Title: 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

i) 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 [2]. 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]. 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 III ovarian cancer in Canada has an expected 1-year survival of 74% compared to just 57% in the UK [11].

ii) 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 enrolled 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 enrolled 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=00017) [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 ≤64, 65-74 and ≥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 45Gy compared to 53Gy 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.

(i) 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, hypoalbuminaemia, 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%, ≥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 < 3.0g/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].

(ii) 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/m2) in women ≥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 ≥70 (n=157 (16%)) 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 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.

(iii) 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 (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) (95% CI 17.8-20.1 months) [51]. The incidence of grade ≥3 bleeding was higher in older patients (3% vs. 0%, respectively) [50]. In keeping with the AURELIA subgroup analysis, hypertension at baseline and on treatment was higher in the ≥65s [52].

Hypertension rates reported so far are higher in older patients receiving bevacizumab. 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. 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

(i) 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.

(ii) 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 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 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 2 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.

(iii) 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.

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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 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 IIII 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].

(iv) 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 hypoalbuminaemia, 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 minutes which may be considered feasible in routine pre-operative assessment clinics.

A retrospective pooled analysis of 83 patients over the age of 70 enrolled into a GINECO group study assessing Carboplatin and Cyclophosphamide (CC) [78] and a further 75 patients over the age of 70 enrolled 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 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 [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 (60mg/m2) in patients

over the age of 70 with a GVS score of ≥ 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 recognized 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 significant 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.

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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

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

Study	Inclusion Criteria	Regimens assessed	n	Survival (PFS and OS)	Key points
GINECO [78]	>70 years Stage III/IV	Carboplatin/Cyclophosphamide	83	OS 21.6 months	Post-hoc analysis. 75% patients completed planned 6 cycles ECOG PS not predictive for survival

GINECO – Analysis of two consecutive trials [79]	>70 years Stage III/IV	Carboplatin/Paclitaxel	75	OS 25.9 months	Prospective study. 68% patients completed planned 6 cycles. Depressive symptoms at baseline predictive for OS
AGO-OVAR [40]	>70 years	Carboplatin/Paclitaxel vs. Cisplatin/Paclitaxel	103	Not reported	Post-hoc analysis. High proportion of PS 0/1 No difference in quality of life 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	OS 32 months	Prospective study. 65% patients completed planned six cycles Favorable toxicity profile
GINECO/GVS [80]	>70 years Stage III/IV	Carboplatin Monotherapy (AUC 5)	109	PFS 9.2 months OS 17.4 months	Prospective study. 74% patients completed planned 6 cycles. Results have informed design of prospective study utilising GVS score
GOG0273 [81]	>70 years	I: Carboplatin AUC5 and Paclitaxel 135mg/m2 or II: Carboplatin AUC 5 3 weekly for 4 cycles	208	Not yet reported	Prospective study. Physicians choice of regimen I or II IADL not associated with ability to complete chemotherapy without delay or dose reduction Limitation of social activities associated with decreased tolerance to chemotherapy 3rd arm of weekly Paclitaxel added; results awaited.

Table 2. Abbreviated geriatric assessment tools

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

GA Tool	Domains assessed	Comments
C-SGA. SAKK cancer-specific geriatric assessment [99]	Age-adjusted Charlson Comorbidity Index (CCI) Vulnerable Elders Survey (VES-13) Geriatric Depression Score (GDS-5) Modified MOS – Social Support Survey (mMOS-SS) Mini-Cog	Feasibility study. Mean time for pt. to complete questionnaire - 17.33 ± 7.34 vs. 20.59 ± 6.53 minutes for physicians No biochemical/laboratory based parameters No assessment of correlation between toxicity/mortality, only feasibility of completion.
GAH. Geriatric Assessment in Hematology [100].	Number of drugs Gait speed Depression score (single-question) 3 ADL questions (from VES-13) Subjective health status 4 items from MNA-SF (BMI, Weight loss during last 3 months, food intake decline over past 3 months, psychological stress/acute disease SPMSQ (short portable mental status questionnaire) Prognostic index for 4-year mortality in Older adults	363 patients newly diagnosed with haematological malignancies. Internally validated and reproducible. Not validated in solid-organ malignancies Mean time to complete 11.9 +/- 4.7 min
CRASH The chemotherapy Risk Assessment Scale for High-Age patients [25]	**Haematological Toxicity:** Diastolic BP IADL LDH Chemotox score (scoring System 0-2 based on relative toxicity; for example, carboplatin/pemetrexed = 1) **Non-Haematological Toxicity:** ECOG Performance status MMSE MNA Chemotox score	460 patients. Valid across a large number of chemotherapy regimens Incorporation of potential toxicity of treatment into the risk scoring (MAX2 index). Predictive for toxicity

G8 [68]	Nutritional (derived from MNA) Weight loss during last 3 months Mobility Neuropsychological/Dementia BMI Polypharmacy (>3 drugs/day) Patient comparison of health status compared to others of their age Age	Validated first as a surrogate for CGA. 202 patients over the age of 65 included with self-completed questionnaires across all tumour types. Patients with a low G8 score of ≤14 were more likely to experience severe chemotherapy toxicity than those with a high G8 score: 64.6% vs.46.9% (χ^2=5.029, p=0.025)
CARG [63]	1. Age: > 72 years 2. Cancer type: GI or genitourinary 3. N^o of chemotherapy drugs: polychemotherapy 4. Chemotherapy dosing: standard dose 5. Hemoglobin: <11 g/dL (male); <10 g/dL (female) 6. Creatinine clearance: <34 mL/min (Jelliffe, ideal weight) 7. Hearing: fair or worse 8. N^o of falls in the last 6 months: ≥ 1 9. IADL: taking medications with some help or unable to take medication 10. Walking one block: somewhat limited or limited a lot 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. Mean age 73. Low (0-5) Intermediate (6-9) and High (10-19). Predictive for chemotherapy related toxicity.
GVS/GINECO[80]	Age ECOG Performance status Hypoalbuminaemia Lymphopaenia Functional: ADL, IADL Depression: HADS	Predictive for chemotherapy related toxicity. Deficit in 3 or more covariates results in a RR of mortality of 2.94.

Table 3. Chemotherapy studies in the elderly population

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