poorer survival outcomes

2) To assess whether loss of muscle mass during chemotherapy is associated with reduced tolerance to chemotherapy and functional decline
3) To explore the relationship between frailty, as identified in a comprehensive geriatric assessment, and sarcopenia

#### 5.4.3.3 Primary Endpoint

1) The proportion of patients for whom the following assessments/ questionnaires were completed during their routine gynaecology oncology clinic: a) the G8 screening questionnaire, b) the instrumental activities of daily living' (IADL) score, c) the Katz 'activities of daily living' (ADL) score, d) the 'Hospital Anxiety and Depression' score, e) a mini-nutritional assessment, f) the 'Charlson comorbidity Index', g) the mini-COG and h) a 'Timed up and Go' test.

#### 5.4.3.4 Secondary Endpoints

2) Proportion of deficits identified that result in a referral or action as per the protocol-led intervention algorithm of those identified by the geriatric assessment in one or more of the following domains; nutrition, function, social, medical comorbidities and cognition.

3) Proportion of patients with grade 3/4 haematological and non-haematological toxicities according to sarcopenic/ non-sarcopenic subgroups.

4) Time on treatment overall and according to sarcopenic/ non-sarcopenic subgroups.

5) Progression-free survival (PFS) from initiation of systemic therapy overall and according to sarcopenic/ non-sarcopenic subgroups.

6) Proportion of patients alive at one year from initiation of systemic therapy overall and according to sarcopenic/ non-sarcopenic subgroups.

7) Proportion of patients who experience a functional decline (as defined by dropping ≥ 1 IADL point or gaining ≥ 2 ADL points at 3, 6, 9 and 12 months after initiation of systemic therapy. This will be assessed overall and according to sarcopenic/non-sarcopenic subgroups.

8) Quality of life at 3, 6, 9 and 12 months

9) Proportion of patients who are eligible for treatment but do not receive at least one cycle of systemic chemotherapy

10) Sensitivity and specificity of sarcopenia in identifying frailty as defined by the G8 score.

To address the first and secondary objectives, the sarcopenic/ non sarcopenic categorisation will be defined a) as per baseline assessment and b) during chemotherapy.

### 5.4.4 Inclusion/Exclusion Criteria

#### 5.4.4.1 Inclusion criteria

1) Age at time of consideration for systemic chemotherapy ≥ 70 years old

2) Histological or cytological confirmation of epithelial ovarian cancer (mixed pathology including sarcomatous component will be included)

3) Planning to commence systemic chemotherapy for either:

4) Newly diagnosed epithelial ovarian cancer OR

5) First disease relapse

6) Life-expectancy > 3 months

7) Able to give informed consent, complete questionnaires in English and comply with study procedures

#### 5.4.4.2 Exclusion criteria

1) In the opinion of the investigator, patient is not fit for systemic chemotherapy or patient declines systemic chemotherapy

2) Patient does not have the capacity to consent for enrolment into the study OR capacity to consent for systemic chemotherapy

### 5.4.5 Choice of Geriatric Assessment (GA) Tools

It is acknowledged that undertaking an additional assessment in the routine oncology clinic places a time pressure on an already time-constrained environment. Allowing as much of the assessment to be undertaken by patients, prior to seeing the study team is therefore a priority. It was also important to choose validated tools that are in common use both in the research and clinical setting. The SIOG consensus on geriatric assessment states that the key domains in a GA considered to be important are: functional status, fatigue, comorbidities, cognitive impairment and mental health status, social support, nutrition and the presence of geriatric syndromes such as falls[112]. The final geriatric assessment tool in the FAIR-O study is therefore comprised of the G8 screening tool, independent activities of daily living (IADL), Katz activities of daily living (ADL), hospital anxiety and depression scale

(HADS), mini nutritional assessment (MNA), Timed up and Go Test (TUGT) and the mini-COG. The G8 score is an abbreviated score designed to identify those patients at need of full comprehensive geriatric assessment[76] that is arguably one of the best validated[212] and most frequently utilised within the literature[18, 77, 213-215]. In 2016 it was modified by adding components from the IADL to improve its' sensitivity and specificity[216]. A score of 14 or less suggests the need to undertake a full CGA. Both the IADL[217] and Katz ADL[218] indices, are very well validated assessments of patients' functional abilities and have been in routine use in care of the elderly inpatients and outpatients for decades. Depression and low mood have been shown to be associated with poorer survival outcomes in older oncology patients[79, 219]. A variety of screening scores are available, most commonly used are the Geriatric Depression Scale[220] and the Hospital Anxiety and Depression scale[221], both well validated and extensively used in the geriatric oncology literature. After discussion with Drs Harari and Kalsi as well as Dr Husson and Miss Lidington, we elected to use the HADS as the questions were deemed more appropriate for a patient with cancer.

Nutritional status in older adults with cancer is one of the most predictive domains for both mortality and adverse chemotherapy-related outcomes[209, 222]. A meta-analysis of the prognostic value of malnutrition including 4692 subjects demonstrated a strong association with all-cause mortality (RR 1.73; 95%CI 1.23-2.41)[209]. Most importantly, it is relatively straightforward to address, oral nutritional

supplementation has been shown to improve quality of life in malnourished cancer patients[210]. Many tools to assess the physical strength of older patients with cancer have been assessed and validated. We elected to use the Timed Up and Go Test (TUGT) as one of the most straightforward tests and used widely in CGA studies in cancer patients[69, 73, 223]. A TUGT of > 10 seconds has been shown to be associated with higher rates of severe chemotherapy related toxicity[73].

Lastly, cognition. The mini-mental state examination (MMSE), modified-mini mental state examination, clock-drawing test and blessed orientation memory concentration (BOMC) test as well as the mini-Cog have all been assessed in an oncology context and been recommended by both SIOG[21] and ASCO[20]. The mini-Cog is significantly quicker to complete than the longer MOCA or MMSE and yet retains similar sensitivity and specificity[224, 225] to the latter and was therefore used with permission from the author.

The investigator should then review these questionnaires with the patient and complete any missing data as well as discuss the results with the patient. The additional assessments that a delegated investigator (this can be any member of staffed deemed by the principal investigator to be competent for example a sub-investigator, research nurse or research assistant) will undertake will include, Charlson comorbidity Index score, a timed up and go test (TUGT) and cognitive assessment (mini-COG).

The outcome of the geriatric assessment will be captured within the FAIR-O Geriatric Assessment (GA) workbook and transcribed into the trial database. Outcomes of the full GA will be reviewed with the patient. The algorithms will direct appropriate management of any deficits that are identified. These should ideally be completed in real-time with the patient however there may be some areas that need to be followed up and undertaken outside of the main clinic appointment. Understanding which deficits are the most challenging to address both from a patient and from an investigators perspective is a key outcome of this study. In order to assess this, investigators are asked to record the date of any referrals made as well as the date any reviews are made as a result of the said referral. If there are investigations or referrals that cannot be completed, the reasons for this should be clearly documented in the FAIR-O workbook to allow barriers to interventions to be assessed.

The perspectives on how feasible and acceptable completing a GA and targeted interventions is a key outcome of the study as without healthcare professional and allied health care professional engagement, it will be challenging to embed the practices outlined within this study into routine clinical practice. Acceptability of completing the full GA will be assessed using a trial specific questionnaire. These will be completed by Health Care Professionals (HCPs), Allied healthcare professionals (AHPs) and patients involved in the FAIR-O study at any stage.

### 5.4.6 Development of protocol led algorithms

In January 2019, I started the development of the study algorithms recognising that this was one of the most challenging aspects of this study being completely novel with no prior template available and having to transform what would ordinarily be an adaptive, intuitive process into a more formulaic process from which reliable data could be generated. The algorithms are divided into the core CGA domains with the addition of urinary incontinence at the request of Dr Kalsi and Dr Harari who suggested this important symptom is often overlooked and under-investigated and would be included in any clinical comprehensive geriatric assessment. A visual flowchart with binary answers at each node seemed the most appropriate design as this allowed both for a logical stepwise approach but also allowed data to be captured regarding where the deficits where identified and what steps were taken by the study team to address these. Each algorithm is followed only if the answer to the “start” question is yes. The algorithms were then sent to the core protocol development team and over a series of teleconferences, further refined. Specific algorithms such as “Falls” required specific input from the physiotherapists on the protocol development team regarding the practicalities of who could access either hospital or community based physiotherapy support. The algorithms are contained within the study workbook rather than the protocol to allow an iterative evolution dependent upon data review by the study management group and from feedback from participating sites once the study opens to recruitment. The algorithms are also designed to be a practical tool for the clinic

beyond the study, my hope is that by bringing this approach into the clinic, an increased awareness of common issues relating to older patients and an up-skilling of oncology teams in how to manage them can be realised.

### 5.4.7 Grant approval and development of protocol/CRFs/PIS/ICFs for local submission prior to REC submission

In recognition of the importance of patient public involvement (PPI) in a study of this nature, I presented the study proposal to the Royal Marsden PPI committee twice, the first prior to initial grant application and the second during the refinement stage following the first review by Wellbeing of Women. We also appointed a PPI representative to the study management group to allow for longitudinal PPI input. The input from the committee was invaluable. Many panel members were themselves older patients many of whom had been treated for cancer themselves. The merit of a holistic approach to an older cancer patient was recognised by the panel and there were many useful suggestions regarding patient reported outcome measures and what additional investigations would likely be deemed acceptable or not by the study population. A specific question regarding acceptability and perceived impact of the assessment and interventions to patients on completion of the study period was suggested by the PPI panel and was therefore incorporated into the protocol.

## 5.5 Statistical considerations

### 5.5.1 Sample Size

The primary endpoint is the feasibility of undertaking the geriatric assessment. Few previous studies exist upon which to base assumptions. One study in rural oncology clinics demonstrated a 29% completion of CGA[208]. We therefore determined as null hypothesis that a completion rate of 35% or less would not be worthwhile whilst a completion rate of 55% or more would be deemed feasible and clinically appropriate according to consensus from the co-investigators and the NCRI older women working group. Based on a Single Stage Phase II A'Hern Design, with one-sided alpha of 5% and 90% power, 53 patients per cohort (i.e. 53 for first line and 53 for first relapse) are required making a total of 106 patients. If at least 25 (per cohort) complete the geriatric assessment the trial will be considered feasible.

We will aim to recruit 120 patients in total to allow for a 12% attrition rate (i.e. 60 for first line and 60 for first relapse). We have not specified a replacement strategy as we anticipate this to be a feasible target given our preliminary work and feasibility questionnaire response as described earlier. We thus estimate that recruitment will be completed within 18 months (6-8 patients/month).

### 5.5.2 Statistical Analysis Plan

All analyses will be conducted by cohort and there will be no statistical comparisons between them. Participant characteristics will be described and numbers with percentages for categorical variables plus means and standard deviations, or medians along with lower and upper quartiles for continuous variables will be presented.

Feasibility for this study will be defined by completing all of the following:

a) the G8 screening questionnaire;

b) the instrumental activities of daily living' (IADL) score;

c) the 'activities of daily living' (ADL) score;

d) the 'Hospital Anxiety and Depression' score;

e) a mini-nutritional assessment;

f) the 'Charlson comorbidity Index';

g) the mini-COG, and

h) a 'Timed up and Go' test.

All proportions will be presented along with 95% confidence intervals (CIs). Comparison between sarcopenic/non-sarcopenic subgroups will use either Chi2 or Fisher's exact test. No multiplicity correction is planned but all results will be interpreted with caution.

Time on treatment (no censoring is anticipated either left or right) will be descriptively reported as median and IQR if however censoring occurs then Kaplan-Meier method will be used instead. PFS will be defined from initiation of systemic therapy to progression or death. OS will be defined from initiation of systemic therapy to death from any cause. Patients without an event will be censored at date of last follow up. The Kaplan-Meier method will be used to summarise both time-to-event endpoints and the log-rank test will be used to compare the intervals according to sarcopenic/non-sarcopenic subgroups. Survival estimates at time points of interest (e.g. proportion alive at 12 months) will be estimated with CIs. Cox regression will be used to obtain hazard ratios (HRs) and 95% CIs and to adjust, if needed, for any confounding factors. Graphical methods will be used for assessing violations of the proportional hazards assumption. Differences in QoL scores from baseline over time will be summarised and presented graphically. The sensitivity/ specificity of sarcopenia in identifying ‘frailty’ using the G8 score will be explored. An ROC curve will be fitted using sarcopenia as golden standard and different cutoffs for sensitivity / specificity will be estimated.

## 5.6 Biomarkers

### 5.6.1 Archival tumour tissue collection

The need for a bio-bank of tissue, in a population often under-represented in clinical trials was felt to be of paramount importance in order to be able to undertake future exploratory, hypothesis-generated research. Biomarkers in cancer are on the whole, cancer-centric, i.e. they are either prognostic and provide information on the natural history of a given cancer or they are predict cancer response to a particular systemic-anticancer therapy. In ovarian cancer, the archetypical example of this would be the presence of a deleterious BRCA 1/2 mutation (germline or somatic) or a homologous recombination deficiency to predict the response to PARP inhibitors[226]. The potential role of biomarkers in older patients with cancer can be considered as more patient-centric. Biomarkers of longevity could predict a given patient's life expectancy excluding the development of a malignancy, which could help inform the risk/benefit ratio of anti-cancer therapy. Biomarkers of frailty could provide further information on a patient's physical reserve and ability to tolerate, for example, complex surgery or intensive anti-cancer therapy as well as risk of significant deterioration during or following on from treatment.

A number of circulating interleukins have been shown to be associated with frailty, in particular IL-6[227]. IL-6 has been shown to be independently associated with increased rates of cognitive impairment

and steeper cognitive decline in a study of elderly patients (median age 75) with a history of cardiovascular disease[228]. CRP, IL-6 and IL-1RA have also been shown to be associated with worse physical performance in a prospective study of 1020 of older study participants living in Chianti, Italy [229]. The Women's Health and Ageing (WHAS 1) study demonstrated that the presence of high levels of IL-6 and low levels of insulin-like growth factor (IGF1) in a population of community-dwelling women aged 65 years or more with moderate or severe disability were associated with an increase in 5 year mortality[230]. Telomeres are short segments of DNA at the end of chromosomes, which, with each successive mitotic division shorten by a process of telomerisation to reduce the risk of replication errors and therefore maintain DNA integrity. Causes of oxidative stress such as smoking may increase the rate of telomere loss. This has led investigations as to whether telomere length may be a marker of "biological age". Short telomere length has been associated with several diseases of ageing such as cardiovascular disease[231] and although has yet to be consistently associated with increased mortality in older patients[232, 233]. Shorter telomere length has been associated with reduced survival from soft tissue, breast, lung and colorectal cancer[234].

PCR-based relative telomere length was assessed from peripheral blood leucocytes in 1042 women with a diagnosis of ovarian cancer between 1995 and 1999 and 2002 and 2004 from the Ontario Cancer Registry. In this study, there was no correlation between relative telomere length and

ovarian cancer survival (p=0.55)[235]. However, the GINECO group recently reported that in elderly patients with ovarian cancer, shorter telomere length was associated with increased chemotherapy related toxicity increased unplanned hospital admissions, serious adverse events and grade 3-4 non-haematological toxicity. Adjusting for FIGO stage, shorter telomere length was also associated with an increased risk of premature death[236].

The secretion of cytokines/chemokines and certain soluble factors such as cathelin-related antimicrobial peptide (CRAMP) and Chitenases[237] has also been shown to be associated with replicative senescence. It remains to be seen whether a single frailty biomarker or indeed a panel of biomarkers may augment a CGA or an abbreviated geriatric assessment. Certainly inflammation appears to be a central process between ageing, frailty and sarcopenia[138]. Incorporation of biomarker tissue studies into prospective clinical studies involving older patients is essential to better understand the potential role these biomarkers may play.

Formalin-Fixed paraffin-embedded (FFPE) blocks obtained at the time of primary diagnosis (and/or if specimen available at progression/relapse) along with a copy of the patient's Histopathology report will therefore be requested and shipped to the Royal Marsden Gynaecology Research Unit at study entry. FFPE blocks containing sufficient tumour content (confirmed by the Histopathologist) will be requested. If obtaining the

FFPE block is not possible, 10 unstained sections cut at 4 µm (unbaked) on positively charged slides will be an acceptable alternative.

### 5.6.2 Optional Biomarker 'research' blood sample collection

If agreed to during the consent process, research blood samples will be collected either at study entry or at cycle 1, day 1. Samples will be taken for storage of serum and extraction of genomic DNA. Blood (2 x 9ml in EDTA tubes) will be collected, centrifuged and plasma (with buffy coat) stored at -80$^{o}$C. All stored samples will be batched and sent to the Royal Marsden Gynaecology unit as and when appropriate. Funding has currently been approved only for the collection and storage of research tissue and blood samples. It is anticipated that a future funding application will be made for undertaking of further analysis of these samples subsequently.

### 5.6.3 Sarcopenia

For the analysis of sarcopenia, CT images acquired as part of standard of care at baseline, after cycle 3 and end of treatment will be anonymised and sent for central review. Professor Andrea Rockall's team (Imperial College) will undertake Sarcopenia analysis. Following on from findings from previous research (detailed here in Chapter 3), body composition (mean muscle attenuation and area, subcutaneous adipose tissue area) at the level of L3 will be assessed.

### 5.6.4 Study timelines

Confirmation of study funding from Wellbeing of Women was received in December 2018. The study was presented to the Royal Marsden CCR in May 2019 and following feedback, submitted for the second and final time in May September 2019. Local CCR approval for sponsorship was received in October 2019. I presented the study on behalf of the Chief Investigator, Dr Banerjee to the National Research and Ethics committee on the 30th October 2019. Final approval from REC and HRA was received in December 2019. A Gantt chart detailed study activities and anticipated timelines, updated in light of delays incurred during the COVID-19 pandemic is below (figure 39). The FAIR-O study opened for recruitment at the Royal Marsden NHS Foundation Trust in January 2021 with 7 further sites due to open in due course.

| Activity | 2019 | 2020 | | | | 2021 | | | | 2022 | | | | 2023 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Q3* | *Q1* | *Q2* | *Q3* | *Q4* | *Q1* | *Q2* | *Q3* | *Q4* | *Q1* | *Q2* | *Q3* | *Q4* | *Q1* | *Q2* | *Q3* | *Q4* |
| **1. Obtain Study Approvals** | | | | | | | | | | | | | | | | | |
| 1.0 HRA / REC Submission | | | | | | | | | | | | | | | | | |
| 1.1 HRA / REC Approval | | | | | | | | | | | | | | | | | |
| **2. Complete Database (MACRO) Specification & Build** | | | | | | | | | | | | | | | | | |
| 2.1. Case report form approval | | | | | | | | | | | | | | | | | |
| 2.2 Complete Database Specification | | | | | | | | | | | | | | | | | |
| 2.3 Complete database UAT (User Acceptance Testing) | | | | | | | | | | | | | | | | | |
| 2.4 Provide Live Database | | | | | | | | | | | | | | | | | |
| 2.5 Provide MACRO Training to delegated site staff | | | | | | | | | | | | | | | | | |
| 2.6 Provide database access to approved site staff | | | | | | | | | | | | | | | | | |
| **3. Lead Site (Royal Marsden) Set Up** | | | | | | | | | | | | | | | | | |
| 3.1 Deliver Site Initation Presentation | | | | | | | | | | | | | | | | | |
| 3.2 Attend Trial Set-Meeting | | | | | | | | | | | | | | | | | |
| 3.3 Receive confirmation of Capability & Capacity (C&C) | | | | | | | | | | | | | | | | | |
| 3.4 Sponsor issues Green Light: Site open to recruitment | | | | | | | | | | | | | | | | | |
| **4. Non-lead Site Set-up (x7 sites)** | | | | | | | | | | | | | | | | | |
| 4.1 Provide Local Information Packs (LIP) to sites | | | | | | | | | | | | | | | | | |
| 4.2 Provide Investigator Site Files | | | | | | | | | | | | | | | | | |
| 4.3 Deliver Site Initiation Presentations | | | | | | | | | | | | | | | | | |
| 4.4 Sign appropriate Site Agreement (Non-commercial) | | | | | | | | | | | | | | | | | |
| 4.5 Provide MACRO database training and access | | | | | | | | | | | | | | | | | |
| 4.6 Receive confirmation of local C&C | | | | | | | | | | | | | | | | | |
| 4.6 Sponsor issues Green Light | | | | | | | | | | | | | | | | | |
| 4.7 All sites Open to recruitment | | | | | | | | | | | | | | | | | |
| **5. Recruitment to Target (n=120)** | | | | | | | | | | | | | | | | | |
| 5.1 Patient recruitment activities with [cumulative recruitment] | | | | | (3) | [6] | [19] | [40] | [62] | [86] | [110] | [120] | | | | | |
| 5.2 Patient follow-up activities | | | | | | | | | | | | | | | | | |
| 5.3 Last Patient Recruited | | | | | | | | | | | | | | | | | |
| 5.4 Last patient follow-up completed | | | | | | | | | | | | | | | | | |
| **6. Data Analysis & Article Production** | | | | | | | | | | | | | | | | | |
| 6.1 Data cleaning | | | | | | | | | | | | | | | | | |
| 6.2 Data Freeze and Export to Statisticians | | | | | | | | | | | | | | | | | |
| 6.3 Data Analysis | | | | | | | | | | | | | | | | | |
| 6.4 Article Production and submission | | | | | | | | | | | | | | | | | |

**Figure 39. FAIR-O Gantt Chart**

## 5.7 Conclusions

The approval and opening of the FAIR-O study represents the culmination of a significant multidisciplinary effort. The novel design and incorporation of elements such as the CGA flowcharts required a significant amount of collaboration and of broader thinking to meet the challenge of a study that sounded fairly simple in its concept at the outset but in actuality was far from it. Without the expert contributions of the protocol development team who were behind this project; this study could not have become a reality.

## 5.8 Gynaecology Unit CRANE assessment (service evaluation)

**Figure 40. Instrumental actitvities of daily living scale (IADL)**

### INSTRUMENTAL ACTIVITIES OF DAILY LIVING SCALE (IADL)

**M.P. Lawton & E.M. Brody**

A. Ability to use telephone

| | |
|---|---|
| 1. Operates telephone on own initiative; looks up and dials numbers, etc. | 1 |
| 2. Dials a few well-known numbers | 1 |
| 3. Answers telephone but does not dial | 1 |
| 4. Does not use telephone at all. | 0 |

B. Shopping

| | |
|---|---|
| 1. Takes care of all shopping needs independently | 1 |
| 2. Shops independently for small purchases | 0 |
| 3. Needs to be accompanied on any shopping trip. | 0 |
| 4. Completely unable to shop. | 0 |

C. Food Preparation

| | |
|---|---|
| 1. Plans, prepares and serves adequate meals independently | 1 |
| 2. Prepares adequate meals if supplied with ingredients | 0 |
| 3. Heats, serves and prepares meals or prepares meals but does not maintain adequate diet. | 0 |
| 4. Needs to have meals prepared and served. | 0 |

D. Housekeeping

| | |
|---|---|
| 1. Maintains house alone or with occasional assistance (e.g. "heavy work domestic help") | 1 |
| 2. Performs light daily tasks such as dish-washing, bed making | 1 |
| 3. Performs light daily tasks but cannot maintain acceptable level of cleanliness. | 1 |
| 4. Needs help with all home maintenance tasks. | 1 |
| 5. Does not participate in any housekeeping tasks. | 0 |

E. Laundry

| | |
|---|---|
| 1. Does personal laundry completely | 1 |
| 2. Launders small items; rinses stockings, etc. | 1 |
| 3. All laundry must be done by others. | 0 |

F. Mode of Transportation

| | |
|---|---|
| 1. Travels independently on public transportation or drives own car. | 1 |
| 2. Arranges own travel via taxi, but does not otherwise use public transportation. | 1 |
| 3. Travels on public transportation when accompanied by another. | 1 |
| 4. Travel limited to taxi or automobile with assistance of another. | 0 |
| 5. Does not travel at all. | 0 |

G. Responsibility for own medications

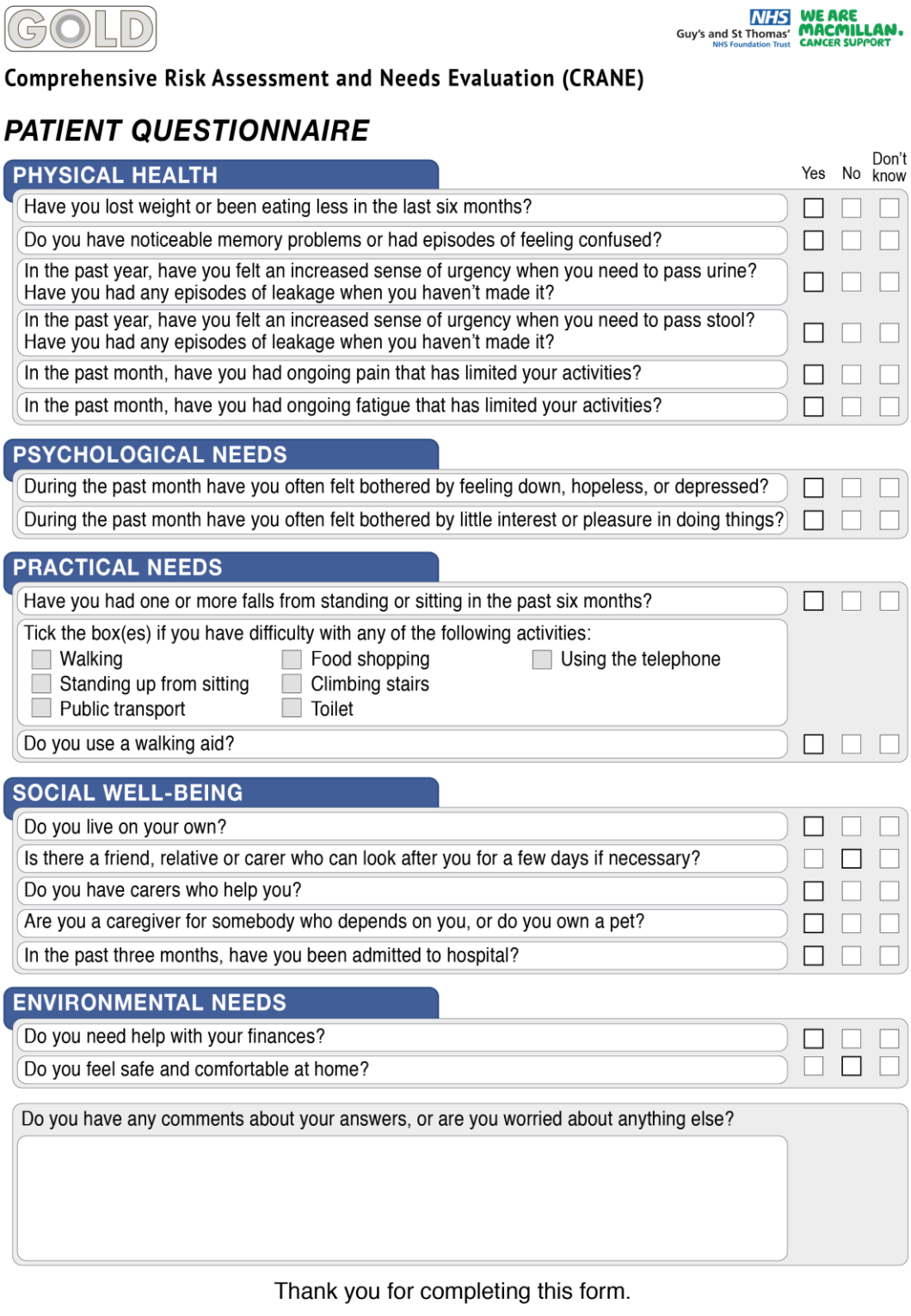
| | |
|---|---|
| 1. Is responsible for taking medication in correct dosages at correct time. | 1 |
| 2. Takes responsibility if medication is prepared in advance in separate dosage. | 0 |
| 3. Is not capable of dispensing own medication. | 0 |

H. Ability to Handle Finances

| | |
|---|---|
| 1. Manages financial matters independently (budgets, writes checks, pays rent, bills goes to bank), collects and keeps track of income. | 1 |
| 2. Manages day-to-day purchases, but needs help with banking, major purchases, etc. | 1 |
| 3. Incapable if handling money. | 0 |

**Source:** Lawton, M.P., and Brody, E.M. "Assessment of older people: Self-maintaining and instrumental activities of daily living." Gerontologist 9:179-186, (1969).

**Figure 41. Comprehensive Risk Assessment and Needs Evaluation (CRANE)**



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## Comprehensive Risk Assessment and Needs Evaluation (CRANE)

## *PATIENT QUESTIONNAIRE*

| PHYSICAL HEALTH | Yes | No | Don't know |
|---|---|---|---|
| Have you lost weight or been eating less in the last six months? | ☐ | ☐ | ☐ |
| Do you have noticeable memory problems or had episodes of feeling confused? | ☐ | ☐ | ☐ |
| In the past year, have you felt an increased sense of urgency when you need to pass urine? Have you had any episodes of leakage when you haven't made it? | ☐ | ☐ | ☐ |
| In the past year, have you felt an increased sense of urgency when you need to pass stool? Have you had any episodes of leakage when you haven't made it? | ☐ | ☐ | ☐ |
| In the past month, have you had ongoing pain that has limited your activities? | ☐ | ☐ | ☐ |
| In the past month, have you had ongoing fatigue that has limited your activities? | ☐ | ☐ | ☐ |

| PSYCHOLOGICAL NEEDS | Yes | No | Don't know |
|---|---|---|---|
| During the past month have you often felt bothered by feeling down, hopeless, or depressed? | ☐ | ☐ | ☐ |
| During the past month have you often felt bothered by little interest or pleasure in doing things? | ☐ | ☐ | ☐ |

| PRACTICAL NEEDS | Yes | No | Don't know |
|---|---|---|---|
| Have you had one or more falls from standing or sitting in the past six months? | ☐ | ☐ | ☐ |
| Tick the box(es) if you have difficulty with any of the following activities: ☐ Walking ☐ Standing up from sitting ☐ Public transport ☐ Food shopping ☐ Climbing stairs ☐ Toilet ☐ Using the telephone | | | |
| Do you use a walking aid? | ☐ | ☐ | ☐ |

| SOCIAL WELL-BEING | Yes | No | Don't know |
|---|---|---|---|
| Do you live on your own? | ☐ | ☐ | ☐ |
| Is there a friend, relative or carer who can look after you for a few days if necessary? | ☐ | ☐ | ☐ |
| Do you have carers who help you? | ☐ | ☐ | ☐ |
| Are you a caregiver for somebody who depends on you, or do you own a pet? | ☐ | ☐ | ☐ |
| In the past three months, have you been admitted to hospital? | ☐ | ☐ | ☐ |

| ENVIRONMENTAL NEEDS | Yes | No | Don't know |
|---|---|---|---|
| Do you need help with your finances? | ☐ | ☐ | ☐ |
| Do you feel safe and comfortable at home? | ☐ | ☐ | ☐ |

Do you have any comments about your answers, or are you worried about anything else?

Thank you for completing this form.

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**Comprehensive Risk Assessment and Needs Evaluation (CRANE)**

## *OBSERVATIONS*

**FOR CLINICIANS**

| | | | |
|---|---|---|---|
| Blood pressure | / | Height | |
| Pulse | | Weight | |
| $O_2$ sat. (if required) | | BMI | |

**Complete the following sections using information from the GP records (if obtainable).**

## *COMORBIDITIES*

Tick all that apply.

- [ ] Cardiac disease
- [ ] Respiratory disease
- [ ] Liver disease
- [ ] Renal disease
- [ ] Neurological disease
- [ ] Diabetes
- [ ] Hypertension
- [ ] Thrombosis
- [ ] Dementia
- [ ] Depression/anxiety/other mental health issues
- [ ] Hearing impairment

## *MEDICATION REVIEW*

List all medications that the person is currently taking.

**Figure 42.Royal Marsden Nutrition Screening Tool**

The ROYAL MARSDEN

# Nutrition screening tool: Outpatients

| Name: | Hospital no: |
|---|---|

1. Nutrition is an important part of your general health and wellbeing. As a result we are interested in your eating, drinking and weight prior to you attending your outpatient appointment.
2. Please fill in the form which asks questions about your weight, eating and any symptoms that you may have which may impact on your ability to eat.
3. Once complete, please hand this form to your clinic nurse.
4. If you would like help completing this form then please ask the clinic nurse.
5. Your clinic nurse will then measure your height and weight and enter this information with the results of this questionnaire on to your records.
6. If you have lost a lot of weight or scored highly and thus will be at risk of malnutrition, you will receive a letter offering you an appointment to see the Dietitian.

| Date: | |
|---|---|
| **1. Have you experienced unintentional or unplanned weight loss in the last 3 months?** | |
| No weight loss | 0 |
| Unintentional or unplanned weight loss over 3 months:<br>Greater than 7kg (1 stone) in men<br>Greater than 5.5kg ( ¾ stone) in women | 10 |
| Unintentional or unplanned weight loss less than the above | 5 |
| **2. Do you consider that you look underweight?** | |
| No | 0 |
| Yes | 5 |
| **3. Have you had a reduced food intake (less than 50% of meals) in the last 5 days (this may be due to loss of interest in food, sore mouth, difficulty swallowing, fatigue, feeling or being sick)?** | |
| No | 0 |
| Yes | 5 |
| **4. Are you experiencing symptoms that are affecting your food intake e.g. sore mouth, feeling sick, being sick, diarrhoea, constipation?** | |
| No | 0 |
| Yes | 3 |
| **Total Score**<br>(To be completed by nurse)<br>Score to be entered in the comments box in the Height and Weight section on Electronic Patient Record.<br>Send completed form to the Department of Nutrition and Dietetics | |

| | | | |
|---|---|---|---|
| **Today's Height (cm)**<br>(To be completed by nurse) | | **Nurse/HCSW name** *(PRINT)* | **Nurse/HCSW Signature and Date** |
| **Today's Weight (Kg)**<br>(To be completed by nurse) | | **Nurse/HCSW name** *(PRINT)* | **Nurse/HCSW Signature and Date** |

**RISK OF MALNUTRITION**

**0 – 4 LOW RISK  5 – 9 MEDIUM RISK  10+ HIGH RISK**

**If you score 5 or more please pick up a Royal Marsden Eating Well When You Have Cancer booklet or ask the nurse for a copy**

| | | |
|---|---|---|
| Title: Nutrition Screening Tool (Adult Outpatients)<br>Department: Nursing & Rehabilitation - Therapies | Version No: 3 Issue Date: March 2018<br>Unique Identification Number: NR514 | Document Type: Clinical Record<br>© 2014 The Royal Marsden NHS Foundation Trust |

## 5.9 FAIR-O Study Algorithms

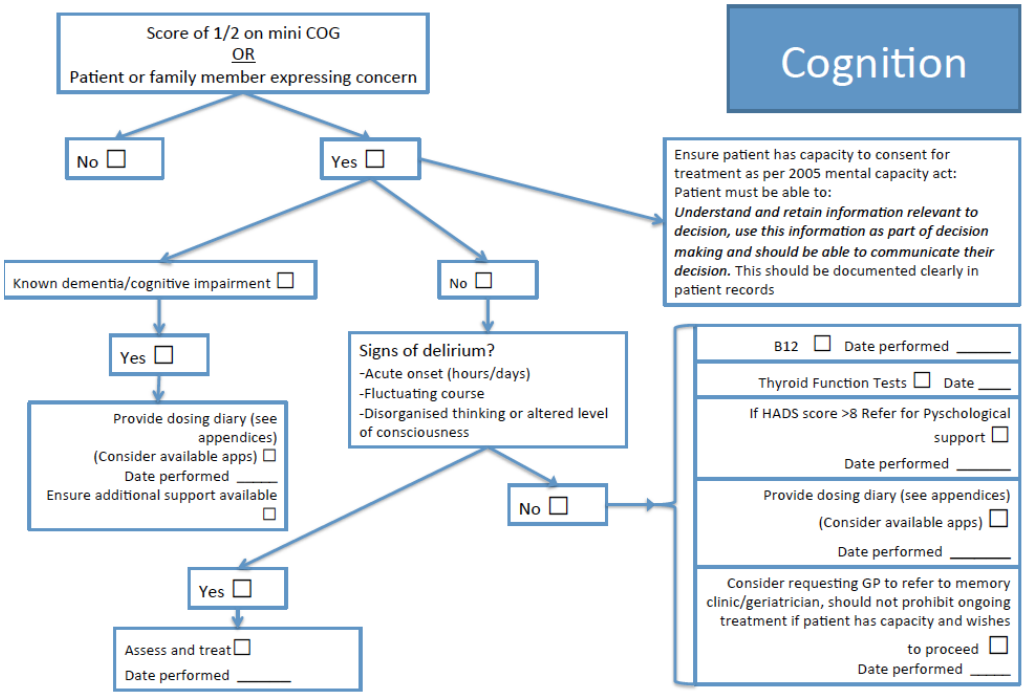


**Figure 43. Cognition FAIR-O Algorithm**

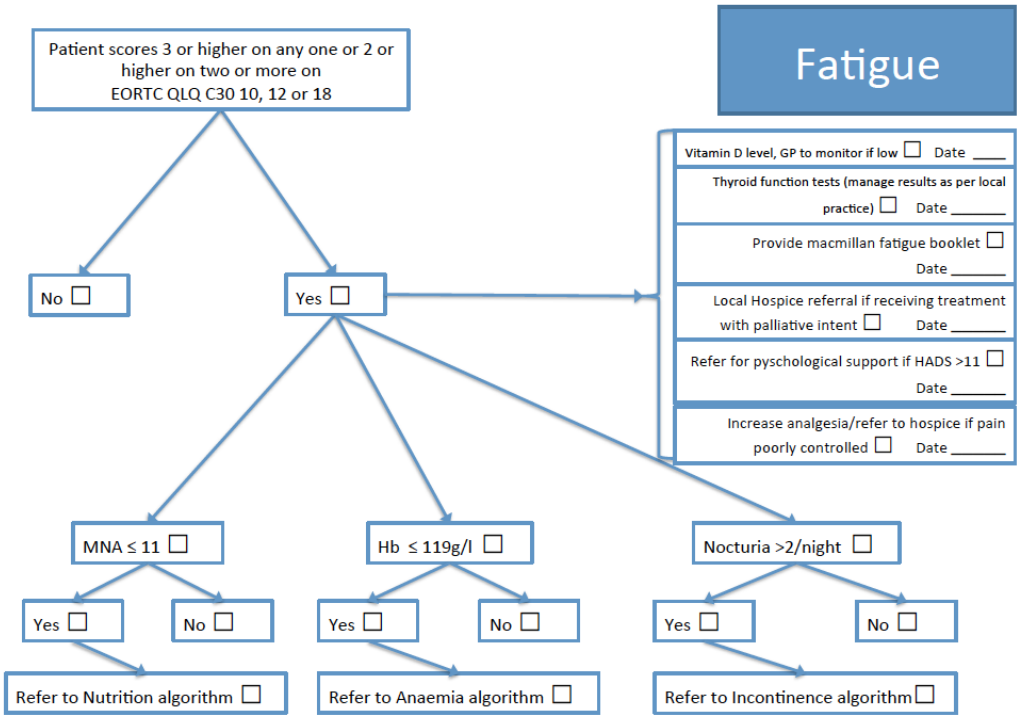


**Figure 44. Fatigue FAIR-O Algorithm**

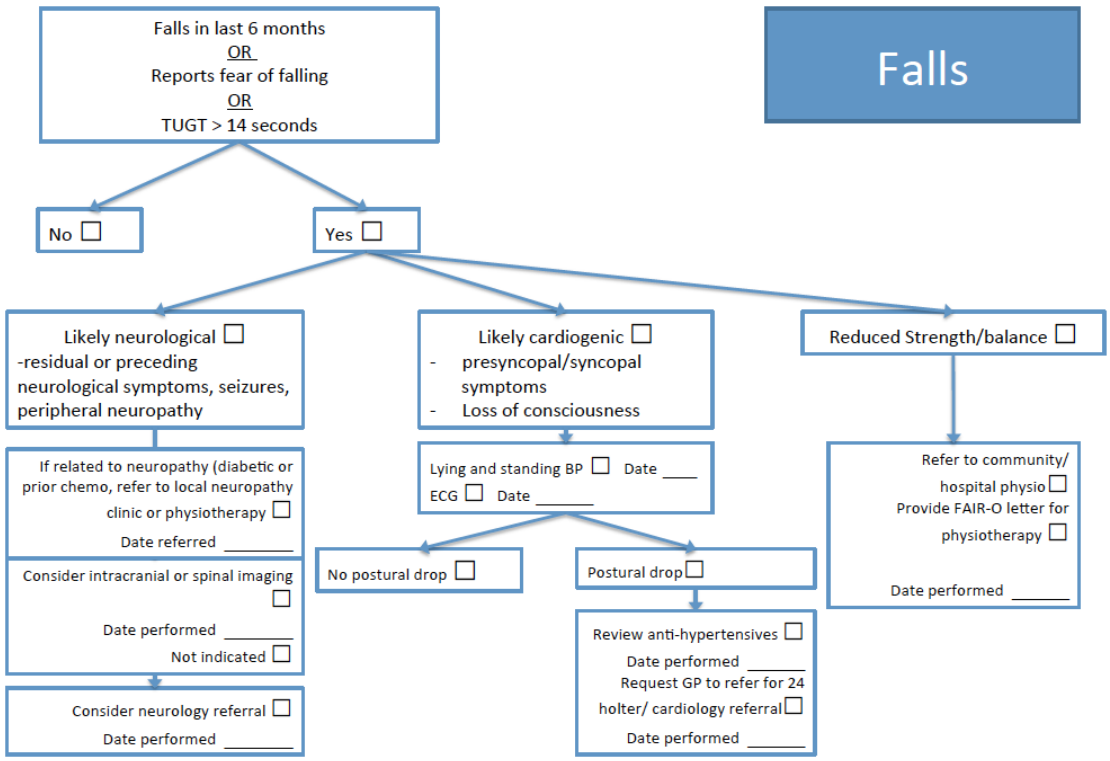


**Figure 45. Falls FAIR-O Algorith**

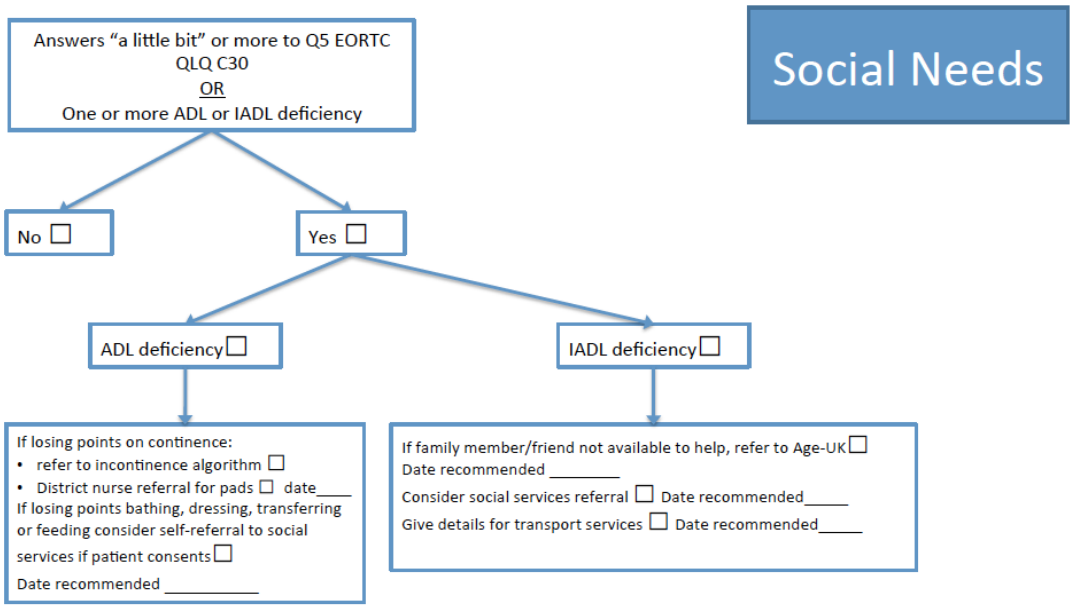


**Figure 46. Social Needs FAIR-O algorithm**

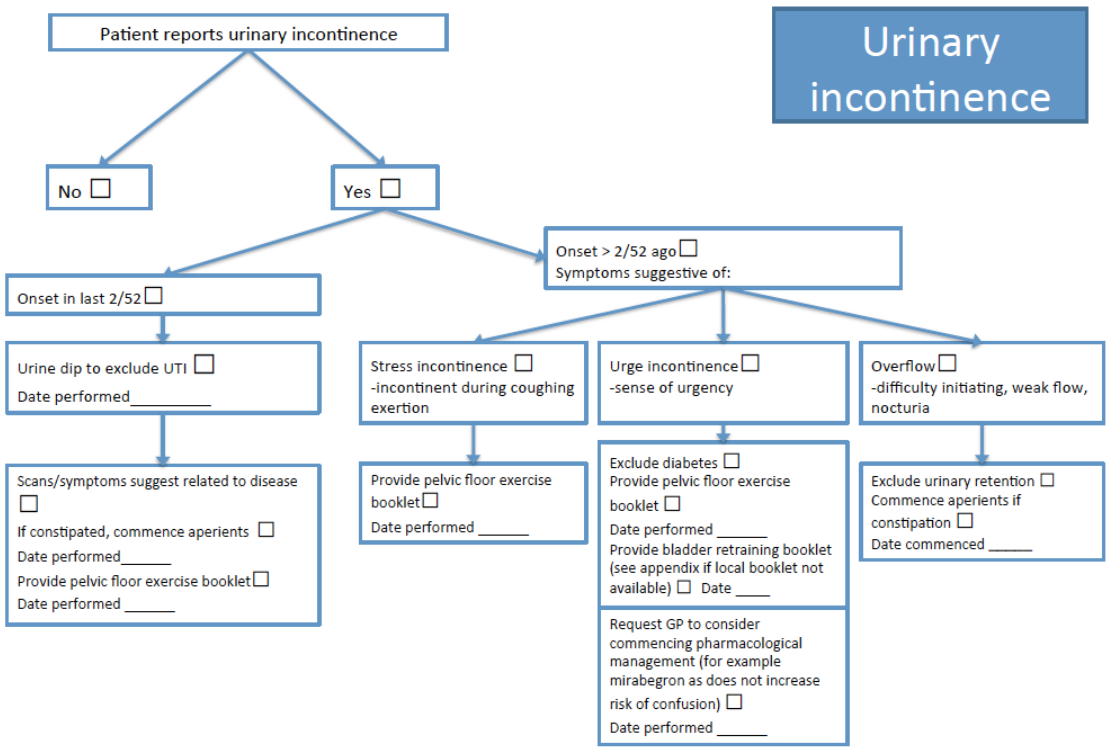


**Figure 47. Urinary incontinence FAIR-O algorithm**

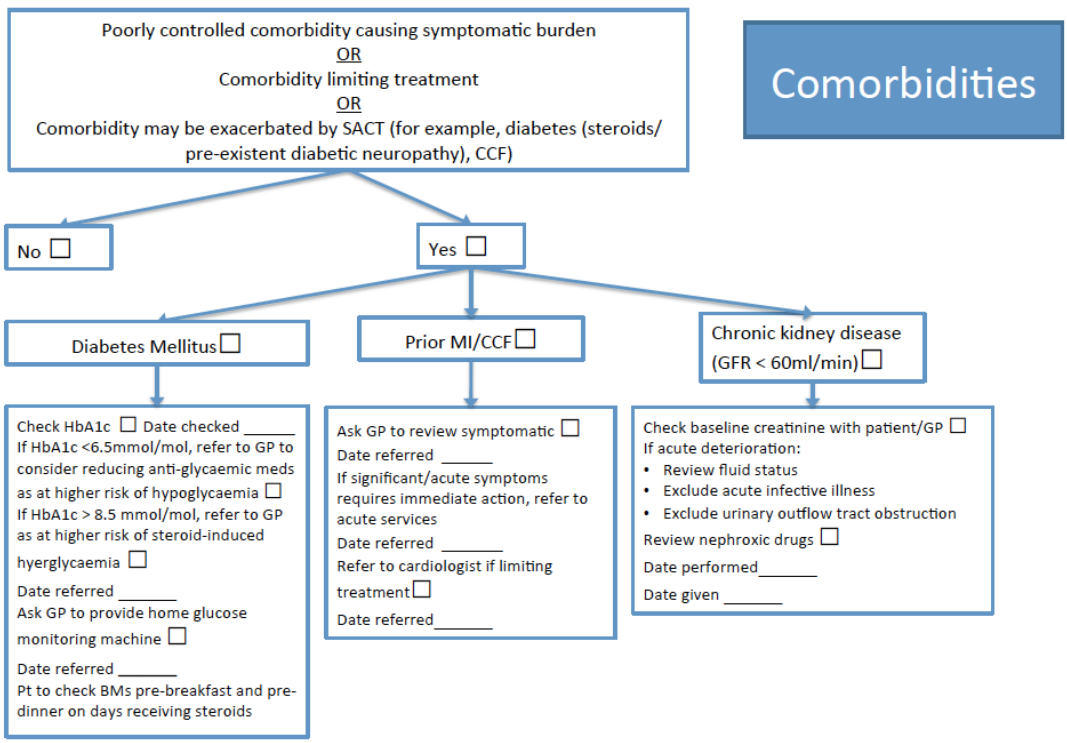


**Figure 48. Comorbidities FAIR-O algorithm**

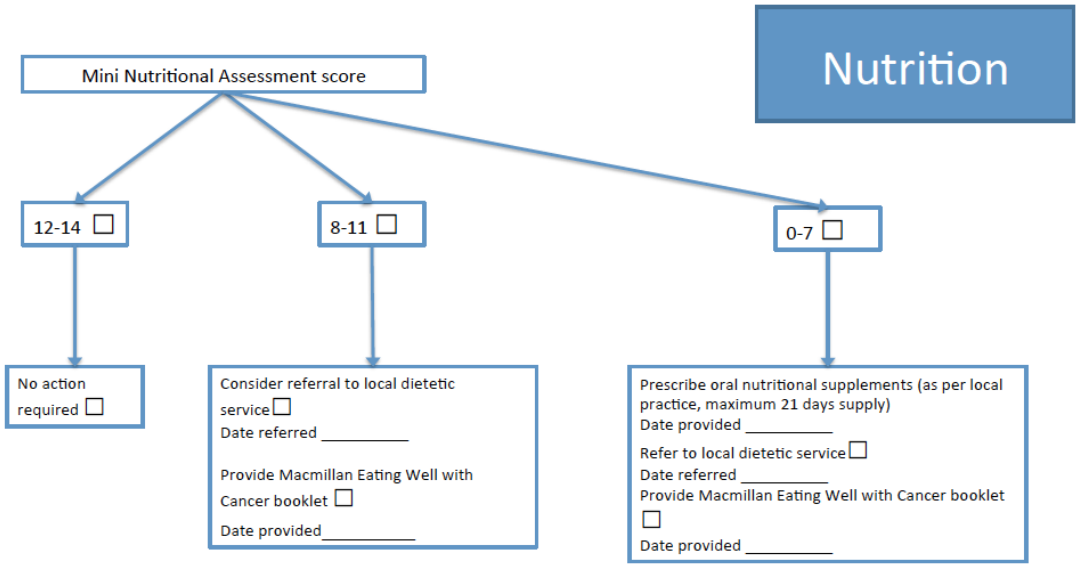


**Figure 49. Nutrition FAIR-O algorithm**

## Polypharmacy

| Category | Stop if | Drug | Date stopped | If not, specify why not e.g. patient preference, clinical decision |
|---|---|---|---|---|
| General | Any drug that patient persistently fails to take or tolerate despite attempts at education or formulation alteration | | | |
| Lipid lowering | Poor expected 1 year survival, severe functional impairment or complaining of myalgia | | | |
| Anti-hypertensives | Stringent blood pressure control is not required in very frail older patients (aside from those receiving bevacizumab), alpha blockers in particular, ACE-inhibitors increase risk of hypotension and falls<br>If systolic BP <120, ask GP to review anti-hypertensives<br>If systolic BP <100, stop anti-hypertensives in clinic | | | |
| Anti-platelets | Primary prevention (not secondary) | | | |
| Full dose PPI/H2 antagonist | If taking >8/52 and asymptomatic or return of symptoms when dose lowered (unless recent history of recent GI bleeding) | | | |
| NSAIDs | Stop, change to alternative analgesia | | | |

**Figure 50. Polypharmacy FAIR-O algorithm**

# 6 CONCLUSIONS AND FUTURE DIRECTIONS

The field of geriatric oncology has been in existence for the last two decades but progress in the early years was made by a valiant yet small group of dedicated researchers. In the last few years that there has been a more widespread interest and significant expansion of the evidence base in treating older adults with both solid organ and haematological malignancies. The literature review presented in Chapter 1 demonstrates the significant and as yet, still unmet need of older women with gynaecological malignancies and specifically ovarian cancer. Despite significant advancements in the treatment of gynaecological malignancies, most pertinently the advent of PARP inhibitors into routine daily practice, survival outcomes continue to be disproportionately poor in older women. It is now the recommendation of both SIOG and ASCO that some form of comprehensive geriatric assessment be undertaken for all older adults who are being considered for systemic anti-cancer therapy however this is far from the daily reality of most oncology practice in the UK[82] and oncology trainees currently receive no education on the specific issues relating to the treatment of older cancer patients[201] despite older patients increasingly, representing the majority of the oncology practice.

The retrospective study presented in Chapter 2 is to my knowledge, one of the largest retrospective series to be presented on the treatment practices and survival outcomes in older women with ovarian cancer and certainly the only recent analysis of its kind in the UK in the last decade. The findings demonstrate once again that despite the advances in the evidence base around treating older adults with cancer, survival

outcomes, in keeping with the ICBP-2[3, 9] analysis, continue to be poorer in the oldest women. Crucially, when older women received the same treatment as their younger counterparts, this difference was not observed. It was also observed that completion of the planned six cycles of chemotherapy was also independently associated with overall survival. The data presented here concurs with the finding of the practice-changing EWOC-1 (NCT02001272) [44, 45], that there is a clear survival advantage of doublet platinum based chemotherapy for older women with newly diagnosed ovarian cancer. A comprehensive geriatric assessment followed by medical and functional optimisation to facilitate the treatment of older women with any deficits identified should be considered a priority in order to narrow the gap in the survival difference between the oldest patients and their younger counterparts. It is however, acknowledged that for some women, doublet chemotherapy is not tolerable and in these patients, treatment completion without untimely delays/interruptions (in themselves associated with poorer survival outcomes[46] and complications should be seen as the treatment priority.

Over the last two decades, since Goodpaster's seminal results published from the longitudinal Health ABC study[130], there has been a significant increase in the volume and quality of work published in the field of sarcopenia and its role as a non-invasive biomarker in cancer patients. Only in the last five years has sarcopenia been more fully explored in the context of gynaecological malignancies. The literature review presented in chapter 3 demonstrates the prognostic and predictive impact of sarcopenia in both non-gynaecological and gynaecological malignancies

demonstrated thus far. The findings presented in chapter 3 represents one of the largest retrospective studies to date examining the role of body composition as a predictive marker in ovarian cancer and is to the researchers knowledge, the only study to assess only an older population where the prevalence and impact of body composition is likely to be different. It was demonstrated that muscle density and not mass was an independent strong predictor of poorer overall survival and progression-free survival.

Since this study was first initiated in 2015, a number of other investigators have corroborated the finding that muscle attenuation, likely to be a better surrogate for function, rather than mass is the more prognostically important factor. Whilst previous researchers have assessed whether isolated muscle domains such as psoas may be able to be used instead of total skeletal muscle volume[151] this finding has not been replicated elsewhere. The finding here that erector spinae muscle density alone is strongly associated with poorer overall and progression-free survival is novel and is potentially of practical clinical significance. In non-gynaecological malignancies, sarcopenia has been shown to be associated with poorer chemotherapy and radiation tolerance[238-240]. This is, to the researcher's knowledge the first study to demonstrate a meaningful relationship between baseline muscle attenuation and poorer chemotherapy tolerance both in terms of a higher rate of severe non-haematological toxicities and poorer chemotherapy completion rates.

With regards the novel finding of erector spinae muscle attenuation as a prognostic marker, the next steps are to assess whether this can reliably be assessed using PACS rather than specific imaging-analysis software. Sarcopenia and body composition will be assessed as part of the prospective FAIR-O study. Whilst this study is not powered to assess the prognostic association of muscle attenuation as this is not the study primary endpoint, associations between frailty and chemotherapy tolerance as well as 1-year survival outcomes will be able to be assessed.

Whilst lower treatment intensity appears to be one of the core factors in the poorer survival outcomes seen in older women with ovarian cancer, there is a relative paucity of data on older women's attitudes to treatment to assess whether this lower treatment intensity is due to patients declining more intensive therapy or whether they are not offered in the first instance due to concerns over age and ability to tolerate treatment. To my knowledge, the study presented in Chapter 4 is the first study to report the attitudes to treatment and survival in a group of older women with ovarian cancer who have all gone through or are continuing to receive systemic anti-cancer therapy.

The participants overwhelmingly reported a very positive experience of their cancer care so far and the significant majority underwent treatment with the primary aim of extending their life and were concerned that age would be counted against them leading to less intensive or no treatment. Many patients within this study had significant barriers to treatment such as medical and functional comorbidities. Some were also primary carers

for dependent spouses or family members. A more holistic assessment such as a geriatric assessment would allow these concerns to be brought to the attention of the oncology teams to facilitate better support of these more vulnerable patients through treatment. Easily addressable logistical issues such as transport were highlighted as a significant source of frustration and anxiety for many, again, highlighting the need for a more holistic assessment at the beginning of a new treatment. Participants reported tolerating treatment better than they thought they would and most indicated they would be willing to undergo treatment again if it should be indicated. Fatigue was the most commonly reported and difficult to manage symptom and further research into improving the fatigue burden, which is likely to be particularly problematic for older patients, is warranted. These findings strengthen the assertion that older women do not desire treatment with the aim of life prolongation any less than their younger counterparts and that efforts should be made to facilitate patient-centred decision making and treatment if appropriate, whilst undertaking a comprehensive geriatric assessment and intervening on any deficits identified to improve treatment tolerance and completion rates.

Chapter 5 presents the findings of the CRANE sub-study, intended as a scoping tool to garner an idea of the incidence of geriatric medicine issues in the routine chemotherapy clinic, it highlighted a higher than anticipated prevalence of problems such as mobility, functional limitations and risk of malnutrition and whilst it provides useful information ahead of FAIR-O trial as to which issues are likely to be of more concern, it also

provided an insight into which components of the comprehensive geriatric assessment are likely to present more of a challenge in terms of reliable and accurate data collection. The results of this small prospective study will also be fed back to the wider gynaecology unit. The CRANE quality improvement project is limited by its small size, which impacts the potential generalisability of the findings. This chapter predominantly however details the evolution of the FAIR-O study, a concept I conceptualised and together with significant support from an expert multidisciplinary team, was successfully awarded grant funding from Wellbeing of Women in 2018. The development of the protocol, with no prior template to follow due to its novel nature was complex and required a great deal of altruistic inter-disciplinary communication and co-operation. The algorithms designed have purposefully been kept in a separate study workbook to allow for an iterative evolution of the flowcharts as the study progresses. The FAIR-O study is, to the best of the researchers' knowledge, the first of its kind in the UK. It has the potential, if positive to lead to rapid implementation into the routine oncology clinic and is therefore potentially practice changing. The FAIR-O study opened in January 2021 at the Royal Marsden NHS Foundation Trust with 7 other sites due to follow. A number of interventional, prospective studies have now been presented demonstrating the improvement in chemotherapy tolerance with geriatric assessment. In all of these studies, the intervention arm was geriatrician-led. Both the GAIN (NCT02517034) [241] and INTERGERATE (ACTRN12614000399695) [242] studies reported improved chemotherapy tolerance and in the case of the latter, Health-related Quality of Life (HRQoL) but have not yet reported on

treatment intensity or survival outcomes. The study led by Mohile et al likewise reported improved chemotherapy tolerance with GA followed by geriatrician led recommendations (delivered by oncologists). Those in the intervention arm had lower treatment intensity without compromise of 6-month survival outcomes. These findings are all encouraging however longer-term survival outcomes are needed and how to interpret the assertion that lower treatment intensity does not compromise outcomes when the robust and well-constructed EWOC-1 study appears to contradict this requires further investigation. As has previously been stated, the outcome of the large PREPARE[81] study is eagerly awaited as this is only study to the researchers knowledge to have been designed with the primary endpoint of survival. Whilst, in the context of an ageing multimorbid population, other endpoints should be considered just as valuable, for example HRQoL or quality-adjusted survival (Q-TWIST)[243], the findings reported in Chapter 4 demonstrate that older patients value survival just as much as their younger counterparts and efforts should not be spared to improve survival outcomes, whilst minimising the impact on the essential outcomes of quality of life and treatment tolerance. If studies such as PREPARE are subsequently reported as positive, in the researchers opinion, there is no indication for this to be replicated within the UK. Further research is then likely to be focused on implementation of CGA, either by geriatrician-led MDTs, the gold standard and yet with resource implications, or by the more pragmatic methods outlined in the FAIR-O trial. The researcher hopes that the approach outlined in FAIR-O trial can be of practical use beyond the scope of the research setting and can provide a framework upon which oncology-team led CGA can be

delivered and managed to ultimately, improve outcomes (survival, functional and quality of life) for older women undergoing treatment for ovarian cancer in the UK.

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# 8 APPENDICES (PUBLISHED PAPERS)

## 8.2 Dumas et al. Improving Outcomes in Older Women with Gynaecological Malignancies. Cancer Treatment Reviews 2016

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Tumour Review

# Improving outcomes for older women with gynaecological malignancies

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ABSTRACT

The incidence of most gynaecological malignancies rises significantly with increasing age. With an ageing population, the proportion of women over the age of 65 with cancer is expected to rise substantially over the next decade. Unfortunately, survival outcomes are much poorer in older patients and evidence suggests that older women with gynaecological cancers are less likely to receive current standard of care treatment options. Despite this, older women are under-represented in practice changing clinical studies. The evidence for efficacy and tolerability is therefore extrapolated from a younger; often more fit population and applied to in every day clinical practice to older patients with co-morbidities. There has been significant progress in the development of geriatric assessment in oncology to predict treatment outcomes and tolerability however there is still no clear evidence that undertaking a geriatric assessment improves patient outcomes. Clinical trials focusing on treating older patients are urgently required. In this review, we discuss the evidence for treatment of gynaecological cancers as well as methods of assessing older patients for therapy. Potential biomarkers of ageing are also summarised.



## Introduction

### *Incidence and survival in older patients*

The EUROCARE project [1], which assesses cancer survival across Europe over time, demonstrated that although for almost all cancers there was a continued improvement in outcomes over time, the rate of progress was slower in older patients – in particular for patients with gynaecological malignancies. However, of note, if older patients with a gynaecological cancer survived the first year after diagnosis, the prognosis for this group was similar to middle-aged patients [2].

The majority of gynaecological cancers (ovarian, endometrial, vulval) are diagnosed in postmenopausal women [3–5]. For cervical cancer, in addition to the incidence peak at age 30–34, there is a second rise in incidence above the age of 70 [6]. The incidence of endometrial cancer peaks in the 70–74 age group (94.1 per 100,000). Between 1993 and 2009, the incidence of endometrial cancer in women over the age of 75 rose by 43% [4,7] and two thirds of deaths from endometrial cancer occur in women over the age of 70 [4].

Ovarian cancer is predominantly a disease of older women; in the UK, around half of all diagnoses are in women over the age of 65 [8] and the median age at diagnosis is 64.7 [9]. This is similar in the USA where 44% of all ovarian cancer cases occur in women over the age of 65 and the median age at diagnosis of 63 [10]. Over the past 20 years, significant advances in the management of ovarian cancer have led to the improved survival rates in all groups with the notable exception of those over the age of 80 [1]. For example, in the UK, the mean 1-year survival for stage IV ovarian cancer patients of all ages is 51.0% but this dramatically falls to 35.7% for women over the age of 70 [11]. The fundamental issue of worsening outcomes with increasing age is applicable worldwide [12].

With an ageing population, although the overall incidence of cancer is not projected to change, the proportion of patients over the age of 65 is expected to rise. For example, in the UK by 2030, 67.5% of all female cancer patients will be over the age of 65 [7]. Survival rates are summarised in Table 1. The UK survival statistics for gynaecological malignancies are known to be poorer compared to the results of other developed countries. Of concern, is the fact that this difference is magnified further for older patients [11]. For example, a woman over the age of 70 diagnosed with stage

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**Table 1**
UK Age-specific relative survival at 1 and 5 years by tumour type.

| Cancer Type | 1-year age-specific relative survival (%) | 5-year age-specific relative survival (%) |
|---|---|---|
| Cervical [6] | | |
| 50–59 years | 85.2 | 59.1 |
| 70–79 years | 70.0 | 34.0 |
| Endometrial [98] | | |
| 55–59 years | 95.6% | 86.2 |
| 75–79 years | 86.5 | 67.7 |
| Ovarian [3] | | |
| 55–59 years | 85.9 | 47.0 |
| 75–79 years | 56.6 | 24.5 |

III ovarian cancer in Canada has an expected 1-year survival of 74% compared to just 57% in the UK [11].

*Potential reasons for poor survival*

The reasons for poorer outcomes in older patients with gynaecological cancers are not fully understood. It has been postulated that delayed presentation for a multitude of psychosocial reasons leading to advanced stage at diagnosis, increasing comorbidities, relative under-treatment as well as potentially adverse tumour biology in cancers diagnosed in older women may all play a role.

A report from the International Cancer Benchmarking Group demonstrated that more advanced stage at ovarian cancer diagnosis was associated with increasing age [9,11]. Furthermore, it has been shown that older patients were significantly less likely to be referred for investigations such as abdominal ultrasound or to a gynaecologist in the year preceding a diagnosis of ovarian cancer [13]. One study reported that the median time for a 75-year old woman to be referred for further investigation following the reporting of symptoms was 20 weeks [13]. Older women with endometrial cancer are more likely to be diagnosed with a later stage and present as an emergency, both factors known to be associated with worse outcomes [14].

The treatment plan for older women is often different compared to younger patients. For example, older patients with cervical cancer are more likely to receive primary radiotherapy rather than surgery, less likely to undergo a radical hysterectomy, lymphadenectomy, adjuvant radiotherapy or brachytherapy [15,16]. In advanced disease, 12.1% of patients over 80 years old compared to 3.9% under 50 years old ($p < 0.0001$) received no anticancer treatment. Adjusting for stage and treatment, disease-specific mortality was increased in those over the age of 70 [16]. Evaluation of data from the SEER database (1992 and 2002) demonstrated that women over the age of 65 were less likely to undergo radical surgery for endometrial cancer [17]. A retrospective study of 20,468 women from the USA National Cancer Database demonstrated that, adjusting for prognostic factors, women between the age of 75 and 84 were less likely to receive surgery, radiotherapy and chemotherapy than women under the age of 55 for high-grade endometrial cancer [18]. Similar findings were found from an analysis of three GOG studies which showed that only 64% of patients over the age of 70 who were offered adjuvant radiotherapy actually went on to receive treatment [19].

Although there have been international efforts to increase the recruitment of older patients into clinical studies, women over the age of 65 remain underrepresented in practice-changing studies [20–22] and yet form a significant proportion of patients being treated in daily clinical practice. For example, among 28,766 patients enroled into 55 registration studies in the US across a number of malignancies including ovarian cancer, 35% of the study population were over the age of 65 compared with 60% in the US population in clinical practice [20]. The discrepancy increases with age; with the exception of hormonal therapy trials in breast cancer, only 4% of patients over the age of 75 entered clinical trials. For example, in the pivotal GOG-158 phase trial which contributed to the establishment of carboplatin in combination with paclitaxel as standard care for first-line treatment in ovarian cancer, 11% of the patients enroled were over the age of 71 and only 1% over the age of 81 [49]. There is a lack of prospective clinical studies focusing on older, less fit patients with gynaecological malignancies.

Finally, it has been recognised that there is a need for an alternative assessment method to guide treatment decisions in the older population. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) is the accepted standard for evaluation of a patient's functional status both in clinical studies and in routine clinical practice. It is widely accepted that this is a limited tool for assessment of older patients and does not accurately represent limitations in functional or cognitive capability [23–25].

In the remainder of this review, the evidence for treatment of gynaecological cancers in older women, methods of assessing older patients for cancer therapy and potential steps towards improving outcomes are discussed.

## Endometrial and cervical cancer

Studies addressing the management of older patients with endometrial and cervical cancer are limited and largely consist of retrospective cohort analyses. The Post Operative Radiation Therapy in Endometrial Carcinoma (PORTEC) 1 trial showed that women over the age of 60 were threefold more likely to have a locoregional recurrence following radical surgery compared to younger patients (HR 3.90 $p = 0.0017$) [26]. Following 15-year follow-up, the local recurrence rate in the overall study population was reduced from 15.5% to 6.0% with the addition of post-operative external beam radiotherapy (EBRT). However, in older patients who may have co-morbidities and/or functional limitations, the potential treatment toxicities (primarily bladder and bowel) as well as the need for a daily treatment over 5 weeks needs to be considered. The PORTEC-2 trial in which almost half of the patients were over the age of 70, high-dose rate (HDR) brachytherapy was shown to be equivalent to EBRT for local control in intermediate-high risk disease with a more tolerable toxicity profile in terms of gastrointestinal side effects [27].

A retrospective case series of 113 women over 70 years old (median age 76) who received brachytherapy for stage I–IV cervical cancer reported grade III/IV rectal, small bowel and urinary tract toxicities rates in 1.8%, 0.9% and 2.7% of patients respectively. The 3-year disease-specific survival was 81% [28]. A retrospective study from Japan evaluated outcomes according to age. 132 of the 727 women whom received radical radiotherapy were over 75 years old. In this case series, there was no significant difference in late radiation bladder toxicity between patients aged $\leqslant$64, 65–74 and $\geqslant$75 years old. There appeared to be lower rectal toxicity in the over 75 year old patients group but this may be a reflection of the lower radiation dose delivered in this group (median dose 45 Gy compared to 53 Gy in those under the age of 64). The 5 and 10-year disease-specific survival rates were not significantly different between the three groups [29].

To date, there have been no prospective studies focusing on treatment tolerance and outcomes in older women with endometrial cancer or cervical cancer. Prospective studies including geriatric assessment to evaluate treatment outcomes and tolerability of chemotherapy and radical treatment options such as external beam radiotherapy, brachytherapy and radical hysterectomy specifically in older patients are required.

## Ovarian cancer

The majority of reports related to older women with gynaecological cancers have focused on ovarian cancer.

### *Surgery*

Achieving optimal cytoreduction remains the most significant prognostic factor for ovarian cancer survival [30]. It has been consistently shown that increasing age is associated with lower rates of referral to oncology specialists, lower rates of cytoreductive surgery and lower rates of optimal cytoreduction [31–34].

Neoadjuvant chemotherapy (NACT) with interval debulking surgery has been shown to be associated with higher rates of optimal cytoreduction, lower perioperative morbidity and mortality rates than primary debulking surgery[35,36]. Although the use of NACT remains a highly debated topic, it is generally accepted that NACT maybe a preferable approach for more frail patients including older women who often present very unwell with concurrent medical conditions.

Preoperative assessments have been studied to identify patients with higher perioperative morbidity and mortality. A review from the USA of over 1000 patients demonstrated that 30-day death and serious morbidity rates rose significantly over the age of 60 and was independently associated with a number of pre and peri-operative factors such as pre-operative weight loss, hypoalbuminemia, prolonged operative time, need for transfusion or splenectomy and contaminated wound [37]. A large-single centre study evaluated the predictive ability of the age-adjusted comorbidity index (ACCI) for peri-operative complications, progression-free survival (PFS) and overall survival (OS) following cytoreductive surgery for ovarian cancer. The ACCI incorporates age into the Charlson-Comorbidity index, a validated score to predict 1 year-mortality comprising of 19 medical comorbidities. Taking into consideration stratification for surgical complexity, an ACCI score of 0–1 (low risk) was significantly associated with complete cytoreduction (0–1 = 44%, 2–3 = 32%, $\geqslant$4 = 32%; $p = 0.02$). The ACCI was predictive for PFS and OS but not for rates of minor or major perioperative complications [38].

A retrospective analysis of all patients undergoing primary cytoreductive surgery from three tertiary cancer centres in the USA concluded that a high-risk group could be identified. Age > 75 was one of the factors defining this group as well as high tumour dissemination/stage IV disease, poor performance status as assessed by ASA score (American Society of Anesthesiologists) and poor nutrition (Albumin < 3.0 g/dl). The median overall survival was 17 months in this group ($n = 38$) compared to 40.2 months in the overall study population ($n = 576$) with stage III and IV disease [39].

### *Chemotherapy*

A relatively limited number of retrospective subgroup analyses have been performed to evaluate the outcomes of older patients receiving chemotherapy. For example, in a retrospective analysis of the phase 3 AGO-OVAR 3 study (Carboplatin/Paclitaxel compared to Cisplatin/Paclitaxel in the first-line setting following cytoreductive surgery for advanced ovarian cancer), 103 patients over the age of 70 were compared to the under 70 years group ($n = 676$). Over 80% of the patients in this analysis were ECOG PS 0 or 1 and the mean age of patients over 70 was 73.5 (range 70–85). The authors concluded that combination chemotherapy was tolerable in an older population but discontinuation rates were double in those over the age of 70 compared to the <70 group [40]. The reason for this remains unclear; toxicity rates, except fatigue, did not differ significantly between younger and older patients. Quality of life assessments were undertaken and comparable between the two groups. The authors suggest that there may be a difference in the attitude of investigators when treating older patients with a tendency towards treatment cessation in the event of toxicity rather than treatment delays and instituting supportive care measures in older patients [40]. This could impact on survival of older patients as was recently reported in a retrospective analysis of 184 patients receiving platinum with or without taxane-based chemotherapy for stage II to IV epithelial ovarian cancer. In this study, dose delays but not dose reductions were independently associated with a reduced overall survival in older patients [41]. Another retrospective study showed that reduced-dose carboplatin and paclitaxel was better tolerated in patients over the age of 70 than standard dosing and did not result in a statistically significant difference in overall survival (OS 41 months in the lower dose group versus 44 months in the standard dose group $p = 0.451$) [42].

The MITO-5 trial [43] prospectively addressed first-line dose-dense weekly carboplatin (AUC 2) and paclitaxel (60 mg/m$^2$) in women $\geqslant$70 years and concluded that this approach is a safe and reasonably well-tolerated regimen in older women with 65% of the patients receiving all six cycles. The MITO-7 subsequently compared weekly carboplatin and paclitaxel to the established standard 3 weekly regimen as first-line treatment [44]. There was no significant difference in overall survival. However, the trend towards improved progression-free survival with weekly chemotherapy appeared greater in those over the age of 70.

In the recurrent disease setting, a sub-analysis of older patients within the CALYPSO trial that compared carboplatin in combination with liposomal doxorubicin to carboplatin in combination with paclitaxel in platinum-sensitive ovarian cancer was undertaken [45]. Overall, patients $\geqslant$ 70 ($n = 157$ (16%)) experienced a higher rate of $\geqslant$grade 2 sensory neuropathy (24.4% versus 15.5%, $p = 0.007$) compared to younger patients. Rates of haematological toxicities did not differ between the age groups. Interestingly, $\geqslant$grade 2 allergic reactions were less frequent in older patients than those less than 70 years old (13.9% versus 5.8%, $p = 0.005$). Older patients completed planned treatment as frequently as younger participants and there was no significant difference in median PFS between older and younger patients. Quality of life did not significantly differ according to age. The carboplatin/liposomal doxorubicin combination was associated with less toxicity than carboplatin in combination with paclitaxel (alopecia, sensory neuropathy, arthralgia/myalgia, febrile neutropenia) in older women. However, it is important to note that around 95% of patients 70 years old or over had a PS of 0 or 1 and therefore the applicability of these results to older patients in clinical practice who may have a worse performance status are unclear.

### *Targeted therapies*

#### *Bevacizumab*

Bevacizumab, an anti-VEGF monoclonal antibody, which targets angiogenesis, has EMA approval in combination with chemotherapy as first-line treatment ovarian cancer, for recurrent (platinum-sensitive and platinum-resistant) ovarian cancer. In both phase III ovarian cancer studies of bevacizumab in combination with chemotherapy followed by maintenance treatment in the first line setting, ICON7 [46] and GOG 218 [47], patients were younger than average. In the ICON7 trial, the median age was 57 and recruitment was limited to patients with ECOG PS 0 or 1. There is currently no published data regarding outcomes and toxicities in the older population within this study. In the GOG 218 trial which included patients with ECOG PS 2, the median age was 60 (range

22–89) and 23% of patients were over the age of 70. The improvement in PFS reported in GOG218 with the addition of bevacizumab was also seen in patients over the age of 70.

In the OCEANS trial, a phase III study which demonstrated that the addition of bevacizumab to carboplatin in combination with gemcitabine followed by maintenance therapy improved PFS for first platinum–sensitive relapse, no significant difference in PFS between women aged above (35% of patients, $n = 85$) and below 65 in the bevacizumab arm (12.3 and 12.5 months respectively) was noted [48]. To date, there has been no subset analysis of treatment tolerance according to age published. Post-hoc exploratory efficacy and safety analyses were performed in patients ⩾65 years (37% of patients, $n = 133$) compared to those <65 in the AURELIA trial which assessed the addition of bevacizumab to investigator's choice of chemotherapy in platinum-resistant ovarian cancer [49]. Significant benefits from the addition of bevacizumab in terms of PFS and response rate were seen in both older patients and the younger group (PFS hazard ratio <65 years 0.49; ⩾65 0.47). There were no major differences in toxicities according to age other than hypertension: ⩾grade 2 hypertension was higher in the ⩾65 years group compared to <65 in the bevacizumab-treated arms (31% vs. 13%). In addition, hypertension at baseline prior to trial therapy was also more frequent in patients ⩾ 65 than <65 years (46% vs. 13%)[49]. The OCTAVIA [50] trial, a single-arm study which evaluated the addition of bevacizumab to 3 weekly carboplatin and weekly paclitaxel (80 mg/m2), included 20% and 9% of patients over the age of 65 and 70 respectively. The median PFS was 20.5 months in the ⩾65 s ($n = 37$) compared to 24.4 months in the <65 group ($n = 152$) (95% CI 17.8–20.1 months) [50]. The incidence of grade ⩾ 3 bleeding was higher in older patients (3% vs. 0%, respectively). In keeping with the AURELIA subgroup analysis, hypertension at baseline and on treatment was higher in the ⩾65 s [51].

Hypertension rates reported so far are higher in older patients receiving bevacizumab. Selle et al. recently presented the results of the ROSiA study evaluating extended bevacizumab administration (up to 24 months). 12% of the study population ($n = 121$) were over the age of 70. Baseline hypertension rates were higher amongst older patients (70% vs. 28%), the rates of ⩾3 hypertension were higher (84% vs. 76%), grade 3/4 toxicity were 80% vs. 65% however there was no excess of fatal AEs in the older cohort [52]. Older patients should therefore not be precluded from consideration of bevacizumab however careful monitoring and treatment of hypertension prior to commencing and during therapy is required. This is particularly relevant for an older population in which ischaemic heart and cerebrovascular disease is not uncommon. A meta-analysis of phase 3 studies with bevacizumab in both the first-line and relapse ovarian cancer failed to demonstrate an improvement in PFS in women over 70 (HR: 0.74, CI: 0.54 to 1.02; $p = 0.067$) [53]. This finding needs to be interpreted with caution given the relatively low numbers and nature of the analysis but clearly further studies, specifically targeting older, patients with co-morbidities are required. A study is due to open of first-line Bevacizumab in patients over the age of 70 with advanced ovarian cancer (NCT02393898).

*PARP inhibitors*

PARP inhibitors have shown significant clinical activity in women with BRCA-mutated ovarian cancer and also in a proportion of patients with sporadic high-grade serous ovarian cancer. In the pivotal study that led to the approval of maintenance olaparib in Europe for women with platinum-sensitive ovarian cancer that harbour a *BRCA* mutation (germline or somatic), 23% ($n = 17$) of the BRCA-mutated cohort and 47% ($n = 27$) of the non-BRCA group that received olaparib were ⩾65 years and the oldest patient in the BRCA-mutated group was 89 years old [54]. Although more commonly found in younger women, it is evident that *BRCA* mutations have been identified in patients over the age of 65 [54–56]. Thus far, data on the tolerability and efficacy of PARP inhibitors in the older population have not been presented. Although PARP inhibitors are better tolerated than chemotherapy, toxicities such as fatigue, nausea, neutropenia and anaemia if severe or mild but prolonged, may impact significantly on the functional capacity and quality of life of older patients. PARP inhibitors have also been shown to increase the risk of myelodysplasia [57], potentially of increased relevance in an older population. Long-term follow up of PARP inhibitor studies will help address this issue. In addition, given the current licensed dose and formulation of olaparib, patients receive 16 capsules per day; support for older patients who are likely to also be taking multiple other medications is important for treatment compliance.

## Geriatric assessments in oncology

*Comprehensive geriatric assessment (CGA)*

Comprehensive geriatric assessment (CGA) is a multi-systems review of frailty, comorbidities, geriatric syndromes, mental health, functional difficulties and social circumstances. It is a four-part clinical process of screening, assessment, intervention and follow-through [58] which has been shown to detect more co-morbidities and functional issues than the standard oncological assessment of performance status [23,59]. In non-oncological settings, CGA has been shown to improve function and quality of life [60–62]. In cancer care, CGA has also been shown to predict treatment tolerance [63] and overall survival in a number of tumour types [25,64].

The term CGA has sometimes been used inaccurately in oncology studies describing screening or assessment capacity rather than also including geriatric interventions and follow-through. The International Society of Geriatric Oncology (SIOG) Consensus Guidelines recommend the use of the term Geriatric Assessment (GA) in future research and publications to describe screening and assessment of older patients [64]. Oncological studies utilising and assessing the implementation of GA thus far have been fairly heterogeneous with no clear agreement on the essential parameters that should be included in a GA to assess older patients with cancer. Over a decade ago, SIOG recommended that a CGA-based approach should be utilised to improve the detection of comorbidities and that follow-up of deficits identified be included in any form of CGA intervention [65]. The SIOG consensus on geriatric assessment states that the key domains in a GA considered to be important are: functional status, fatigue, comorbidities, cognitive impairment and mental health status, social support, nutrition and the presence of geriatric syndromes such as falls. To date, there is no one GA tool that has been recommended over another to reliably predict tolerance to cancer therapy or clinical outcomes [64]. It may well be that there is no one tool that is all encompassing for every tumour type and treatment modality.

*Examples of geriatric assessment tools*

Geriatric assessment in the oncological literature has taken a variety of forms including patient-completed questionnaires, healthcare professional-led questionnaires and a combination of both. Biological factors such as hypoalbuminemia, haemoglobin levels and estimated glomerular filtration rate have sometimes been included. The time it takes to perform a GA in the oncology setting is a practical issue and hence there has been much interest in the development of abbreviated and screening tools. For example, it has been shown that the questions from the full activities of

daily living (ADL) and instrumental activities of daily living (IADL) assessments can be condensed from a total of 18 to 6 questions and still recognise 98% of those who had a deficit identified from the full questionnaire [66].

A comprehensive review of all GA tools that have been tested in oncology is beyond the scope of this review and has previously been published [64,67]. Table 3 summarises the key features of the most well described tools used in cancer patients and a selection are briefly described below.

In one of the largest prospective studies undertaken, Hurria et al prospectively assessed the predictive value of a number of geriatric assessment variables for chemotherapy toxicity [63]. 500 patients were assessed with a median age of 73. 17% of the patients included had a gynaecological malignancy. The assessment consisted of the physician evaluated Karnovsky Performance Status (KPS), "Timed up and Go" (a measure of functional status) and a cognitive test. Patients also completed a geriatric-assessment questionnaire evaluating functional status, medical comorbidities, mental state, social activity, social support and nutrition assisted by a healthcare professional when necessary. An 11-point model (CARG) was derived from evaluation of risk factors associated with severe toxicity combined with factors also considered to be important such as chemotherapy dosing (summarised in Table 2). A "high-risk" score was associated with 83% grade 3 or 4 toxicity compared to 30% for a "low-risk" score, highlighting a substantial, clinically relevant rate of severe treatment-related toxicity even in a "low-risk" elderly population. Of note, physician-evaluated KPS was not shown to correlate with risk of chemotherapy toxicity.

The G8 score was evaluated as a screening tool to identify older patients who may benefit from a full CGA in a prospective study that included 364 patients with solid malignancies over the age of 70 [68]. G8 consists of a brief questionnaire of 8 questions (7 of which are derived from the mini nutritional assessment (MNA)) with each individual score ranging from 0 to 2 and a total maximal score of 17. A cut-off value of 14 or less was identified as providing reasonable sensitivity for requiring a full CGA. In the most recent SIOG recommendations, G8 was evaluated as one of the most reliable and sensitive of the screening tools available [69] to predict the need for a full CGA.

### *The impact of geriatric assessment on decision-making and treatment outcomes*

Although Geriatric Assessment Tools can identify deficits that may not have been picked up in a routine oncological assessment, the impact of the additional information provided on treatment decision-making and more importantly, improving outcomes for older cancer patients is difficult to assess and not fully established [65].

In a prospective pilot, of 168 patients with gastrointestinal or lung cancer over the age of 70 deemed eligible for CGA, only 29% were referred for assessment. CGA altered the existing treatment plan in 1 out of 24 patients and influenced decision-making in a further 5 out of 6 patients whom did not have a management plan at the time of referral [70]. In a prospective study that included 937 cancer patients over the age of 70, GA was undertaken prior to the commencement of either first line or treatment at relapse. In 56% of patients, the GA was consulted before making a treatment decision but in only 6.1% did the GA further influence the treatment decision suggesting that clinical assessment by the treating oncologist remains dominant in the decision-making process in the majority of cases [71]. In contrast, in a cohort study of 161 older men and women (mean age 82.4), GA influenced treatment decisions in 49% of cases. For 57% of these patients, the change was to increase intensity of therapy [72]. A similar pilot study undertaken in France of 105 patients with a median age of 79 demonstrated that the results of a GA consisting of a screening questionnaire undertaken by an oncologist with geriatric training influenced the treatment decision in 38.7% of patients [73].

Kalsi et al undertook a prospective cohort-controlled study of patients over the age of 70 being considered for systemic therapy for solid-organ malignancies [74]. All patients completed a

**Table 2**
Chemotherapy studies in the elderly population.

| Study | Inclusion Criteria | Regimens assessed | *n* | Key points |
|---|---|---|---|---|
| GINECO [78] | >70 years<br>Stage III/IV | Carboplatin/Liposomal Doxorubicin | 83 | Post-hoc analysis.<br>75% patients completed planned 6 cycles<br>ECOG PS not predictive for survival |
| GINECO – analysis of two consecutive trials [79] | >70 years<br>Stage III/IV | Carboplatin/paclitaxel | 75 | Prospective study.<br>68% Patients completed planned 6 cycles.<br>Depressive symptoms at baseline predictive for OS |
| AGO-OVAR [40] | >70 years | Carboplatin/paclitaxel vs. cisplatin/paclitaxel | 103 | Post-hoc analysis.<br>High proportion of PS 0/1<br>No difference in quality of life<br>Older patients more likely to discontinue treatment early despite comparable reported toxicity rates |
| MITO-5 [43] | >70 Stage IC-IV | Dose-dense weekly Carboplatin/weekly Paclitaxel | 27 | Prospective study.<br>65% Patients completed planned six cycles<br>Favourable toxicity profile |
| GINECO/GVS [80] | >70 years<br>Stage III/IV | Carboplatin Monotherapy (AUC 5) | 109 | Prospective study.<br>74% patients completed planned 6 cycles.<br>Results have informed design of prospective study utilising GVS score |
| GOG0273 [81] | >70 years | I: Carboplatin AUC5 and Paclitaxel 135 mg/m2 or II: Carboplatin AUC 5 3 weekly for 4 cycles | 208 | Prospective study.<br>Physicians choice of regimen I or II<br>IADL not associated with ability to complete chemotherapy without delay or dose reduction<br>Limitation of social activities associated with decreased tolerance to chemotherapy<br>3rd arm of weekly Paclitaxel added; results awaited. |

*Abbreviations:* AUC, area under the curve; ECOG PS, eastern cooperative oncology group performance status; OS, overall survival; PFS, progression-free survival; GVS, geriatric vulnerability score; IADL, instrumental activities of daily living.

**Table 3**
Abbreviated geriatric assessment tools.

| GA Tool | Domains assessed | Comments |
|---|---|---|
| C-SGA.<br>SAKK cancer-specific geriatric assessment [99] | Age-adjusted Charlson Comorbidity Index (CCI)<br>Vulnerable Elders Survey (VES-13)<br>Geriatric Depression Score (GDS-5)<br>Modified MOS – Social Support Survey (mMOS-SS)<br>Mini-Cog | Feasibility study. Mean time for pt. to complete questionnaire – 17.33 ± 7.34 vs. 20.59 ± 6.53 minutes for physicians<br>No biochemical/laboratory based parameters<br>No assessment of correlation between toxicity/mortality, only feasibility of completion. |
| GAH.<br>Geriatric assessment in haematology [100] | Number of drugs<br>Gait speed<br>Depression score (single-question)<br>3 ADL questions (from VES-13)<br>Subjective health status<br>4 items from MNA-SF (BMI, Weight loss during last 3 months, food intake decline over past 3 months, psychological stress/acute disease<br>SPMSQ (short portable mental status questionnaire)<br>Prognostic index for 4-year mortality in Older adults | 363 patients newly diagnosed with haematological malignancies.<br><br><br>Internally validated and reproducible.<br>Not validated in solid-organ malignancies<br>Mean time to complete 11.9 ± 4.7 min |
| CRASH<br>The chemotherapy risk assessment scale for high-age patients [25] | Haematological Toxicity:<br>Diastolic BP<br>IADL<br>LDH<br>Chemotox score (scoring System 0–2 based on relative toxicity; for example, carboplatin/pemetrexed = 1)<br><br>Non-Haematological Toxicity:<br>ECOG Performance status<br>MMSE<br>MNA<br>Chemotox score | 460 patients.<br>Valid across a large number of chemotherapy regimens<br><br>Incorporation of potential toxicity of treatment into the risk scoring (MAX2 index).<br>Predictive for toxicity |
| G8 [68] | Nutritional (derived from MNA)<br>Weight loss during last 3 months<br>Mobility<br>Neuropsychological/Dementia<br>BMI<br>Polypharmacy (>3 drugs/day)<br>Patient comparison of health status compared to others of their age<br>Age | Validated first as a surrogate for CGA.<br>202 patients over the age of 65 included with self-completed questionnaires across all tumour types.<br><br>Patients with a low G8 score of $\leqslant$14 were more likely to experience severe chemotherapy toxicity than those with a high G8 score: 64.6% vs.46.9% ($\chi 2 = 5.029$, $p = 0.025$) |
| CARG [63] | 1. Age: >72 years<br>2. Cancer type: GI or genitourinary<br>3. N° of chemotherapy drugs: polychemotherapy<br>4. Chemotherapy dosing: standard dose<br>5. Haemoglobin: <11 g/dL (male); <10 g/dL (female)<br>6. Creatinine clearance: <34 mL/min (Jelliffe, ideal weight)<br>7. Hearing: fair or worse<br>8. N° of falls in the last 6 months: $\geqslant$1<br>9. IADL: taking medications with some help or unable to take medication<br>10. Walking one block: somewhat limited or limited a lot<br>11. Decreased social activity because of physical and/or emotional health | Predictive score derived from prospective analysis of 500 patients over the age of 65 with various cancers.<br>Mean age 73.<br>Low (0–5) Intermediate (6–9) and High (10–19).<br>Predictive for chemotherapy related toxicity. |
| GVS/GINECO[80] | Age<br>ECOG Performance status<br>Hypoalbuminemia<br>Lymphopenia<br>Functional: ADL, IADL<br>Depression: HADS | Predictive for chemotherapy related toxicity.<br><br>Deficit in 3 or more covariates results in a RR of mortality of 2.94. |

*Abbreviations:* ADL, activities of daily living; MNA-SF, mini-nutritional assessment short form; BP, blood pressure, IADL, instrumental activities of daily living; LDH, lactate dehydrogenase; MMSE, mini mental state examination; MNA, mini nutritional assessment; BMI, body mass index; HADS, hospital anxiety and depression scale.

screening questionnaire (CGA-GOLD) and a quality of life (QoL) questionnaire (EORTC-QLQ-C30). In the intervention arm ($n = 65$), patients considered high-risk (1 or more active comorbidity, CGA deficit, significant QoL or functional difficulty) received geriatrician-led CGA. 70.7% patients were assigned to CGA in the intervention arm. As a result, the mean number of interventions was 6.6. In the intervention arm, 33.8% of patients completed chemotherapy as planned compared to 11.4% in the control arm ($p = 0.0006$) with a non-significant trend towards reduced grade 3 toxicity in the intervention arm (43.8% versus 52.9% in the control arm ($p = 0.292$). This study was not powered to detect a survival benefit from CGA intervention but was the first study to demonstrate a benefit from the use of CGA in terms of chemotherapy tolerance. The majority of patients included in this study were undergoing treatment for a gastrointestinal malignancy. It is not known whether this approach would be implementable and successful in gynaecological cancers but is worthy of consideration. In a phase IIIl study of patients over the age of 70 with stage IV non-small cell lung ($n = 494$), patients were randomized to treatment allocation according to standard assessment using age and ECOG performance status or according to the outcome of a cancer physician-led CGA. The primary outcome was treatment failure-

free survival (TFFS) with secondary endpoints of OS, PFS, tolerability and quality of life. According to the outcome of the CGA, patients were classed as fit, vulnerable or frail. Frail patients received best supportive care where fit patients received a platinum-doublet (according to histological subtype) and vulnerable patients received single-agent Docetaxel. No significant difference was found between either group in either TFFS, PFS or OS. The CGA group experienced less toxicity and improved treatment-tolerability however (treatment failure due to toxicity 4.8 vs. 11.8%, $p = 0.007$). Crucially this study did not involve any form of intervention to address issues identified in the CGA [75].

*Studies incorporating geriatric assessments in gynaecological malignancies*

Both surgical and medical studies of GA specifically in gynaecological cancers have been limited. The largest surgical retrospective review in ovarian cancer assessed 751 patients over an 8-year period who underwent primary surgery [76]. The rate of major complications (as defined by a grade 3–5 complication on the validated clavien-dindo classification) was 16.4%. Ascites, pre-operative hypoalbuminemia, raised white cell count and raised serum creatinine were all associated with an increased likelihood of a major post-operative complication. The authors propose a predictive model of post-operative complications in older patients following primary cytoreductive surgery based on the above, also including smoking status, ethnicity, haematocrit and platelet count. Prospective validation studies are necessary and application of a similar approach to NACT and interval debulking surgery would be useful.

A prospective study which addresses whether a pre-operative risk stratification score (GA-GYN) collated from a number of geriatric variables collected at baseline will predict for perioperative morbidity in patients over the age of 70 who are planned to receive primary cytoreductive surgery for epithelial ovarian cancer is currently recruiting (NCT02315469).

PACE, a pre-operative assessment tool in elderly cancer patients is an approach recommended by SIOG for adoption in routine clinical practice [77]. A study of 460 consecutive patients over the age of 70 undergoing elective cancer surgery for a variety of solid organ tumours was undertaken to assess the predictive capability of a complete geriatric assessment. The geriatric tools used at baseline were MMSE, ADL, IADL, GDS, BFI (brief fatigue inventory), ECOG PS, ASA and Satariano's index of comorbidities. IADL, moderate to severe BFI, abnormal ECOG PS (>1) predicted 30-day morbidity and mortality [77]. Of note, the full assessment undertaken by a specialist nurse or student doctor, took 20 min which may be considered feasible in routine pre-operative assessment clinics.

A retrospective pooled analysis of 83 patients over the age of 70 enroled into a GINECO group study assessing Carboplatin and Cyclophosphamide (CC) [78] and a further 75 patients over the age of 70 enroled into a subsequent study evaluating Carboplatin and Paclitaxel (CP) was performed to provide a multivariate analysis of predictive factors for survival in older patients [79]. Elements of a geriatric assessment were performed at baseline including Mini-mental state examination (MMSE, regarding a score >24/30 as normal), polypharmacy, patient dependence as well as ECOG PS and baseline routine blood tests. In the CP group, a Hospital Anxiety and Depression score (HADS) and Instrumental Activities of Daily Living Score (IADLS) were also performed. 75% of patients in the CC group and 68% in the CP group completed the planned 6 cycles of chemotherapy without severe toxicity. The only reported statistically significant prognostic factor for overall survival was the presence of depressive symptoms at baseline. No specific predictive factors for toxicity including age and ECOG PS were determined.

A further study from the same group led to the development of the Geriatric Vulnerability Score (GVS) [80]. 111 patients with a median age of 79 (range 71–93, 41% of whom were over the age of 80) and a diagnosis of advanced epithelial ovarian cancer received single-agent Carboplatin at AUC5. 74% of patients completed the planned 6 cycles; 10 patients stopped treatment early due to toxicity and 5 patients subsequently died from toxicity-related complications. The GVS survival score developed retrospectively is a sum of five covariates (ADL, IADL, Lymphopenia, HADS (Hospital Anxiety and Depression scale) and hypoalbuminemia)) each assigned a value of one. A deficit in 3 or more covariates resulted in a risk ratio of mortality of 2.94 ($p = 0.0006$). This cut-off, also discriminated two groups with significantly different treatment completion, severe adverse events and unplanned hospital admissions rates [80]. The GINECO group are currently recruiting to a prospective phase 2 study evaluating standard 3 weekly dosing of Carboplatin and Paclitaxel, single-agent Carboplatin (AUC 5 or 6) every 3 weeks and dose dense weekly Carboplatin (AUC2) and weekly Paclitaxel (60 mg/m2) in patients over the age of 70 with a GVS score of $\geqslant 3$ (NCT02001272). To date, there are no clinical studies evaluating the role of GA in endometrial, cervical cancer or recurrent ovarian cancer.

A prospective cohort study, GOG-0273 [81], evaluated the role of geriatric assessment to predict toxicity to one of two regimens, single-agent carboplatin or carboplatin/paclitaxel (patient and physician's choice) as first line therapy. In this study, rates of completion of 4 cycles of chemotherapy were higher in the combination cohort (92% combination arm vs. 75% single agent). Overall, the patients in the combination cohort were younger (mean age 73 versus 83) and fitter (PS 2 or 3 11% combination arm versus 37% single agent). In this study, IADL was not found to correlate with tolerance to chemotherapy. However, limitation in social activities was significantly associated with reduced chemotherapy tolerance. A 3rd arm consisting of weekly Paclitaxel has been added and is currently recruiting.

## Biological markers of frailty

The development of biological markers of frailty that have the ability to successfully differentiate between older patients who are fit for cancer therapies and those who are more at risk, predict toxicity and survival outcomes is much needed. This area remains relatively under studied but some of the potential biomarkers will be discussed here.

IL-6 has been shown to be independently associated with increased rates of cognitive impairment and steeper cognitive decline in a study of elderly patients (median age 75) with a history of cardiovascular disease [82]. CRP, IL-6 and IL-1RA have also been shown to be associated with worse physical performance in a prospective Italian study of over a thousand older participants [83]. The Women's Health and Ageing (WHAS 1) study demonstrated that the presence of high levels of IL-6 and low levels of insulin-like growth factor (IGF1) in a population of women aged 65 years or more with moderate or severe disability were associated with an increase in 5 year mortality [84]. So far, the significance of the above markers in older cancer patients is not known.

Telomeres are short segments of DNA at the end of chromosomes, which, with each successive mitotic division shorten by a process of telomerisation to reduce the risk of replication errors and therefore maintain DNA integrity. Causes of oxidative stress such as smoking may increase the rate of telomere loss. This has led investigations as to whether telomere length may be a marker of "biological age" rather than chronological. Short telomere length has been associated with several diseases of ageing such as cardiovascular disease [85] but has yet to be consistently associated with

increased mortality in older patients [86,87]. Shorter telomere length has been associated with reduced survival from soft tissue, breast, lung and colorectal cancer [88–92].

Two studies have explored the potential significance of telomere length in ovarian cancer. The first study used PCR-based techniques to assess telomere length from peripheral blood leucocytes in 1042 women with a diagnosis of ovarian cancer from the Ontario Cancer Registry. No correlation between relative telomere length and ovarian cancer survival was noted ($p = 0.55$) [93]. However, the GINECO group recently reported that in older patients with ovarian cancer, shorter telomere length was associated with increased chemotherapy related toxicity, increased unplanned hospital admissions, serious adverse events and grade 3–4 non-haematological toxicity. Shorter telomere length was also associated with an increased risk of premature death [94]. Further studies in this area are warranted to clarify the clinical relevance.

The secretion of cytokines/chemokines and soluble factors such as cathelin-related antimicrobial peptide (CRAMP) and Chitenases [95] have also been shown to be associated with replicative senescence. It remains to be seen whether a single frailty biomarker or indeed a panel of biomarkers adds any further information to either CGA or an abbreviated geriatric assessment.

## Steps to improving outcomes in older patients

In an international study commissioned by the NCEI/POI collaboration, clinicians from a group of countries (UK, Canada, Sweden, Germany, Denmark and Spain) when asked via a questionnaire on the key factors used in order to be able to decide a patient's fitness for systemic therapy reported that biological age, performance status and comorbidities were all more influential than chronological age. This is in contrast to the results seen from case studies submitted to the same audience where chronological age was seen to be the main determining factor on whether to subject a patient to higher intensity treatment. This suggests that, attitudes towards treating older patients are already in favour of assessing biologically rather than chronologically but in the absence of a proven, validated tool to predict frailty and toxicity from treatment, chronological age remains a crucial determinant of treatment decisions [96].

An ongoing lack of evidence in the area has led to the convening of an ASCO subcommittee in 2015 to develop recommendations to improve the evidence base for treating older adults with cancer [21]. These were fivefold: "(1) Use clinical trials to improve the evidence base for treating older adults with cancer, (2) leverage research designs and infrastructure for generating evidence on older adults with cancer, (3) increase US Food and Drug Administration authority to incentivize and require research involving older adults with cancer, (4) increase clinicians' recruitment of older adults with cancer to clinical trials, and (5) use journal policies to improve researchers' reporting on the age distribution and health risk profiles of research participants". The importance of improving outcomes for older patients including women with gynaecological cancers is gaining international recognition and is a priority for oncology organisations including ESMO and ESGO.

Better education of oncogeriatric issues for not only oncologists but all health care professionals involved in the multidisciplinary management of older patients is much needed. Not all cancer centres currently have the infrastructure and resources to refer all older cancer patients to a geriatric specialist department. A significant step would be working towards implementing the use of a GA tool in oncology clinics and cancer teams considering which interventions (e.g. occupational therapy, physiotherapy, polypharmacy management) are achievable in clinical practice currently and desired for the future.

An internationally accepted consensus agreement on one CGA to be used for all older cancer patients is yet to be reached. It may well be however that this is unattainable in the near future. The impact of factors such as comorbidities and functional limitations on outcomes is likely to be influenced by the treatment modality and tumour type and therefore more than one tool may be applicable. A good starting point for both clinical practice and clinical trials is to include some form of GA. The key domains to be evaluated when assessing older women with gynaecological malignancies for all treatment modalities are: 1. Function and mobility (as assessed by ADL, IADL, self-reported falls, "timed-up and go" test), 2. Comorbidities (e.g. Charlson comorbidity index or Cumulative illness rating scale – geriatrics, 3. Cognition (e.g. MMSE, min-COG), 4. Pyschological (e.g. Geriatric depression scale or hospital anxiety and depression scale), 5. Nutrition (e.g. mini-nutritional assessment, BMI, serum albumin), 6. Performance status (ECOG PS, Karnovosky), Social support eg. (MOS social support survey) [65,67]. Clinical trials in older patients should be encouraged to include a form of Geriatric Assessment. A challenge will be the application of results in clinical practice if multiple different GAs are utilised in different clinical trials.

Prospective studies evaluating and validating the currently available screening/abbreviated geriatric scores as a risk prediction method for morbidity, toxicity and mortality from surgery, chemotherapy or radiotherapy would help to build the evidence base for the risk predicting ability of these tools in gynaecological malignancies and help rationalise which older patients should undergo full multidisciplinary CGA.

The major gap in the current evidence base, continues to be whether or not undertaking full CGA including interventions and follow-through with a multidisciplinary team impacts on tolerance to treatment, survival or improved quality of life for older women with gynaecological malignancies. Randomised, multi-centre prospective studies comparing current standard practice to including geriatric assessment and interventions in decision-making are required. One of the challenges is the reproducibility of assessments and interventions.

The endpoints of clinical studies specifically in older patients need to be considered. OS has been the gold standard endpoint for treatment trials but disease-specific survival should also be collected as death in older patients can be due to other diseases and toxicities. Functional dependency, toxicities (acute and chronic) and quality of life are being increasingly recognised as important outcomes specifically for the older population along with more conventional, 'standard' endpoints such as PFS and OS. 'Active life' expectancy (e.g caring for grandchildren, working) should also be recorded. Trials in older patients incorporating some of the above as composite and/or co-primary endpoints are warranted [97] with the aim of then introducing these into future clinical trials irrespective of age so that appropriate sub-group analyses can be undertaken prospectively in older patients.

Finally, the incorporation of biobanking patient material into prospective clinical studies involving older patients is essential to better understand the potential role these biomarkers may play.

## Conclusion

There has been much progress in the development of both screening geriatric assessments and full comprehensive geriatric assessment in oncological patients over the past decade. However, full, Geriatrician-led CGA with follow-up has yet to be demonstrated to improve outcomes treating older patients with gynaecological cancers. It also has significant resource implications and this has led to the interest in developing abbreviated geriatric assessments, primarily thus far, to attempt to risk stratify older

patients into those who are likely to suffer from excess toxicity. An ageing population and the rising incidence of gynaecological malignancies with increasing age means that all oncologists will be treating a population with a substantial number of older, potentially frailer patients and expertise in geriatric oncology will be increasingly required for the majority of practicing oncologists. Further education is needed for oncologists in the assessment of older patients and the management of common issues affecting older patients that may impair their ability to tolerate cancer treatment and have long-term consequences. The results of Elderly Women Ovarian Cancer (EWOC)-1 are eagerly awaited to better inform the first-line treatment of older patients. Given the majority of stage III and IV gynaecological cancer patients will relapse, there is an urgent need for studies in the recurrent setting. Finally, collaboration and integration with geriatric experts are critical for the success of improving outcomes for older women with gynaecological malignancies.

## Conflict of interest

The authors declare no conflict of interest.

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## 8.3 Dumas L et al. Exploring older women's attitudes to and experience of treatment for advanced ovarian cancer: a qualitative phenomenological study. Cancers 2021

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# Exploring Older Women's Attitudes to and Experience of Treatment for Advanced Ovarian Cancer: A Qualitative Phenomenological Study

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**Simple Summary:** Older women with ovarian cancer often receive less anti-cancer treatment than younger women despite evidence showing they may benefit from similar levels of treatment. Little is known, however, about older women's preferences toward chemotherapy and treatment experience. We aimed to understand the lived experience of older women with ovarian cancer undergoing chemotherapy though interviews and focus groups. Participants expressed a strong desire to undergo full treatment to improve survival for themselves and for their families. Women did not see their age as a reason to have less intensive treatment. Despite feeling overwhelmed with information and daily tasks due to fatigue, participants did not want cancer to interfere with their daily lives. Women felt distressed by logistical issues with transportation and communication between healthcare providers; however, they still felt positive about their care experience and desire for treatment. Older women may benefit from additional help to support effective communication around treatment preferences.

**Abstract:** Older women with ovarian cancer more often receive less intensive treatment and early discontinuation compared to younger women. There is little understanding of older women's treatment experience and whether this contributes to declining intensive treatment. We aimed to explore the lived experience of older patients with advanced ovarian cancer undergoing chemotherapy, their treatment preferences and treatment burden. We conducted a phenomenological qualitative study with 15 women who had completed at least three cycles of first-line chemotherapy for advanced epithelial ovarian cancer, aged 65 years or older at the first cycle, at one tertiary cancer centre. We conducted interviews and focus groups and analysed the transcripts using inductive thematic analysis. Women reported a strong preference for active treatment despite treatment burden and toxicities. Participants undertook treatment to lengthen their lives for themselves and their families. Participants did not see age as a barrier to treatment. Patients expressed determination not to let cancer interfere with daily life. Women felt overwhelmed with information and struggled with daily tasks due to fatigue. Logistical issues, such as transportation and ineffective communication between healthcare providers, caused substantial distress. Despite these logistical burdens and toxicities, participants were positive about their care experience and desire for anticancer treatment. Older women may benefit from additional support to facilitate effective communication during the early stages of treatment.

**Keywords:** ovarian cancer; qualitative research; thematic analysis; geriatric; lived experience; treatment preference; chemotherapy



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## 1. Introduction

Research has established that older women with ovarian cancer have disproportionately poorer survival outcomes than younger women [1]. Older women receive less intensive treatment which may in part may explain the discrepancy [2–5].

Some of this variation is likely due to clinicians appropriately not pursuing intensive treatment with older women at higher risk of treatment toxicity [6]. However, without utilising an objective geriatric assessment, as recently recommended in American Society of Clinical Oncology guidance [7], older patients' fitness may be underestimated or modifiable risk factors may not be addressed leading to unnecessary under-treatment. In these cases, psychological and practical factors, including inherent age bias, may contribute to the provision of less intensive care [8]. The Elderly Women with Ovarian Cancer (EWOC-1) study demonstrated that in women over age 70, standard three-weekly carboplatin with paclitaxel chemotherapy was superior to single-agent three-weekly carboplatin without significant compromise on tolerability. The findings strongly support offering combination chemotherapy in newly diagnosed older women as in younger patients [9].

From the patient perspective, it is unclear if treatment burden encourages older women to decline intensive treatment, further contributing to treatment variation. Previous research has found there is no difference between older and younger women's desire for cure from gynaecological cancers and older patients often choose to undertake additional treatment for survival benefits [10,11]. While research has found that older adults tend to place more value on quality of life than younger cancer patients, older patients still place importance on survival [12–14].

To help better understand the treatment preferences and treatment experiences of older women with advanced ovarian cancer undergoing chemotherapy, we explored these topics in a qualitative phenomenological study.

## 2. Materials and Methods

Patients currently receiving chemotherapy for advanced epithelial ovarian cancer or in follow-up at the Royal Marsden NHS Foundation Trust were identified in clinic lists by the treating team between April and July 2019. Eligible women were aged 65 years or older at the time of their first chemotherapy cycle, had completed at least three cycles in the first line setting or at relapse, and were proficient in English. This age threshold was chosen to align with the American Society of Clinical Oncology guidance on the management of older patients being considered for systemic anti-cancer therapy and the European Medical Association cut-off from a pharmacovigilance perspective [7,15]. Patients with significant cognitive impairment, mental health problems or severely unwell, as determined by the clinician, were ineligible. Care was taken to invite patients that were unwell but potentially fit enough to participate where possible. Recruitment occurred concurrently with data analysis. Participants were purposively sampled for breadth in disease and toxicity severity. Potential participants were posted patient information sheets followed-up by telephone after one week.

Participants chose to take part in focus groups or individual interviews facilitated by two of the authors (EL or LD). The authors chose to use both methods of data collection for data completeness. Interviews allowed the researchers to explore personal experiences in-depth, while focus groups elicited shared and discordant opinions and beliefs [16]. Individual interviews also enabled women who were too unwell to attend the focus group to take part in the study, a key group of interest in this study. Participants provided written informed consent and completed a short background questionnaire before taking part. Focus groups took place in hospital meeting rooms. Facilitators followed a semi-structured interview schedule which was reviewed by patients and members of the public (Table 1). Discussions were audio-recorded. Field notes were taken during focus groups.

**Table 1.** Semi-structured interview schedule.

| Question |
| --- |
| 1. What were the biggest challenges you faced while receiving treatment? |
| 2. Do you feel, before starting treatment, that you had a good idea of the potential risks and benefits of treatment? |
| 3. Is there any information you wish you had received that you didn't prior to starting chemotherapy? |
| 4. What were your main goals of treatment/Why did you decide to have treatment? |
| 5. How much did the opinions of your clinicians impact on your decision to have treatment? |
| 6. How much did the feelings and opinions of your family and friends impact on your decision to have treatment? |
| 7. Knowing now the side-effects you have experienced, would you make the same decision again to undergo treatment? |
| 8. When you think about your health, what would you say the term quality of life means to you? |
| 9. With that in mind, in what ways has your diagnosis and treatment for ovarian cancer affected your quality of life? |
| 10. If you experienced side effects during treatment, did you feel well-supported? |
| 11. How well do you think your GP * and other community teams were kept informed of your progress during treatment? |

* general practitioner.

The Royal Marsden Committee for Clinical Research reviewed and approved the study in October 2018 (SE764). The data that support the findings of this study are available from the corresponding author upon reasonable request.

Analysis followed the six phases of inductive thematic analysis described by Moules: (1) engaging with the data, (2) generating initial codes, (3) identifying themes, (4) reviewing themes, (5) defining and naming themes and (6) writing the report [17].

Audio recordings were transcribed verbatim. LD and EL conducted initial coding, following Saldana's techniques [18]. To reduce bias, each researcher undertook initial coding independently before reviewing and agreeing final initial codes. Researchers consulted field notes while generating initial codes and during reconciliation to justify code choice.

The agreed initial codes and related excerpts were then manually analysed by LD and EL to identify potential themes and subthemes. Again, field notes added further insight to analytical decisions. The study team reviewed potential themes and subthemes to assess coherence and relevance. LD conducted two further telephone interviews at this stage. LD and EL independently coded the new transcripts and checked the codes against existing data. As no new codes were identified, the study team felt confident in theoretical saturation and data collection ended [19]. Themes and subthemes were then reviewed by the whole study team to refine the names and definitions.

## 3. Results

Of 36 eligible patients invited to the study, 15 agreed to take part (Figure 1). Reasons for declining the study included time or logistical constraints, burden of hospital appointments and feeling too unwell. Focus groups each took two hours whilst interviews ranged from 29 to 60 min.

Table 2 summarises the participant characteristics. Mean age at diagnosis was 75.0 years (range 68–89 years). Mean age at participation was 78.4 years (range 71–90 years). Twelve (80%) participants received standard three-weekly carboplatin and paclitaxel chemotherapy as first-line treatment and nine (60%) received treatment for relapsed disease. Three (20%) patients received single-agent carboplatin. In total, 4 (27%) patients required a dose-reduction during chemotherapy due to toxicity. In total, 4 (27%) had caring responsibilities for a family member. Six of the 15 patients were receiving chemotherapy at the time of study entry (all for recurrent disease). The remaining nine were in follow up, six following first-line treatment and three following treatment for recurrent disease.

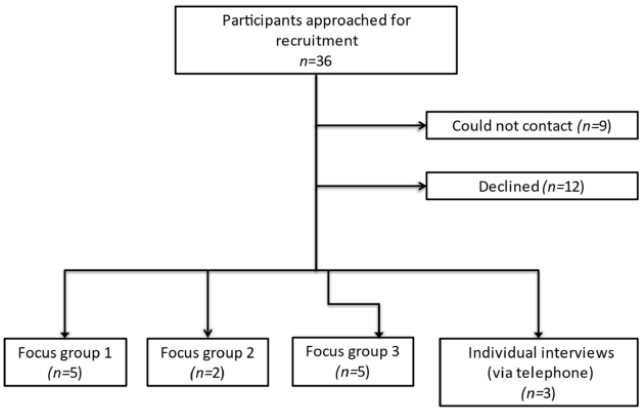


**Figure 1.** Flowchart of participant recruitment.

**Table 2.** Patient characteristics.

| Patient Characteristic | *n* | (%) |
|---|---|---|
| Living situation | | |
| Lives alone | 6 | (40.0) |
| Lives with spouse | 6 | (40.0) |
| Lives with other family members | 2 | (13.3) |
| Lives in sheltered accommodation | 1 | (6.7) |
| Has caring responsibilities | 4 | (26.7) |
| Employment status | | |
| Retired | 14 | (93.3) |
| Financial impact | | |
| Cancer has had no financial impact | 13 | (86.7) |
| Cancer has had a little financial impact | 2 | (13.3) |
| Stage at diagnosis | | |
| 1 | 0 | (0) |
| 2 | 4 | (26.7) |
| 3 | 9 | (60.0) |
| 4 | 2 | (13.3) |
| Primary treatment | | |
| Platinum doublet chemotherapy | 12 | (80.0) |
| Single-agent carboplatin | 3 | (20.0) |
| Surgery | 11 | (73.3) |
| Primary treatment tolerance | | |
| No delays | 6 | (40.0) |
| Delay 1 week or less | 3 | (20.0) |
| Delay >/= 2 weeks | 2 | (13.3) |
| Dose reduction at beginning | 0 | (0) |
| Dose reduction during chemotherapy | 4 | (26.7) |
| Has had disease recurrence | 8 | (53.3) |
| Second line treatment | | |
| Chemotherapy (doublet) | 3 | (20.0) |
| Chemotherapy (single agent) | 2 | (13.3) |
| Clinical Trial | 2 | (13.3) |

Initial codes were incorporated into three themes: Multifactorial decision-making, burden of logistical issues and coping with side effects.

### 3.1. Theme: Multifactorial Decision-Making

#### 3.1.1. Subtheme: Reception and Retention of Information Clouds Decisions

Participants frequently felt overwhelmed by the volume of information shared at diagnosis and memories around diagnosis were often unclear. Shock at the diagnosis, particularly for patients who had enjoyed relative health throughout their lives, was apparent and contributed to feeling overwhelmed.

*"When you're first diagnosed, it's such a shock to you, you don't absorb everything that's being said."*

*(Patient 4, 82 years at diagnosis, receiving first-line chemotherapy)*

*"I sort of went into zombie mode, it never occurred to me to say no."*

*(Patient 12, 70 years at diagnosis, in follow up from first-line chemotherapy)*

Fatigue and severe illness further inhibited understanding of complex information and involvement in treatment decisions. Participants appreciated pamphlets received during their first appointments, but many admitted not reading them.

*"I was desperately tired at this stage and an awful lot of information is given to you".*

*(Patient 14, 72 years at diagnosis, in follow up from first-line chemotherapy)*

Participants felt decisions, including clinical trial participation, were rushed due to pressure to start treatment. For most, this was a stressor, however, one woman felt it reduced the worry around the decision.

*"Well I had to make the decision on the spot . . . so there was no time to think about it."*

*(Patient 14, 72 years at diagnosis, in follow up from first-line chemotherapy)*

For some participants, the internet was a crucial source of information, challenging the notion that older patients are less adept with technology. In contrast, some participants felt strongly that information found online, particularly around prognosis, would be unhelpful and cause distress.

*"I can't bear looking on the internet, I just don't want to know."*

*(Patient 8, 69 years at diagnosis, receiving chemotherapy for relapsed disease)*

This avoidance was more frequently expressed by patients who had relapsed disease. Others wanted more information, with uncertainty around prognosis a clear source of anxiety.

*"You've gone through six months of chemo feeling blimmin awful for no . . . you know, nobody knows the answer."*

*(Patient 2, 78 years at diagnosis, receiving chemotherapy for relapsed disease)*

#### 3.1.2. Subtheme: Lengthening Life Expectancy

An important, common expression was the clear determination to be treated with no reference to age or comorbidities. A sense of deciding between life and death was apparent and participants worried that age might be considered to be a reason against treatment.

*"I was told I could go profoundly deaf . . . but I had to take that chance."*

*(Patient 7, 74 years at diagnosis, in follow up from first-line chemotherapy)*

*"I would have done anything to have treatment, gone through anything."*

*(Patient 1, 77 years at diagnosis, in follow up from first-line chemotherapy)*

Many participants feared treatment reduction or discontinuation. One patient suffering from severe peripheral neuropathy with significant functional limitation admitted needing persuasion to allow chemotherapy dose-reduction, fearing this would shorten her life-expectancy. Negative impacts on functional ability and quality of life did not appear to deter women from treatment.

*"I'd still want to be alive because there's other things I'm sure I'd be able to do."*

*(Patient 1, 77 years at diagnosis, in follow up from first-line chemotherapy)*

One participant, who had not received full standard chemotherapy and cytoreductive surgery owing to anaesthetic risk, expressed disappointment. All participants, when asked individually, agreed they would undertake treatment again given their experience with treatment and side-effects so far.

#### 3.1.3. Subtheme: Family Influence

Participants commonly reported that they underwent treatment for their family members, rather than themselves. Women often expressed concerns about the ramifications of their death on their family. For some participants, adult children played an active role in treatment decisions.

*"They didn't want me to have six months or less to live, it's not nice for them knowing one's going to die so that's why they said yes to chemo, to see how much longer it would give them."*

*(Patient 2, 78 years at diagnosis, receiving chemotherapy for relapsed disease)*

Participants caring for dependent spouses faced additional pressure during treatment.

*"I think the thing that put most pressure on me was my husband being ill."*

*(Patient 13, 76 years at diagnosis, in follow up after first-line chemotherapy)*

Patients with dependent spouses also expressed concern over how their spouse would manage without them. Worry that their spouse would become a burden to their children with their death compelled some women to undertake treatment.

*"I want to be here for him, rather than leaving him for my family to look after"*

*(Patient 2, 78years at diagnosis, receiving chemotherapy for relapsed disease)*

### *3.2. Theme: Burden of Logistical Issues*

#### 3.2.1. Subtheme: Care Coordination

Generally, participants felt they had excellent care and support from the cancer centre and expressed sincere gratitude.

*"It's like a blanket around you isn't it."*

*(Patient 1, 77 years at diagnosis, in follow up from first-line chemotherapy)*

However, women were concerned about the lack of communication between their oncology team and other specialists at external institutions, particularly those with comorbidities. Some patients described waiting months to be seen by another specialist after referral.

Many participants found navigating logistical issues difficult, forming a substantial discussion in each focus group. Patients felt burdened by the responsibility of communicating with hospital staff to manage appointments. This was particularly difficult in the early stages of treatment when concurrently dealing with severe physical illness. Participants had varied access to informal charitable support, largely due to geographical barriers.

*"It's just these things on the ground that you have to do as a patient when you're feeling exhausted."*

*(Patient 14, 72 years at diagnosis, in follow up after first-line chemotherapy)*

Participants also discussed a lack of communication between primary care and the cancer centre and often did not realise primary care could be involved in cancer treatment or support. Women felt involvement may be limited by resource strain and a lack of continuity in provider. Some participants had experienced a significant delay before diagnosis culminating in emergency presentation. This understandably had an impact on willingness to engage with primary care throughout treatment.

*"I don't actually know who my doctor is."*

*(Patient 4, 82 years at diagnosis, receiving first-line chemotherapy)*

#### 3.2.2. Subtheme: Transport

Difficulties arranging transport to appointments caused significant stress. Many patients were unaware of hospital transport until after attending a number of appointments. Information received about transport frequently came from administrative staff rather than the clinical team, leading to delays in acquiring assistance. The need to arrive earlier or leave later than appointments for those using hospital transport added to the stress and fatigue associated with hospital visits.

#### 3.2.3. Subtheme: Informal Support

Friends and family played an invaluable role in supporting women with the burden of treatment by attending clinic or chemotherapy appointments or providing emotional support.

*"Oh your family back you up don't they."*

*(Patient 2, 78 years at diagnosis, receiving chemotherapy for relapsed disease)*

Faith was brought up independently by a number of participants. Women found solace in faith during treatment, potentially as a way to cope with the lack of control of treatment outcomes. For some, the regular routine of worship and associated community support provided comfort during treatment.

*"The only thing I can do is put my hand in the hand of god and you, I can't do anything more"*

*(Patient 8, 69 years at diagnosis, receiving chemotherapy for relapsed disease)*

### *3.3. Theme: Side-Effects*

#### 3.3.1. Subtheme: Weighed Down by Side-Effects

Chemotherapy tolerability varied widely. Some women expressed surprise at how few side-effects they experienced. For many, however, issues such as myalgia and arthralgia were difficult to tolerate. Peripheral neuropathy and its impact on function, particularly for participants who previously enjoyed physical activity, was a significant and long-term issue.

Overwhelmingly, the most profound issue reported was fatigue, or as subjects termed it, "utter exhaustion". Participants described fatigue as the most challenging aspect of their treatment experience, able to manage only the most basic activities of daily living.

*"I was incredibly weak and then you still have to do things and you can't manage it."*

*(Patient 11, 70 years at diagnosis, in follow up after first-line chemotherapy)*

*"It's a matter of dragging my body around to keep up with essentials."*

*(Patient 14, 72 years at diagnosis, in follow up from first-line chemotherapy)*

For some, this level of fatigue continued for months after treatment. Severe fatigue had ramifications beyond physical limitations. Many participants expressed a real sense of loss as a result of their cancer treatment. Participation in previously enjoyed activities, even simple endeavours such as walking the dog, were "taken away". Fatigue and weakness, which for some persisted for months after treatment, contributed to a loss of confidence in their ability to remain independent or travel alone. Those who lived alone also reported a fear of falling or having an accident and being unable to access help. Some participants felt this had an effect on mood, admitting they "get very depressed at times".

#### 3.3.2. Subtheme: Determination Not to Let Cancer Interfere

Despite the clear physical impact of the treatment, participants had a shared ambition not to let the diagnosis or treatment impact on day-to-day life, maintaining independence and self-sufficiency. One participant, discharged from hospital following a midline-laparotomy, found online videos for instructions on how to safely sit up in bed. Others refused aids from well-meaning family members to avoid being seen as ill. Participants

expressed a reluctance to approach their medical team with what they perceived as minor symptoms to avoid being a 'burden'.

Women prioritised participating in leisure and hobby activities. Those who were previously physically active viewed their current treatment as a temporary setback. An unwillingness to be hampered by the medical diagnosis was clear.

> *"I just carry on as normal, I do my Pilates, I go to a club, but I've forgotten what it's like to feel normal."*
>
> *(Patient 1, 77 years at diagnosis, in follow up from first-line chemotherapy)*

Despite physical limitations, in particular fatigue and weakness, participants continued with life to the best of their abilities with a markedly stoic outlook.

> *"I live life normally and I will go on like that until it's my time to go."*
>
> *(Patient 11, 70 years at diagnosis, in follow up after first-line chemotherapy)*

## 4. Discussion

Despite most participants receiving standard treatment, women overwhelmingly preferred treatment with the chance of lengthening survival despite side-effects and would undertake treatment again. Participants chose to undergo treatment for their own sake or to please family members. Though patients struggled with fatigue and logistical challenges, these older women were determined to maintain independence and continue treatment.

Our findings suggest that the preferences of older patients with ovarian cancer toward anti-cancer treatment are unlikely to substantially contribute towards lower treatment intensity. Whilst the decision not to offer cytoreductive surgery or platinum-doublet chemotherapy may be based on sound medical concerns, this study demonstrates that older women do not consider age a barrier to treatment. All participants expressed the preference for full standard treatment, including those who suffer treatment-related toxicities or were not offered standard treatment.

Recent developments provide strong evidence that geriatric assessment can not only improve the prediction of treatment tolerance and mortality [7], but also, when combined with targeted interventions, reduce the frequency of severe treatment-related toxicity [20,21]. For example, fatigue, highlighted by participants as one of the most debilitating issues, may contribute to the need to reduce chemotherapy dose-intensity. However, fatigues is often multifactorial and addressing factors such as anaemia, vitamin deficiencies, thyroid dysfunction, physical exercise, nutrition and social support could reduce fatigue and allow patients to maintain treatment intensity, meeting both patient needs and preferences [22].

Treatment preferences and expected outcomes should be clearly discussed with all patients irrespective of age. As demonstrated here, older women may be more unwell and less able to participate in treatment decisions after likely emergency presentation or delayed diagnosis [23,24]. Reduced information reception and retention also limited involvement in treatment decisions. A systematic review found that audio-recording consultations improved information retention, particularly in older adults, and question lists encouraged active participation [25]. With the use of the Internet demonstrated by older women in this study, these tools, coupled with online resources, could be useful adjuncts to standard consultations. Older women may also benefit from opportunities to re-discuss treatment aims later in the pathway when patients are less overwhelmed.

Diversifying methods for information provision may help address the aversion to prognostic information some women described. Avoidant coping styles have been shown to be maladaptive and associated with distress and low emotional wellbeing [26]. However, evidence on coping strategies in older adults have shown mixed results, with one study showing older adults are more likely to adopt avoidant strategies and another finding they are more likely to exhibit passive reactions [27,28]. Further research is needed to explore how best to support older women in coping with a cancer diagnosis.

As many older adults face social isolation and functional limitations cancer treatment may impose a large burden [29]. Logistical issues coordinating and attending appointments with multiple providers posed a particular challenge in this study. While this did not hamper willingness to undertake treatment, efforts should be taken to assess the burden of treatment from the patient perspective, particularly for older patients with multimorbidity [30]. Practical issues, such as transport, need to be incorporated into routine assessment. A number of methods previously shown to lessen the burden of treatment were employed by participants, such as enlisting the help of others and turning to faith to cope [31]. Ascertaining levels of social support is essential for older patients who may live alone.

These findings may not be applicable to other hospitals as this study was conducted in a single cancer centre. The small sample size inherent in qualitative research also limits generalisability. One focus group contained only two participants due to last minute cancellations for the reasons described. This limited the ability to explore similar and discordant beliefs in one of the groups but further serves to highlight the changing health status and logistical burden for these patients. This study is also subject to survivor bias as only patients who received at least three cycles of systemic therapy were included, meaning patients whose condition deteriorated early on or who chose not to undertake treatment were excluded.

We also acknowledge the possibility of selection bias. While investigators made every effort to include patients with a range of disease severities, it was considered unethical to invite severely unwell patients, causing undue stress. This likely introduced some level of bias. Additionally, despite the use of both focus groups and individual interviews, patients declined due to illness and logistical constraints, potentially further introducing bias. Even with these limitations, the interviews describe important experiences of cancer management in older women with ovarian cancer from the patient perspective.

Future work should build on the current study and recent research to ensure older women with advanced ovarian cancer receive optimal treatment. A longitudinal survey study looking at treatment preferences and health-related quality of life would mitigate survivor bias and improve generalisability.

## 5. Conclusions

The older women in this study were overwhelmingly positive about their experience of cancer care and desire for anticancer treatment, despite facing treatment burden and therapy-related toxicities. Older women may face additional challenges in terms of information retention and managing medical comorbidities. Additional methods of delivering information could be useful to improve patient centred decision making.

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**Institutional Review Board Statement:** The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Royal Marsden NHS Foundation Trust and the Institute of Cancer Research Joint Committee for Clinical Research (SE764 05/10/2018).

**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study.

**Data Availability Statement:** The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## 8.4 Dumas et al. Under-treatment of Older Patients with Newly Diagnosed Epithelial Ovarian Cancer Remains an Issue. Cancers 2021.

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# Under-Treatment of Older Patients with Newly Diagnosed Epithelial Ovarian Cancer Remains an Issue

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**Simple Summary:** Cancer treatment and survival in older women is topical and important in an era where the proportion of older adults being treated for cancer in the clinic is rising. As survival outcomes in older women continue to lag behind those of younger and middle-aged women, further investigation is required into current treatment practices to identify target areas to address this deficit. We present treatment patterns, tolerance and outcomes of 280 women aged 65 and above treated for newly diagnosed ovarian cancer at two UK cancer centres between 2009 and 2015. We demonstrate that older women continue to receive lower rates of standard care first line therapy. When adjusted for stage at diagnosis, surgical outcome and chemotherapy given, age was not an independent risk factor for poorer overall survival.

**Abstract:** Older women with ovarian cancer have disproportionately poorer survival outcomes than their younger counterparts and receive less treatment. In order to understand where the gaps lie in the treatment of older patients, studies incorporating more detailed assessment of baseline characteristics and treatment delivery beyond the scope of most cancer registries are required. We aimed to assess the proportion of women over the age of 65 who are offered and receive standard of care for first-line ovarian cancer at two UK NHS Cancer Centres over a 5-year period (December 2009 to August 2015). Standard of care treatment was defined as a combination of cytoreductive surgery and if indicated platinum-based chemotherapy (combination or single-agent). Sixty-five percent of patients aged 65 and above received standard of care treatment. Increasing age was associated with lower rates of receiving standard of care (35% > 80 years old versus 78% of 65–69-year-olds, $p = 0.000$). Older women were less likely to complete the planned chemotherapy course ($p = 0.034$). The oldest women continue to receive lower rates of standard care compared to younger women. Once adjusted for Federation of Gynaecology and Obstetrics (FIGO) stage, Eastern Cooperative Oncology Group (ECOG) performance status and first-line treatment received, age was no longer an independent risk factor for poorer overall survival. Optimisation of vulnerable patients utilising a comprehensive geriatric assessment and directed interventions to facilitate the delivery of standard of care treatment could help narrow the survival discrepancy between the oldest patients and their younger counterparts.

**Keywords:** ovarian cancer; older; treatment



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## 1. Introduction

Ovarian cancer (including primary peritoneal and fallopian tube cancer) is predominantly diagnosed in older women with around half of all new diagnoses occurring in women over the age of 65. Older patients are less likely to be enrolled in clinical trials [1,2] that go onto to shape current gold standards. Treatment decisions are usually based on clinical trial results, which include a younger, less frail population and are applied to an

older and often less well group. The efficacy and tolerability of standard of care and novel therapies in an older, potentially frailer population are therefore not clearly understood.

It has long been shown that survival outcomes are disproportionately lower in older patients [3] and delayed diagnosis/late presentation [4], more advanced disease at diagnosis [5–7], higher rates of emergency presentation [8], higher rates of unclassified or unclassifiable tumours [3] as well as lower physical performance status and higher prevalence of medical and functional comorbidities [9] contribute to this. Recent studies have reported high rates of no recorded treatment in older patients, for example 60% of ovarian cancer patients aged over 79 had no record of any treatment in England between 2016 and 2018 [10,11]. Developing our understanding of the "real-world" experience of treatment for ovarian cancer in an older population is necessary. Until the reasons for the difference in survival between older and younger women are more clearly understood, efforts to address the gaps and improve outcomes in our older population will be hampered. Large-scale cancer registry data by both the EUROCARE [12–15] series and the International Cancer Benchmarking Partnership (ICBP) [6,7,16,17] demonstrate that both short and long-term survival outcomes in older women continue to be significantly inferior to those seen in middle-aged and younger women [12,17,18]. Notably, an improving trend in 1- and 5-year survival for all age groups has been reported excepting those aged over 75 years [19].

The field of geriatric oncology has rapidly developed over the last two decades. The core principles outline the need to holistically assess patients using a comprehensive geriatric assessment rather than basing treatment decisions purely on chronological age. Both the International Society of Geriatric Oncology (SIOG) [20] and the American Society of Clinical Oncology (ASCO) [21] have now recommended that geriatric assessment (GA) be undertaken in all adults aged 65 years and over being considered for systemic anticancer therapy. Crucially, clinicians should implement GA-directed interventions in order to optimise patient care.

## 2. Results

### 2.1. Patient Baseline Characteristics

Two hundred and eighty patients met the inclusion criteria. Patients were divided into four age cohorts (65–69 years, 70–74 years, 75–79 years and >80 years). The majority (76%) of patients had stage 3 or 4 disease at presentation (Table 1). Stage distribution did not alter with increasing age ($p = 0.293$). 29% of patients were ECOG performance status 2 or 3. Increasing age was significantly associated with a worsening ECOG performance status ($p = 0.008$). Forty-nine percent of patients over the age of 80 were PS 0 or 1 compared to 70.4% of patients in the 65–69 years cohort (Table 1). The majority (69.6%) of patients were diagnosed with high-grade serous carcinoma. Histological subtype did not vary according to age ($p = 0.547$).

The most commonly documented comorbidities were cardiovascular disease (27.5%), hypertension (40.4%), respiratory disease (10%) and diabetes (10.4%). Polypharmacy at the initial consultation, defined as taking 3 or more daily prescribed medications, was present in 40% of patients. Neither cardiovascular disease nor hypertension was associated with increasing age. 48.9% women were anaemic (any grade) at baseline with 11.4% patients having a Grade 2 or higher anaemia. Impaired renal function at the start of treatment was also common with 37% of all patients having at least a mild-moderate reduction of glomerular-filtration rate (GFR) of 60 mL/min or less, amounting to chronic kidney disease grade 3. A total of 40.7% patients had an albumin below 35 g/L at baseline and 22.5% of patients had an albumin less than 30 g/L. Hypoalbuminaemia was not associated with increasing age ($p = 0.36$) (Table 2). Factors and comorbidities significantly associated with advancing age were polypharmacy ($p = 0.01$), respiratory disease ($p = 0.007$) and cognitive impairment ($p = 0.001$) (Table 2.) Increasing age was associated with a higher proportion of women living alone (51% of those >80 years compared with 22% of those aged 65–69 years, $p = 0.000$). Older women were also significantly more likely to live in supported accommodation ($p = 0.032$), use a walking aid ($p = 0.026$) or have a degree of

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visual impairment ($p = 0.016$). A quarter of all patients reported reduced activities of daily living in the weeks and months preceding their diagnosis. Self-reported weight loss was also prevalent with 23.6% of patients reporting weight loss over the 3 months prior to their diagnosis (Table 2.)

**Table 1.** Patient characteristics: stage and ECOG performance status at baseline.

| | 65–69 Years *n* = 91 *n* (%) | 70–74 Years *n* = 79 *n* (%) | 75–79 Years *n* = 53 *n* (%) | >80 Years *n* = 57 *n* (%) | Total *n* = 280 *n* (%) | *p* |
|---|---|---|---|---|---|---|
| | | | **FIGO Stage** | | | |
| **1** | 13 (14.3) | 4 (5.1) | 8 (15.1) | 12 (21.1) | 37 (13.2) | 0.293 |
| **2** | 9 (9.9) | 10 (12.7) | 3 (5.7) | 3 (5.3) | 28 (10.0) | |
| **3** | 52 (57.1) | 44 (55.7) | 33 (62.3) | 29 (50.9) | 158 (56.4) | |
| **4** | 16 (17.6) | 21 (26.6) | 6 (11.3) | 12 (21.1) | 55 (19.6) | |
| **Unknown** | 1 (1.1) | 0 | 0 | 1 (1.8) | 2 (0.7) | |
| | | | **ECOG PS** | | | |
| **0** | 30 (33.0) | 12 (15.2) | 9 (17.0) | 5 (8.8) | 56 (20.0) | 0.008 |
| **1** | 34 (37.4) | 38 (48.1) | 27 (50.9) | 23 (40.4) | 122 (43.6) | |
| **2** | 14 (15.4) | 18 (22.8) | 8 (15.1) | 15 (26.3) | 55 (19.6) | |
| **3** | 5 (5.5) | 9 (11.4) | 3 (5.7) | 9 (15.8) | 26 (9.3) | |
| **Unknown** | 8 (8.8) | 2 (2.5) | 6 (11.3) | 5 (8.8) | 21 (7.5) | |
| | | | **Histological subtype** | | | |
| **High grade serous** | 62 (68.1) | 57 (72.2) | 36 (67.9) | 40 (70.2) | 195 (69.6) | 0.547 |
| **Low grade serous** | 3 (3.3) | 3 (3.8) | 3 (5.7) | 3 (5.3) | 12 (4.3) | |
| **Carcinosarcoma** | 6 (6.6) | 5 (6.3) | 4 (7.5) | 6 (10.5) | 21 (7.5) | |
| **Clear cell** | 8 (8.8) | 1 (1.3) | 2 (3.8) | 1 (1.8) | 12 (4.3) | |
| **Endometrioid** | 7 (7.7) | 3 (3.8) | 2 (3.8) | 2 (3.5) | 14 (5.0) | |
| **Mucinous** | 1 (1.1) | 2 (2.5) | 0 | 0 | 3 (1.1) | |
| **Adenocarcinoma/ Mixed/ Undifferentiated** | 4 (4.4) | 8 (10.1) | 6 (11.3) | 5 (8.8) | 23 (8.2) | |

### 2.2. First Line Treatment

Sixty-five percent of patients received standard of care cytoreductive surgery and platinum-based chemotherapy in keeping with the European Society of Medical Oncolgogy ESMO)-European-Society of Gynaecological Oncology (ESGO) consensus recommendations [22]. Increasing age was associated with reducing rates of receiving standard of care therapy with 35.1% of those over the age of 80 receiving both chemotherapy and surgery compared to 78% in those aged 65–69 years ($p = 0.000$). Ten percent of patients over the age of 80 received no cancer treatment (Figure 1). Six (2%) patients declined surgery and three (1%) declined chemotherapy. Increasing age was associated with lower rates of undergoing cytoreductive surgery ($p = 0.001$) as well as complete cytoreduction (defined according to the post-operative report) ($p = 0.006$) with complete cytoreduction obtained in only 28% of those over the age of 80 compared to 69% in those aged 65–69. When optimal cytoreduction (<1 cm residual disease) is reported as a proportion of those patients who underwent surgery, the rates of optimal cytoreduction was 76% in all age cohorts apart from those over 80 where it was 49%. 53.7% of women received standard carboplatin and paclitaxel chemotherapy as first-line treatment. Older women were less likely to receive doublet chemotherapy (19.3% in those over the age of 80 compared to 73.6% in those aged 65–69 years, $p = 0.000$). Overall, 7.8% women aged 65 and above any form of targeted therapy during first-line treatment. This proportion decreased with advancing age (2.3% of women over the age of 80 compared to 12.4% women between the ages of 65–69 received some form of targeted therapy during first-line treatment ($p = 0.05$).

**Table 2.** Patient characteristics. Medical comorbidities and functional status at baseline.

| | 65–69 Years *n* = 91 | 70–74 Years *n* = 79 | 75–79 Years *n* = 53 | >80 Years *n* = 57 | Total *n* = 280 | *p* |
|---|---|---|---|---|---|---|
| | *n* (%) | *n* (%) | *n* (%) | *n* (%) | *n* (%) | |
| **Medical comorbidities** | | | | | | |
| **Cardiovascular disease** | 26 (28.6) | 21 (26.6) | 16 (30.2) | 14 (24.6) | 77 (27.5) | 0.907 |
| **Hypertension** | 37 (40.7) | 28 (35.4) | 22 (41.5) | 26 (45.6) | 113 (40.4) | 0.650 |
| **Previous malignancy** | 5 (5.5) | 4 (5.1) | 6 (11.3) | 1 (1.8) | 16 (5.7) | 0.183 |
| **Endocrine disease** | 7 (7.7) | 5 (6.3) | 5 (9.4) | 3 (5.3) | 20 (7.1) | 0.834 |
| **Osteoarthritis** | 4 (4.4) | 5 (6.3) | 7 (13.2) | 4 (7.0) | 20 (7.1) | 0.252 |
| **Rheumatological disease** | 2 (2.2) | 7 (8.9) | 2 (3.8) | 1 (1.8) | 12 (4.3) | 0.122 |
| **CVA/MI/CAD** | 7 (7.7) | 4 (5.1) | 6 (11.3) | 3 (5.3) | 20 (7.1) | 0.512 |
| **Haematologicaldisease** | 0 | 2 (2.5) | 0 | 0 | 2 (0.7) | 0.167 |
| **Previous DVT** | 15 (16.5) | 8 (10.1) | 8 (15.1) | 4 (7.0) | 35 (12.5) | 0.345 |
| **Polypharmacy (>3 meds)** | 31 (34.1) | 27 (34.2) | 23 (43.4) | 30 (52.6) | 111 (39.6) | 0.010 |
| **Respiratory disease** | 6 (6.6) | 15 (19.0) | 6 (11.3) | 1 (1.8) | 28 (10.0) | 0.007 |
| **Diabetes** | 9 (9.9) | 7 (8.9) | 6 (11.3) | 7 (12.3) | 29 (10.4) | 0.850 |
| **Cognitive impairment** | 0 | 2 (2.5) | 0 | 6 (10.5) | 8 (2.9) | 0.001 |
| **Depression** | 6 (6.6) | 4 (5.1) | 0 | 1 (1.8) | 11 (3.9) | 0.193 |
| **Functional baseline** | | | | | | |
| **Lives alone** | 20 (22.0) | 31 (39.2) | 18 (34.0) | 29 (50.9) | 98 (35.0) | 0.000 |
| **Lives in supported accommodation** | 0 | 1 (1.3) | 2 (3.8) | 4 (7.0) | 7 (2.5) | 0.032 |
| **Use of walking aids** | 7 (7.7) | 12 (15.2) | 11 (20.8) | 14 (24.6) | 44 (15.7) | 0.026 |
| **Reduced activities of daily living** | 16 (17.6) | 22 (27.9) | 13 (24.5) | 19 (33.3) | 70 (25.0) | 0.226 |
| **Assistance with activities of daily living** | 7 (7.7) | 10 (12.7) | 8 (15.1) | 10 (17.5) | 35 (12.5) | 0.441 |
| **History of delirium in last 12 months** | 0 | 0 | 0 | 3 (5.3) | 3 (1.1) | 0.007 |
| **Cognitive impairment** | 0 | 2 (2.5) | 0 | 6 (10.5) | 8 (2.9) | 0.001 |
| **Weight loss in last 3 months** | 22 (24.2) | 22 (27.9) | 11 (20.8) | 11 (19.3) | 66 (23.6) | 0.799 |
| **Visual impairment** | 3 (3.3) | 1 (1.3) | 2 (3.8) | 9 (15.8) | 15 (5.4) | 0.016 |
| **Hearing impairment** | 1 (1.1) | 0 | 2 (3.8) | 3 (5.3) | 6 (2.1) | 0.242 |
| **History of falls in last 12 months** | 1 (1.1) | 0 | 1 (1.9) | 3 (5.3) | 5 (1.8) | 0.106 |

Subsequently, the primary treatment of only those women with advanced (Federation of Gynaecology and Obstetrics (FIGO) stage III/IV) disease was assessed. A total of 62.9% of women aged 65 and over received standard of care, with this proportion decreasing significantly with increasing age ($p = 0.000$). 46.3% of women aged 80 years and over underwent cytoreductive surgery. In these women complete cytoreduction was achieved in 31.6%, compared to those aged between 65–69 years of whom 82.4% underwent surgery, and 69.6% had complete cytoreduction ($p = 0.014$).

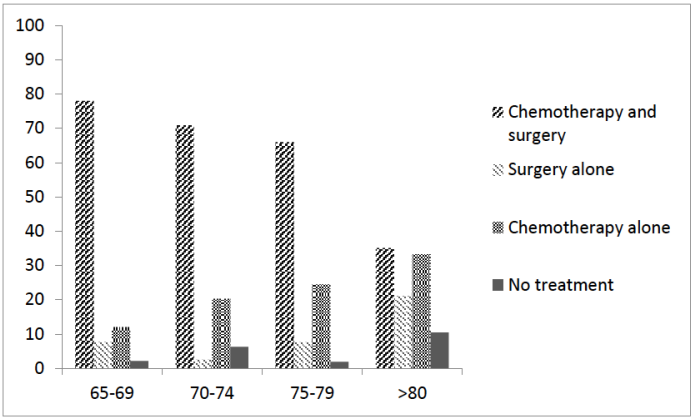


**Figure 1. First**-line treatment received according to age cohort.

### *2.3. Treatment Tolerance*

Overall, 27.3% of patients developed a grade two or higher haematological toxicity. Neutropenia was more common in younger patients (69.6% in those aged 65–69 vs. 18.8% in those aged 75–79, $p = 0.007$). Older patients did not experience higher rates of severe haematological toxicity ($p = 0.554$). However, increasing age was associated with a trend towards a higher rate of G3 or 4 non-haematological toxicities although this did not reach statistical significance (32.5% vs. 13.4% in those aged >80 years vs. those aged 65–69 years, $p = 0.082$). Increasing age was significantly associated with a lower likelihood of completing 6 cycles ($p = 0.034$). Of the 38 (15.8%) women who discontinued treatment early, 21 (55%) did so because of toxicity. Discontinuation due to toxicity was higher in older patients, for example 54.5% of 75–79-year-olds compared to 36.4% of those aged 65–69 years, although this did not reach statistical significance ($p = 0.15$). 28.5% of all patients were admitted to hospital as an emergency at some stage during their primary treatment with no variation due to age ($p = 0.135$), 30-day mortality was 1.24% across the whole cohort and did not vary according to age ($p = 0.184$) (Table 3).

**Table 3.** Treatment tolerance.

| | **65–69 Years** *n* = 82 | **70–74 Years** *n* = 72 | **75–70 Years** *n* = 48 | **>80 Years** *n* = 39 | **Total** *n* = 241 | ***p*-Value** |
|---|---|---|---|---|---|---|
| | % | % | % | % | % | |
| Dose modification at baseline | 9.8 | 12.5 | 6.3 | 17.5 | 11.6 | 0.365 |
| Dose modification during chemotherapy | 29.3 | 30.6 | 52.1 | 37.5 | 35.5 | 0.193 |
| Completed 6 cycles of chemotherapy | 86.6 | 86.1 | 77.1 | 65.0 | 82.2 | 0.034 |
| ≥ G2 Haematological toxicity | 29.3 | 19.4 | 33.3 | 30.0 | 27.3 | 0.554 |
| ≥ G3 Non-haematological toxicity | 13.4 | 19.4 | 27.1 | 32.5 | 21.1 | 0.082 |
| Febrile neutropenia | 4.9 | 2.8 | 2.1 | 0.00 | 2.9 | 0.540 |
| Hospital admission during chemotherapy | 20.7 | 34.7 | 25.0 | 37.5 | 28.5 | 0.135 |
| Death within 30 days of chemotherapy | 1.2 | 0.00 | 4.2 | 0.00 | 1.2 | 0.184 |

### 2.4. Treatment at Relapse

At first relapse, 50.4% of women received chemotherapy; however, older women were significantly less likely to receive second-line chemotherapy at progression. A total of 35.5% of women over the age of 75 received chemotherapy at relapse, compared to 62.5% of those aged 65–69 years ($p = 0.021$). One patient (aged 75 years) underwent secondary debulking surgery. Seventy-five women (59% of those who had treatment for relapsed disease) received carboplatin-based chemotherapy at first relapse. Of those who received chemotherapy at first relapse, 56 (45%) received a carboplatin doublet regimen (paclitaxel, pegylated liposomal doxorubicin or gemcitabine with or without a targeted agent for example, bevacizumab). Nineteen (15%) women received single-agent carboplatin. Of those who received platinum at first relapse, 65% achieved some degree of tumour shrinkage as their best response according to the local radiological report with 89% achieving at least stable disease. In those patients who received non-platinum containing regimens, 21 patients (15%) received weekly paclitaxel resulting in a 33.3% radiological response rate and a 52% clinical benefit rate (defined as patients who achieved at least stable disease as their best response documented). Twenty-three (18.9%) patients received either pegylated liposomal doxorubicin or doxorubicin. No responses were seen in this group although 6 (26%) patients had stabilisation of their disease.

### 2.5. Survival Outcomes

Median overall survival (OS) for all patients was 31.5 months. For patients diagnosed with stage III and stage IV disease, median OS was 28.3 and 14 months respectively. 1-year and 5-year survival was 78.1% (95% CI 72.7–82.5) and 28.7% (95% CI 22.5–35.2) respectively. Overall survival was broadly equivalent over the first three age cohorts however patients over the age of 80 had a significantly lower survival than those aged 65–69 years (median OS 20.02 months vs. 44.91 months, $p = 0.000$) (Figure 2). First line carboplatin/paclitaxel combination chemotherapy was associated with improved survival outcomes compared to single-agent carboplatin (OS 39.5 vs. 30.6 months), those patients who received no chemotherapy had an OS of 9.7 months ($p = 0.003$). Progression-free survival (PFS) was similar across all age groups up to the age of 80 but patients aged 80 years and over had a median PFS of 12.3 months compared to 16.4 in those aged 65–69 years (HR 2.0 $p = 0.00$) (Figure 2).

In univariate analysis, age over 80 years at diagnosis, FIGO stage III/IV disease, incomplete cytoreduction and an ECOG PS of greater than 1 were all associated with poorer survival outcomes. Of the baseline factors and comorbidities collected, the presence of cardiovascular disease ($p = 0.043$), polypharmacy ($p = 0.011$) or having a current or past history of smoking ($p = 0.008$) were all associated with poorer survival outcomes. Requiring assistance with activities of daily living (ADL) ($p = 0.000$), reporting reduced ADLS ($p = 0.000$) and weight loss at diagnosis ($p = 0.015$) were associated with poorer survival outcomes (Table 4). Of the biochemical parameters collected, having any degree of hypoalbuminaemia ($p = 0.000$) or baseline haemoglobin of less than 110 g/L ($p = 0.000$) were associated with poorer survival outcomes. GFR was associated with poorer survival as a continuous variable ($p = 0.036$) however using a threshold of a GFR of 60 mL/min (CKD 3) was not associated with poorer survival outcomes ($p = 0.064$) (Table 4).

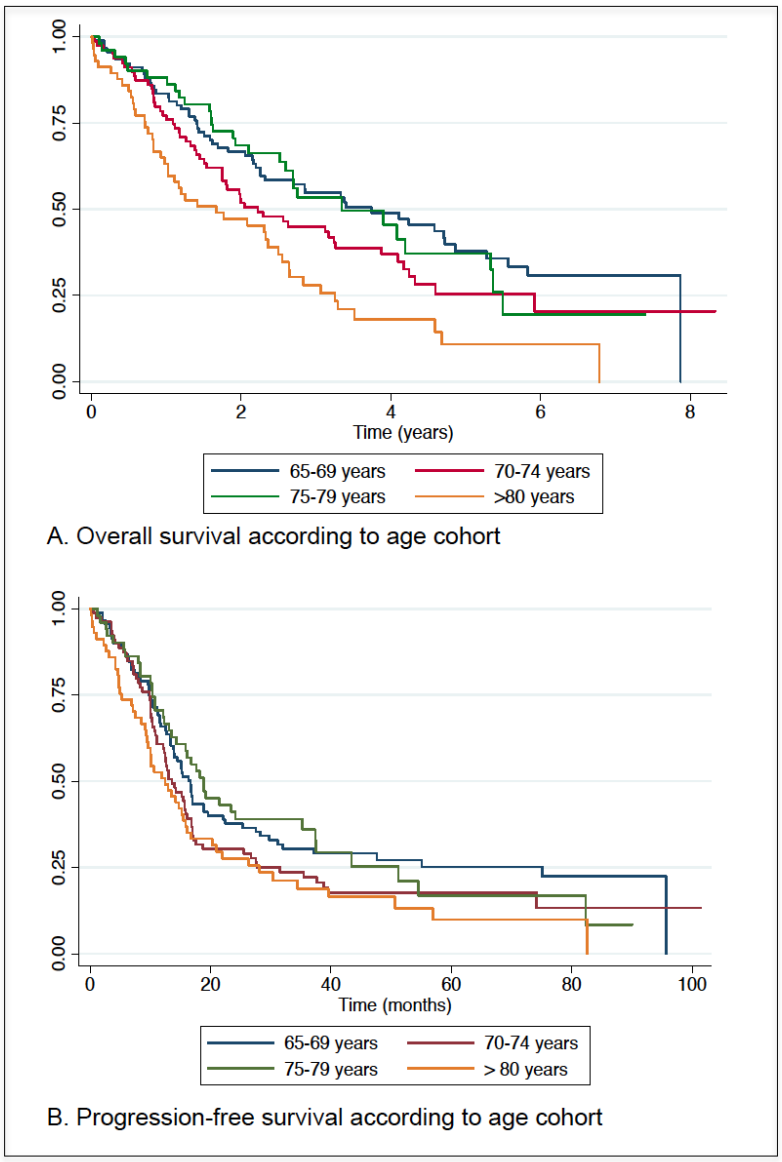


**Figure 2.** (**A**) Overall survival according to age cohort. (**B**) Progression-free survival according to age cohort.

A cox proportional hazards multivariate model was built including treatment-related factors that were predictive, by univariate analysis for overall survival. When adjusted for FIGO stage, surgical outcome, chemotherapy treatment and completion of chemotherapy, age over 80-years-old was no longer an independent risk factor for poorer overall survival. Completion of chemotherapy remained independently associated with overall survival where single-agent versus platinum-doublet chemotherapy was not associated with a significantly different in overall survival in either univariate or multivariate analysis (Table 5).

**Table 4.** Univariate and multivariate analysis of factors associated with poorer overall survival.

| | | | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|---|---|
| | | *n* | HR | 95% CI | *p* | HR | 95% CI | *p* |
| Age Cohort | 65–69 | 91 | - | - | - | - | - | - |
| | 70–74 | 79 | 1.40 | (0.96–2.05) | 0.081 | 0.95 | (0.60–1.52) | 0.833 |
| | 75–79 | 53 | 1.07 | (0.68–1.68) | 0.772 | 0.79 | (0.44–1.43) | 0.441 |
| | >80 | 57 | 2.20 | (1.47–3.27) | 0.000 | 1.76 | (1.03–3.02) | 0.04 |
| FIGO Stage | 1 | 37 | | | | - | - | - |
| | 2 | 28 | 1.30 | (0.55–3.07) | 0.553 | 7.91 | (0.98–63.61) | 0.052 |
| | 3 | 158 | 3.69 | (1.98–6.89) | 0.000 | 12.99 | (1.77–95.20) | 0.012 |
| | 4 | 55 | 6.00 | (3.08–11.68) | 0.000 | 16.16 | (2.11–123.61) | 0.007 |
| ECOG PS | 0 | 56 | | | | - | - | - |
| | 1 | 122 | 1.86 | (1.18–2.93) | 0.007 | 2.14 | (1.21–3.79) | 0.009 |
| | 2 | 55 | 4.02 | (2.47–6.53) | 0.000 | 2.53 | (1.20–5.35) | 0.015 |
| | 3 | 26 | 7.36 | (4.13–13.13) | 0.000 | 3.51 | (1.37–8.99) | 0.009 |
| Cardiovascular disease | | 77 | 1.38 | (1.01–1.90) | 0.043 | 0.99 | (0.62–1.57) | 0.95 |
| Taking 3 or more medications | | 111 | 0.07 | (0.01–0.55) | 0.011 | 1.12 | (0.72–1.74) | 0.62 |
| Osteoarthritis | | 16 | 1.70 | (0.96–3.01) | 0.070 | 1.62 | (0.76–3.44) | 0.209 |
| Reduced activities of daily living | | 70 | 2.89 | (2.10–3.98) | 0.000 | 1.53 | (0.90–2.62) | 0.118 |
| History of depression | | 11 | 1.86 | (0.95–3.65) | 0.071 | 1.89 | (0.83–4.30) | 0.128 |
| History of weight loss | | 66 | 1.51 | (1.09–2.11) | 0.015 | 0.93 | (0.59–1.47) | 0.754 |
| Albumin <35 g/L | | 114 | 2.09 | (1.56–2.81) | 0.000 | 1.52 | (0.97–2.38) | 0.065 |
| Haemoglobin <120 g/L | | 141 | 1.28 | (0.9601.72) | 0.093 | 0.80 | (0.53–1.23) | 0.311 |
| GFR <60 mL/min | | 104 | 1.33 | (0.98–1.79) | 0.064 | 1.11 | (0.74–1.68) | 0.607 |

**Table 5.** Univariate and multivariate factors associated with poorer overall survival.

| | | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|---|
| | | HR | 95% CI | *p* | HR | 95% CI | *p* |
| Age Cohort | 65–69 years | - | - | - | - | - | - |
| | 70–74 years | 1.40 | (0.96–2.05) | 0.081 | 1.22 | (0.77–1.95) | 0.386 |
| | 75–79 years | 1.07 | (0.68–1.68) | 0.772 | 0.85 | (0.46–1.54) | 0.582 |
| | >80 years | 2.20 | (1.47–3.27) | 0.000 | 0.81 | (0.40–1.61) | 0.541 |
| FIGO stage | 1 | | | | - | - | - |
| | 2 | 1.30 | (0.55–3.07) | 0.553 | 2.39 | (0.86–6.64) | 0.094 |
| | 3 | 3.69 | (1.98–6.89) | 0.000 | 4.38 | (2.02–9.52) | 0.000 |
| | 4 | 6.00 | (3.08–11.68) | 0.000 | 6.96 | (2.81–17.24) | 0.000 |
| Surgical outcome | Residual disease | 2.71 | (1.82–4.03) | 0.000 | 2.09 | (1.32–3.30) | 0.002 |
| Chemotherapy | Platinum-combination | - | - | - | - | - | - |
| | Single-agent carboplatin | 1.29 | (0.93–1.77) | 0.123 | 1.34 | (0.85–2.17) | 0.203 |
| | No chemotherapy | 2.19 | (1.43–3.35) | 0.000 | 4.49 | (1.99–10.13) | 0.000 |
| | Completed 6 cycles | 0.34 | (0.23–0.49) | 0.000 | 0.33 | (0.19–0.59) | 0.000 |

## 3. Discussion

This study provides a useful insight into the current real-world treatment of older women diagnosed with epithelial ovarian cancer in two UK cancer centres. There were very low rates of unclassifiable tumours in this series compared to national cancer registry data where over 50% of women over the age of 80 had an unclassified epithelial or miscellaneous tumour [3]. The lack of relationship between unclassifiable tumours and increasing age suggests either an improvement in the approach to the diagnostic process in older patients with more women having a true histological diagnosis being pursued, or the importance of cancer centre management of presumed ovarian cancer. Delayed time to diagnosis and therefore later stage at diagnosis has also been postulated as a cause for poorer survival rates however, stage distribution also did not vary with age in this population with the majority of women of all ages being diagnosed with stage 3 and 4 disease.

In this series, older patients were more likely to have a poorer ECOG performance status however it is well recognised that ECOG performance status alone is a crude measure in an elderly population that does not accurately reflect the functional and comorbid status of older patients [23,24] and it has also been previously shown that poor performance status should not necessarily preclude first-line treatment in epithelial ovarian cancer due to the high response rates observed to platinum-based chemotherapy [25]. Although many older women maintain fit and active lives, a quarter of the study population reported reduced activities of daily living in the preceding weeks and months before their diagnosis. A significant proportion of women in this study also reported living alone, whilst not a concern in and of itself, living alone without sufficient social network or community support particularly in the context of frailty is a challenge for both patients and oncologists when systemic anti-cancer therapy is being considered.

The most striking difference between the oldest patients and those younger than 80 years was that seen in primary treatment received. Under-treatment has long been postulated as one of the primary reasons for the poorer outcomes in older patients. A large retrospective study in France assessed the impact of age on treatment and survival outcomes whether or not guideline-recommendations for therapy were followed between 1997 and 2011. Women 70 years and over compared to those younger were less likely to undergo surgery (60.9% versus 89.6%, $p < 0.0001$) or receive chemotherapy (57.4% versus 76.4%, $p < 0.0001$). Only 31.9% of patients 70 years and over underwent both surgery and chemotherapy [26]. A prospective study (OVCAD) that included 275 women treated for primary ovarian cancer between 2005 and 2008 also showed that older women were less likely to receive optimal therapy and had poorer progression-free and overall survival. In multivariate analysis, age was an independent risk factor for poorer overall but not progression-free survival [27]. Our findings confirm that older women continue to receive less treatment than their younger and middle-aged counterparts and this is likely to be a significant factor in explaining the poorer outcomes seen in this population. A limitation of this work is that it was not possible from this retrospective study to ascertain whether, in those patients who did not receive either surgery or chemotherapy whether this decision was patient or clinician-led. Documentation of the rationale for a decision for not treatment should be consistently recorded in patient records. In addition, interview studies of the multidisciplinary team making treatment decisions may shed more light on the rationale for patients not receiving standard of care. It has previously been shown that older women desire cure as much as their younger counterparts and are more willing to undergo potentially disfiguring surgery to achieve this than younger patients [28]. In work also undertaken by our group (manuscript under review), we report that older patients desired active treatment and did not consider their age to be a hindrance.

The difference in survival for the oldest patients becoming no longer statistically significant once FIGO stage, surgical outcome and crucially, chemotherapy received are incorporated into the model provides further evidence that if even the oldest patients receive optimal therapy, survival outcomes are comparable. It has been shown that medical and social optimisation of older patients prior to and during systemic anti-cancer therapy can improve chemotherapy completion rates [29]. This approach is being tested in a wider scale in both the PREPARE [30] and GIVE (NCT02785887) studies; these potentially practice-changing results are awaited. We report here that older patients were less likely to receive targeted therapy, however, the only targeted therapy available during the study period was bevacizumab, which only received NICE approval in 2013 (i.e., the final two years of the study period) and thus these rates may not be fully representative.

Haematological toxicity rates were comparable across the age groups however increasing age was associated with a trend towards a higher rate of non-haematological toxicities. Increasing age was associated with higher early treatment discontinuation rates. This is in keeping with post-hoc analysis from the first-line phase 3 AGO-OVAR3 study, which also showed that women 70 years and over experienced comparable rates of toxicity but were more likely to discontinue treatment early [31]. The AGO-OVAR authors in 2007

suggested a potential difference in attitude towards the treatment of older adults. It can be postulated that this difference persists today. It was relatively rare for patients in our study to decline treatment with six patients declining surgery and three declining chemotherapy; however, the more nuanced decision-making over reducing treatment intensity and early treatment cessation is difficult to reliably elucidate retrospectively. A recent study from the Netherlands reported no treatment rates of 16%; in 40% of these cases it was patient choice, and in 29% it was poor condition in the opinion of the physician [32]. The perspectives of older women on treatment intensity, tolerance and treatment goals are worthy of further study, as the reasons for the reduced treatment intensity remain unclear.

## 4. Materials and Methods

Local study approvals were received from the Royal Marsden NHS Foundation Trust and The Royal United Hospitals Bath NHS Foundation Trust (SE486). This was a retrospective observational evaluation of all women over the aged 65 and over treated consecutively for newly diagnosed epithelial ovarian cancer (including tubal and primary peritoneal) over a 5-year period (December 2009 to August 2015) in two UK NHS Cancer Centres. Standard of care treatment was defined as undergoing cytoreductive surgery at any stage in the primary treatment pathway in combination with platinum-based chemotherapy. Details of treatment received, medical comorbidities, polypharmacy, functional level at baseline (where possible) as well as routinely assessed haematological and biochemical parameters were collected. Where toxicities had not been graded in real-time, according to the description of the event, retrospective grading was applied using CTCAE v4.0 for all grade haematological and grade $\geq$3 non-haematological toxicities.

The primary objective was to assess the proportion of women over the age of 65 who are offered and receive standard of care first-line management. Secondary objectives included assessment of progression-free and overall survival from first diagnosis and first relapse; proportion of patients who suffered a severe haematological or non-haematological chemotherapy toxicity; proportion of patients who received treatment for relapsed disease; rate of hospitalisation and 30-day mortality during chemotherapy. Patients were considered eligible if they were aged 65 years or older at the time of a first new patient appointment with a histologically or cytologically confirmed diagnosis of epithelial ovarian, primary peritoneal and fallopian tube carcinoma at either institution.

### *Statistical Considerations*

Chi squared test was used to compare patient baseline characteristics and treatment patterns according to age. Progression-free survival was measured from start of treatment to date of progression or death from any cause. Overall survival was defined as the time from date of diagnosis or date of relapse (depending on the endpoint) to death. Patients without an event were censored at last follow up. Data were censored on the 1 August 2016. Survival outcomes were estimated using the Kaplan–Meier method. Hazard ratios for survival, adjusted for factors likely to be of significance such as age, stage and treatment received were calculated using a cox proportional hazards model. All tests are two sided. A $p$-value of $< 0.05$ was used to determine statistical significance. All statistical analyses were performed using Stata IC v15.

## 5. Conclusions

The oldest women continue to receive lower rates of optimal first-line therapy compared to younger women. Once adjusted for FIGO stage, surgical outcome and first-line treatment received, age was no longer an independent risk factor for poorer overall survival. Not receiving standard of care platinum-based chemotherapy and cytoreductive surgery would therefore appear to be a critical factor for the poorer survival outcomes seen in our oldest patients. In the absence of a formal geriatric or frailty assessment, using age alone may lead to inappropriate under-treatment, adversely affecting cancer outcomes in these women. Further assessment of the reasons behind the lower treatment rates in

the oldest patients are essential to further understand and were beyond the scope of this retrospective study. Previous work by this group (manuscript under review) has demonstrated that older women desire active treatment and do not consider their age to be a hindrance. A formal frailty or geriatric assessment together with interventions to address issues identified would assist in optimising vulnerable patients. This could improve the rates of treatment delivery and completion in older adults thereby improving outcomes in this key demographic. The prospective UK FAIR-O study (NCT04300699) seeks to address the issue of assessment and management of frailty and medical comorbidities in the general oncology clinic.

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**Data Availability Statement:** The data presented here are available on request from the corresponding author.

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