ORIGINAL RESEARCH

European Journal of ATP Gynaecological Oncology

Management of advanced epithelial ovarian cancer in the older patient: an age stratified cohort study of a gynaecological cancer centre in Southern England

Alistair Ward^{1,}*[®], Eleanor van der Zanden¹[®], Vangelis Mone², Stephen A. Bremner³[®], Florian Drews¹[®]

¹Department of Gynaecological Oncology, Royal Sussex County Hospital, University Hospitals Sussex NHS Trust, BN2 5BE Brighton, UK ²School of Computing, Engineering and Mathematical Sciences, University of Brighton, BN1 9PH Brighton, UK ³Department of Primary Care and Public Health, Brighton and Sussex Medical School, University of Sussex, BN1 9PX Brighton, UK

*Correspondence Alistair.ward@nhs.net (Alistair Ward)

Abstract

This was an age-stratified, retrospective, cohort study of patients between the ages of 65–69, 70–75 and \geq 76 years diagnosed with high grade serous ovarian cancer of FIGO (2014) Stage 3a or higher between 01 January 2017 and April 2020. The study aimed to examine and compare patient characteristics, treatments and outcomes, including survival, of elderly patients within a single cancer centre in the south of England. Data collection began in January 2021 and concluded in March 2022. Ninety patients were eligible for the study. A correlation was observed between increasing age and worsening performance status (p = 0.044). Other variables assessed included age at diagnosis and time between decision to treatment, however, there was no evidence of correlations. The majority of patients studied received neoadjuvant chemotherapy followed by cytoreductive surgery as their primary treatment modality, however, 53% of our eldest cohort underwent treatment types that did not involve surgery. Of those who did undergo surgery, there was no observed correlation between age and the rates of complete cyto-reductive surgery, intra-operative complications, admission to High Dependency Unit, or length of hospital stay. Median length of stay across all age groups was 5 days. Patients \geq 76 years were more likely to receive singleagent carboplatin (p = 0.009) than dual-agent chemotherapy. There was no increase in chemo-toxicity events with increasing age. While primary cytoreductive surgery is favoured by many gynaecological oncology teams, neoadjuvant chemotherapy still offers a viable treatment alternative for elderly and frail patients with advanced stage ovarian cancer by minimising operative times, reducing admissions to high dependency units and shortening lengths of hospital stay. Geriatric assessments, in combination with performance status, may aid treatment decisions made by the multi-disciplinary team.

Keywords

Care of the older patient; Ovarian cancer; Cancer surgery; Operative time; Chemotherapy

1. Introduction

Each year in the United Kingdom, approximately 6500 women are diagnosed with ovarian cancer [1] with an incidence of approximately 25 cases per 100,000 women [2]. Epithelial ovarian cancer (EOC) is the most common morphological subtype of ovarian cancer and carries the highest mortality of all gynaecological malignancies [3]; 30% of EOC patients will die within one year of presentation [4]. The risk is greatest amongst women between the ages of 75 and 79 years [4] and as the population ages, a greater proportion of diagnoses is likely to be made in the elderly woman.

One of the main outcomes of the National Ovarian Cancer Audit Feasibility Pilot (NOCAFP) conducted in England, United Kingdom, was that older patients, especially those over the age of 80, were much less likely to receive chemotherapy or surgery [2]. The concept of elderly ovarian cancer patients receiving less treatment than young patients is well documented [5]. Analyses of Surveillance, Epidemiology and End Results (SEER)-Medicare data in the United States have suggested that patients over the age of 80 were less likely to receive surgery or achieve an optimal cytoreduction and twice as likely to not complete chemotherapy [6]. Similar studies from France have also suggested that the elderly patient with ovarian cancer is at higher risk of incomplete surgery or less adjuvant chemotherapy [7]. Older patients represent a diverse selection of physiology and fitness. While there is an assumed trend of increasing frailty with age, some elderly patients maintain high levels of physical activity and independence late into life which can often translate into better health outcomes. The elderly are significantly underrepresented in clinical trials, therefore increasing the clinical uncertainty in managing this growing population of patients [8]. The literature is conflicting as to whether age is an independent risk factor for poor survival [9] due to physiology, or because physicians withhold treatments in an element of conscious or subconscious bias [10, 11]. Despite these uncertainties and perceptions, elderly patients desire radical surgery and disease cure just as much as the young [12].

This study aimed to examine and compare the patient characteristics, treatments and outcomes of elderly patients diagnosed with advanced stage, high grade serous ovarian, fallopian tube or primary peritoneal cancer between the ages of 65-69, 70-75 and ≥ 76 years within a single cancer centre cohort in the south of England.

2. Materials and methods

This was a retrospective cohort study on patients who were diagnosed with high grade serous ovarian cancer [13], between 01 January 2017 and April 2020 when cancer treatment pathways within the United Kingdom (UK) changed secondary to the onset of the Covid-19 pandemic. Data collection began in January 2021 and concluded in March 2022 with completion of statistical analysis in September of the same year.

Patients eligible for the study were aged 65 years or over with a diagnosis of high grade serous ovarian, tubal or primary peritoneal malignancy of at least FIGO (The International Federation of Gynecology and Obstetrics) Stage 3a. Patients were all discussed at a central Multi-Disciplinary Team (MDT) within a single cancer centre in the South of England that received referrals from three other local district general hospitals. All surgery was performed at the cancer centre, although chemotherapy was often carried out closer to patients' homes if they lived closer to a district general hospital that provided this treatment. Data was collected in retrospect from several electronic databases including "Somerset Cancer Register" (SCR), "Integrated Clinical Environment" (ICE), "Care Flow" electronic patient record and "ChemoCare".

The following demographic and clinical data were collected: age, time from decision to treatment, the tumour marker Ca-125 at diagnosis, World Health Organisation (WHO) Performance Status, medical comorbidities, stage of tumour as classified by International Federation of Gynaecology and Obstetrics (FIGO) 2014 [14], and the patient's route of referral to the cancer centre's MDT, e.g., urgent cancer pathway. An ageadjusted, modified Charlson Comorbidity Index was also used as an alternative to the American Society of Anaesthesiologists (ASA) Physical Status Classification System, as ASA Grade was not routinely entered into the electronic databases interrogated for this study. The Charlson Comorbidity index was adjusted for the patient's age and the presence of metastatic tumour as the index would normally add two points for patients between the ages of 60 and 69 years, three points for patients between the ages of 70 to 79 years and four points for patients over 80 years. The Charlson Comorbidity Index would have also normally assigned six points to metastatic solid tumours [15].

Patients who were under the age of 65 years or those who

were coded incorrectly with histology types other than high grade serous, or FIGO stage less than stage 3 were excluded. Patients who were treated for relapsed disease were also excluded. Patients were divided into three cohorts: 65–69 years, 70–75 years and \geq 76 years.

Patients were also divided into groups by their treatments: "No surgery or chemotherapy", "Primary surgery with adjuvant chemotherapy", "Neoadjuvant chemotherapy (NACT) with cytoreductive surgery", "Chemotherapy but no surgery" and "Primary surgery but no chemotherapy". The following data were also collected: length of time of surgical procedure (as defined as knife-to-skin to closure), length of hospital stay, amount of residual disease (0 cm, <1 cm, \geq 1 cm), the complexity of the surgery using Aletti's surgical complexity score between 1, 2 and 3 [16], and whether there were any intra-operative complications. Data were also collected on whether admission to the Intensive Treatment Unit or High Dependency Unit (ITU/HDU) was required as planned, or as an emergency event.

The following data were collected for chemotherapy: Type of chemotherapy, i.e., "Carboplatin and Paclitaxel" "Carboplatin monotherapy" or another form of or chemotherapy ("Other"), which included carboplatin, paclitaxel, and bevacizumab, or if they received another form of chemotherapy obtained through a clinical trial. Data were also extracted as to whether patients were treated to optimum dosage area under the curve (AUC) 6 for carboplatin monotherapy and AUC-5 for combined carboplatin/paclitaxel doublet, and the number of chemotoxicity events. А chemotherapy toxicity event was defined as either a software notification as input by a care provider within the chemotherapy administration program, or a reduction in dose due to an unwanted side effect of any magnitude.

Skewed continuous data were described using the median \pm interquartile range (IQR). The median values of the three groups were compared using the Kruskal-Wallis test. All categorical variables were described using frequencies and presented as percentages. Fisher's exact test was used to test the association between the categorical variables and age groups. For all numeric variables, the non-parametric Spearman's rank correlation coefficient was computed. Missing data was input as "Not recorded".

Overall survival was calculated from the date of diagnosis through to the date of death and analysed with the Kaplan-Meier method. Women who were alive at the end of the data collection period were censored. Comparison of the analysis of survival was carried out with the Wilcoxon test in cases where the survival curves crossed, otherwise the log-rank test was calculated. Effects were expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). A *p*-value lower than 0.05 was considered statistically significant. All statistical analysis was performed using the Statistical Analysis System (SAS®) Studio program (Release 3.8, SAS Institute Inc., Cary, NC, USA).

3. Results

The distribution of the 90 women across the three age groups were as follows: 19 women (21.1%) aged 65–69 years, 43

women (47.8%) aged 70–75 years, and 28 women (31.1%) aged 76 years or older. The median age at diagnosis was 73 years. The patient and clinical characteristics of the cohort by age group are reported in Table 1.

The only observed correlation seen between age group and patient characteristics was in WHO performance status (p = 0.044), suggesting that older women were less physically active. However, there was no correlation seen between age group and the age-adjusted, modified, Charlson score. There was also no observed correlation between "Time from decision to treatment", and age group. No age group was seen to seen to utilise one route of referral more than another.

Frequencies of treatment types by age group are shown in Fig. 1. There were no statistically significant associations found between age group and treatment type. However, the eldest age group showed a higher frequency of undergoing treatment types that did not involve surgery, *i.e.*, "chemotherapy only" and "no surgery and chemotherapy" (Age \geq 76 = 53.5%, Age 65–69 = 15.8%).

The most frequently used type of treatment throughout all the study's patients was neoadjuvant chemotherapy and cytoreductive surgery (52.2%).

Surgical treatment patterns are shown in Table 2. Patients within the eldest cohort who had surgery were just as likely to receive complete cytoreductive surgery as their younger counterparts. There was also no association seen between age group and operating time, length of stay, operative complications, or admission to the HDU. Median length of stay across all age groups was 5 days.

Chemotherapy data are displayed in Table 3. A correlation

TABLE 1. Patient and disease characteristics.										
	Total Sample		Age 65–69		Age 70–75		Age ≥ 76			
	n (10	= 90 00%)	n (21	= 19 .1%)	n (47	= 43 7.8%)	n (3)	= 28 [.1%]	<i>n</i> -value	
Median (IOR)	(((()	F ·····	
Age at diagnosis	73.0	(7.0)	67.0	(3.0)	72.0	(3.0)	79.5	(4.0)	_	
Time from decision to treatment (days)	13	(14)	12	(13)	13	(17)	14	(12)	0.718	
Ca-125 at diagnosis units/mL	712	(2306)	950	(2320)	733	(3099)	402	(1208)	0.249	
Frequencies and Percentages		. ,				. ,		. ,		
WHO Performance status $(n = 73)$										
0	12	13.3%	4	21.2%	4	9.3%	4	14.3%		
1	34	37.8%	10	52.6%	13	30.2%	11	39.3%		
2	16	17.8%	0	0.0%	12	27.9%	4	14.3%	0.044	
3	9	10.0%	1	5.3%	3	7.0%	5	17.9%		
4	2	2.2%	0	0.0%	0	0.0%	2	7.1%		
Not recorded	17	18.9%								
Age-adjusted modified Charlson score (n =	89)									
0	70	77.8%	15	78.9%	32	74.4%	23	82.1%		
1	13	14.4%	2	10.5%	6	13.9%	5	17.9%		
2	4	4.4%	1	5.3%	3	7.0%	0	0.0%	0.569	
3	2	2.2%	0	0.0%	2	4.6%	0	0.0%		
4	1	1.1%	1	5.3%	0	0.0%	0	0.0%		
Pre-treatment FIGO stage										
3a	12	13.3%	4	21.1%	4	9.3%	4	14.3%		
3b	4	4.4%	2	10.5%	2	4.6%	0	0.0%		
3c	42	46.7%	8	42.1%	19	44.2%	15	53.6%	0.659	
4a	23	25.6%	3	15.8%	13	30.2%	7	25.0%		
4b	9	10.0%	2	10.5%	5	11.6%	2	7.1%		
Route of Referral										
Suspected cancer referral	47	52.2%	9	47.4%	24	55.8%	14	50.0%		
Consultant (not A&E)	36	40.0%	9	47.4%	15	34.9%	12	42.9%	0.912	
Emergency (A&E or other specialty)	7	7.8%	1	5.3%	4	9.3%	2	7.1%		

Data are represented as the median with interquartile ranges and frequencies with percentages as appropriate. IQR: interquartile range; WHO: World Health Organisation; FIGO: International Federation of Gynaecology and Obstetrics; A&E: Accident and Emergency.



Treatment by age group at diagnosis

FIGURE 1. Treatment types by age group at diagnosis.

was observed between age group and type of chemotherapy; this was statistically significant. Patients \geq 76 years were more likely to receive single-agent carboplatin therapy than patients from the other two groups (p = 0.009), however, 83.3% of these women had their chemotherapy optimally dosed. The eldest patients did not experience a significantly higher number of chemotherapy-related toxicity events, despite receiving similar numbers of chemotherapy cycles as their younger counterparts.

Fig. 2 shows overall survival time by age group. Due to the nature of this cross-sectional, retrospective cohort study, the follow up period was between two and five years. There was no evidence of a relationship between age and survival. Overall survival rates in patients aged 65–69, 70–75, >76 years at one year were 42.1%, 40.5% and 32.1% (median survival was 25.0, 24.8 and 16.2 months) respectively. In the univariate Cox proportional hazard regression (HR) model, the estimated HR was 0.874 for patients aged 65–69, and 1.259 for >76 years, when compared with the 70–75 years age group. Likelihood ratio testing showed no statistically significant difference.

Fig. 3 shows overall survival time by treatment type. Treatment type was associated with worse overall survival; the lowest chance of survival was observed in patients who underwent no form of treatment (p = 0.001). No patients who received "No surgery or chemotherapy" were alive at one year. Three

patients underwent surgery but did not then receive chemotherapy. Unexpectedly, they were all alive at the end of the study period. On multivariate analysis, there was also no difference in survival between age groups, once accounted for complete cytoreductive surgery or adjusted Charlson comorbidity score.

4. Discussion

4.1 Results in the context of published literature

Demographic analysis of our cohort revealed no correlation between increasing age and the age-adjusted, modified Charlson comorbidity score. However, in our study, we witnessed an increased probability of worsening performance status with increasing age, also reported in other publications [8]. Poor performance status is associated with a poorer survival [17], which may explain our oldest age group's poor survival rate of 32% at one year.

The British Gynaecological Cancer (BGCS) 2019 guidelines for epithelial ovarian/fallopian tube/primary peritoneal cancer state that "Primary debulking surgery is the standard of care where complete or optimal cytoreduction appears achievable in patients with good performance status" [3]. For our patient cohort, NACT and cytoreductive surgery represented the most

					Median	(IQR)			
	Total S	Sample	Age	65–69	Age	70–75	Age	$e \ge 76$	<i>p</i> -value
Operation time $(n = 55)$ (min)	122.0	(53.0)	120.0	(68.0)	116.5	(49.5)	124.5	(53.0)	0.856
Hospital stay $(n = 58) (d)$	5.0	(1.0)	5.0	(1.0)	5.0	(1.0)	5.0	(2.0)	0.999
Frequencies and Percentages									
Residual Disease $(n = 88)$									
0 cm	42	46.7%	12	75.0%	20	62.5%	10	83.3%	
<1 cm	9	10.0%	2	12.5%	6	18.8%	1	8.3%	
>1 cm	9	10.0%	2	12.5%	6	18.8%	1	8.3%	0.836
No surgery	28	31.1%	3	-	10	-	15	-	
Not recorded	2	2.2%							
Aletti's surgical complexity sco	ore								
1	53	88.3%	16	100.0%	26	83.7%	11	84.6%	0.240
2	7	11.7%	0	0.0%	5	16.1%	2	15.4%	0.240
Operative complications $(n = 8)$	6)								
Bladder	1	1.1%	0	0.0%	0	0.0%	1	11.1%	
Bowel	3	3.3%	1	6.7%	2	7.1%	0	0.0%	
Other	1	1.1%	0	0.0%	0	0.0%	1	11.1%	0.163
No complications	47	52.2%	14	93.3%	26	92.9%	7	77.8%	
No surgery	34	37.8%	3	-	13	-	18	-	
Not recorded	4	4.4%							
ITU/HDU admission ($n = 86$)									
Emergency	6	6.7%	1	7.7%	4	12.5%	1	7.7%	
Planned	2	2.2%	0	0.0%	2	81.2%	0	0.0%	
No	50	55.6%	12	92.3%	26	6.3%	12	92.3%	1.000
No surgery	28	31.1%	3	-	10	-	15	-	
Not recorded	4	4.4%							

TABLE 2. Procedure characteristics and results.

Data are represented as the median with interquartile ranges and frequencies with percentages as appropriate. *IQR: interquartile range; ITU: Intensive Treatment Unit; HDU: High Dependency Unit.*

commonly-used treatment modality for all patients. A reduction in the frequency of surgery corresponding with increasing age is seen across most age-stratified studies [2, 7, 8]. However, this reduction in surgery in older patients can vary, depending on the year of study. The changing trend in treatment patterns was demonstrated by a Dutch nationwide analysis of treatment and outcomes of older patients with advanced stage EOC from 2006 to 2013 [18]. During this period, the work of Vergote [19] demonstrated non-inferiority in the survival of patients treated with NACT and cytoreductive surgery in comparison with primary surgery and adjuvant chemotherapy. Preferences for treatment modalities vary within MDTs across England [2] and internationally. For example, one Greek study published in 2021 assessed 735 patients, of whom 165 patients were older than 70 years. Of the 165 older patients, 70.9% underwent primary surgical treatment [8]. In our study, 14% of patients between the ages of 70 and 75 years underwent upfront operative treatment and in the NOCAFP, 21.1% of patients aged between 70 and 79 years fell in this treatment category [2].

We found that within our eldest patient cohort, women who underwent surgery were just as likely to undergo optimal cytoreductive surgery as our younger patients. This is in contrast to several other studies [7-9] which showed that elderly patients were more likely to be left with residual disease. This may be as a result of subconscious clinician bias or a conscious decision to not complete more complex, and therefore more lengthy procedures which may increase the risk of post operative morbidity. We found however, that there was no statistically significant difference in operating time, length of stay, operative complications or admission to the HDU between age groups, and elderly patients were just as likely to receive surgery with relatively higher complexity scores. It is worth noting however, that the maximum Aletti's surgical complexity score achieved within this cohort was 2 and our median operating time for each age group was 120, 116.5 and 124.5 minutes for 65–69, 70–75 and \geq 76 years respectively. This may be as a result of patient selection or that the majority of our patients who did undergo surgery were more likely to have undergone neoadjuvant chemotherapy, which may have

	Median (IQR)								
	Total Sample		Age 65–69		Age 70–75		Age ≥ 76		<i>p</i> -value
Total chemo cycles $(n = 67)$	6.0	(2.0)	7.0	(9.5)	6.0	(2.0)	6.0	(3.0)	0.129
Frequencies and Percentages									
Chemotherapy type $(n = 84)$									
Carboplatin & Taxol	28	31.1%	8	53.3%	16	42.1%	4	21.1%	
Carboplatin monotherapy	29	32.2%	2	13.3%	13	34.2%	14	73.7%	
Other*	14	15.6%	5	33.3%	8	21.1%	1	5.3%	0.000
Unknown	1	1.1%	0	0.0%	1	2.6%	0	0.0%	0.009
No chemotherapy	12	13.3%	2	-	3	-	7	-	
Not recorded	6	6.7%							
Optimal dosage (AUC-6-carbo	platin m	onotherapy,	AUC-5	carboplatin/	paclitax	el)			
Yes	49	54.4%	11	84.6%	23	71.9%	15	83.3%	
No	14	15.6%	2	15.4%	9	28.1%	3	16.7%	0 563
No chemotherapy	11	12.2%	1	-	5	-	5	-	0.303
Not recorded	16	17.8%							
Reasons for dose reduction (n	= 74)								
Frailty/Co-morbidity	5	5.6%	0	0.0%	2	22.2%	3	75.0%	
Patient choice	1	1.1%	0	0.0%	0	0.0%	1	25.0%	
Toxicity event	8	8.9%	2	100.0%	6	66.7%	0	0.0%	0.082
Unknown	1	1.1%	0	0.0%	1	11.1%	0	0.0%	0.082
No dose reduction	59	65.6%	12	-	28	-	19	-	
Not recorded	16	17.8%							
Chemotoxicity event $(n = 71)$									
CNS/PN	6	6.7%	2	10.5%	4	9.3%	0	0.0%	
Gastro-intestinal	1	1.1%	0	0.0%	1	2.3%	0	0.0%	
Generalised side effects	1	1.1%	0	0.0%	1	2.3%	0	0.0%	
Haematological	5	5.6%	1	5.3%	1	2.3%	3	10.7%	0.207
Renal	2	2.2%	0	0.0%	2	4.6%	0	0.0%	0.307
Other	1	1.1%	1	5.3%	0	0.0%	0	0.0%	
None	55	61.1%	10	52.6%	27	62.8%	18	64.3%	
Not recorded	19	21.1%							

TABLE 3. Chemotherapy characteristics and toxicities.

*"Other" included: carboplatin, paclitaxel and bevacizumab or another form of chemotherapy obtained through a clinical trial. Data are represented as the median with interquartile ranges and frequencies with percentages as appropriate. IQR: interquartile range; AUC: Area under the curve; CNS: Central Nervous System; PN: Peripheral nervous system.

resulted in a reduced tumour volume and relatively reduced operating times. We also found that there was no correlation seen between age and length of hospital stay. This may have been due to limited comorbidities in our eldest age group, similar numbers of complications seen across each cohort or

Elderly patients were more likely to be treated with carboplatin monotherapy, which has also been demonstrated in several other studies [7–9]. Although dual therapy maybe perceived by patients and some oncologists to have higher rates of chemo-toxicity events, studies have shown that this may not be the case [20]. In addition, towards the end of our study

an emphasis on enhanced recovery within the studied institute.

period, Falandry *et al.* [21] demonstrated that patients over the age of 70 years with advanced stage epithelial ovarian cancer and a geriatric vulnerability score over 3, significantly benefit in terms of survival from carboplatin and paclitaxel chemotherapy over 3 weekly or weekly single agent carboplatin, to the extent that the study ended recruitment prematurely [21]. The majority of our patients treated with chemotherapy were adequately dosed to AUC-6. We also saw no increase in chemotoxicity events with increasing age despite some studies observing the opposite [22].

We observed that the eldest age group had the shortest median survival duration, however, statistical significance was

The LIFETEST Procedure



FIGURE 2. Overall survival by age group.



FIGURE 3. Overall survival by treatment type. CTx: Chemotherapy; NAC: Neo-adjuvant chemotherapy; CRS: Cytoreductive surgery; PS: Primary surgery; AC: Adjuvant chemotherapy.

not reached, most likely due to the small sample size. In patients \geq 76 years, survival rate at one year was 32.1%. In the NOCAFP's short-term mortality analysis, patients in the age groups 70–79 years and >80 years had survival rates at one year of 63.8% and 34.5% respectively [23]. The present study also adds to the established literature that the poorest survival is seen in patients who undergo no treatment [2].

Although survival between elderly and younger patients are most pronounced the first year following diagnosis, for patients who do undergo both surgery and chemotherapy, survival rates are comparable at five years and ten years of treatment [24]. An American study published in 2011 found that although the risk of surgery for patients over the age of 80 years was high at 45%, (defined by poor peri-operative outcome of 3-month mortality, grade 3 morbidity or unable to receive chemotherapy) this group of patients had a median survival of 5 years, similar to that of the 65-69 years age group. It is worth noting however, that all the patients in the study underwent primary surgery as opposed to NACT followed by surgery and 55% of the eldest cohort underwent procedures with an Aletti's surgical complexity score of 4 or more. The team found that pre-operative albumin of less than 3 g/dL was the strongest predictor of surgical complication [25].

4.2 Strengths and weaknesses

A strength of this study is its relevance to smaller cancer centres working outside of superspecialist ovarian cancer hubs with older patients. The limitations of this study include its small sample size and therefore lack of statistical power. The information was collected in retrospect from other clinicians' records and therefore some datasets were incomplete. Survival data were sometimes incomplete due to a varying follow up period. Another limitation of our study is the lack of information behind the reasons for treatment decisions, such as NACT over primary surgery. Reasons were not routinely recorded in the MDT outcomes, although from the authors' experience, main reasons included severe pre-existing co-morbidities and frailty or patients declining treatment.

4.3 Implications for practice and future research

Treatment of older patients with ovarian cancer represents a multi-dimensional challenge for the MDT: some institutions have consequently invested in geriatric assessment, "prehabiliation" and specialised post operative care [26]. However, the NOCAFP showed large variations in treatment patterns in age, especially for patients over 80 years old.

Clegg defined frailty as "A state of vulnerability to poor resolution of homoeostasis after a stressor event and is a consequence of cumulative decline in many physiological systems during a lifetime" [27], while Fried and colleagues characterized the condition as a combination of unintentional weight loss, self-reported fatigue, diminished physical activity, reduced strength and gait speed [28]. Advanced stage ovarian cancer can significantly worsen existing frailty due to its global effect on the body's anatomy and physiology and several studies have demonstrated an association between Short Physical Performance Battery (SPPB), gait speed, and survival in gynaecological cancer patients [29, 30]. The present study suggests that NACT offers the opportunity to improve the older patient's performance status, reduce operating times, improve rates of complete cyto-reduction and achieve shorter hospital lengths of stay.

Our results also add further evidence that older patients with ovarian cancer are more likely to receive single agent carboplatin, however, we observed no increase in chemotoxicity events with increasing age. In the context of the EWOC-1 (Multicenter, Randomized Trial of Carboplatin +/- Paclitaxel in Vulnerable Elderly Patients with Stage III-IV Advanced Ovarian Cancer) study [21] and these findings, the authors recommend a risk versus benefit discussion with patients regarding dual agent chemotherapy but when single agent is used, patients should be offered optimally dosed regimes.

While performance status is a useful tool to guide treatment planning, frailty assessments may provide more detailed information to assist the MDT and patient in shared decisionmaking. Indeed, the American Society of Clinical Oncology published guidelines in 2018 to assist clinicians with treatment decisions in older patients receiving chemotherapy based on expert opinion and Delphi consensus [31]. A 2021 American randomised controlled trial examining outcomes of chemotherapy in patients over 70 years, randomised participants to formal geriatric assessment and treatment or treatment alone. The study showed that a lower proportion of patients in the study group had grade 3–5 toxic events and fewer falls [32]. The authors recommend similar research in surgical patients to assess whether geriatric assessments can be utilised to aid treatment decisions and therefore improve outcomes.

5. Conclusions

Treatment of the older, advanced-stage ovarian cancer patient, remains challenging due to the heterogeneity of this increasingly populous group. Primary maximal effort cytoreductive surgery may be favoured by many centres and indeed internationally, however, NACT may offer the opportunity to improve an older patient's performance status and optimise them physiologically for surgery. As the gynaecological cancer community begins to care for an increasingly older population, both medical and surgical treatment decisions may be improved by formal geriatric assessments and shared decision making.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

AW—conceptualisation, methodology, validation, investigation, resources, data curation, writing original draft, visualisation, project administration. EVDZ—investigation, data curation. VM—data curation, formal analysis. SAB—formal analysis, supervision. FD—conceptualisation, methodology, validation, writing-review and editing, supervision.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Data was collected from several electronic databases in retrospect on data that had already been collected so neither new patient consent nor ethical approval was required.

ACKNOWLEDGMENT

The authors would like to thank Kate Lankester of University Hospitals Sussex, for her assistance with the medical oncology content of this paper.

The authors would also like to thank Juliet Bell, who kindly proofread the article to correct typographical errors, improved syntax and offered an expert scientific opinion from outside gynaecologic oncology.

The authors would also like to thank the gynaecological oncology team of University Hospitals Sussex, particularly of the Royal Sussex County Hospital who cared for the patients during their ovarian cancer treatment.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

- [1] Office for National Statistics. Cancer registration statistics. 2017. Available at: www.ons.gov.uk/file?uri=/peoplepopulationandcommunity/ healthandsocialcare/conditionsanddiseases/datasets/cancerregistration statisticscancerregistrationstatisticsengland/2016/2016cancerregistrati onsreferencetablesfinal.xls (Accessed: 21 April 2024).
- [2] National Ovarian Cancer Audit Feasibility Pilot (NOCAFP). Disease profile in England: incidence, mortality, stage and survival for ovary, fallopian tube and primary peritoneal carcinomas. 2020. Available at: https://digital.nhs.uk/ndrs/data/data-outputs/ovariancancer-audit-feasibility-pilot-ocafp---projectsummary-report/disease-profile-in-england (Accessed: 25 May 2024).
- [3] Fotopoulou C, Hall M, Cruickshank D, Gabra H, Ganesan R, Hughes C, et al. British Gynaecological Cancer Society (BGCS) epithelial ovarian/fallopian tube/primary peritoneal cancer guidelines: recommendations for practice. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2017; 213: 123–139.
- [4] Cancer Research UK. Ovarian cancer survival. 2023. Available at: https://www.cancerresearchuk.org/about-cancer/ovariancancer/survival (Accessed: 21 April 2024).
- ^[5] Dumas L, Bowen R, Butler J, Banerjee S. Under-treatment of older patients with newly diagnosed epithelial ovarian cancer remains an issue. Cancers. 2021; 13: 952.
- [6] Fairfield KM, Murray K, Lucas FL, Wierman HR, Earle CC, Trimble EL, et al. Completion of adjuvant chemotherapy and use of health services for older women with epithelial ovarian cancer. Journal of Clinical Oncology. 2011; 29: 3921–3926.
- [7] Joueidi Y, Dion L, Bendifallah S, Mimoun C, Bricou A, Nyangoh Timoh K, *et al.* Management and survival of elderly and very elderly patients with ovarian cancer: an age-stratified study of 1123 women from the FRANCOGYN group. Journal of Clinical Medicine. 2020; 9: 1451.
- [8] Liontos M, Papatheodoridi A, Andrikopoulou A, Thomakos N, Haidopoulos D, Rodolakis A, et al. Management of the elderly patients

with high-grade serous ovarian cancer in the REAL-WORLD setting. Current Oncology. 2021; 28: 1143–1152.

- [9] Jørgensen TL, Teiblum S, Paludan M, Poulsen LØ, Jørgensen AYS, Bruun KH, et al. Significance of age and comorbidity on treatment modality, treatment adherence, and prognosis in elderly ovarian cancer patients. Gynecologic Oncology. 2012; 127: 367–374.
- [10] Langstraat C, Cliby WA. Considerations in the surgical management of ovarian cancer in the elderly. Current Treatment Options in Oncology. 2013; 14: 12–21.
- [11] Tortorella L, Vizzielli G, Fusco D, Cho WC, Bernabei R, Scambia G, et al. Ovarian cancer management in the oldest old: improving outcomes and tailoring treatments. Aging and Disease. 2017; 8: 677.
- [12] Janda M, Youlden DR, Baade PD, Jackson D, Obermair A. Elderly patients with stage III or IV ovarian cancer: should they receive standard care? International Journal of Gynecologic Cancer. 2008; 18: 896–907.
- [13] World Health Organisation. International statistical classification of diseases and related health problems 10th revision. 2023. Available at: https://icd.who.int/browse10/2019/en#/C56 (Accessed: 21 April 2024).
- [14] Prat J; FIGO Committee on Gynecologic Oncology. Staging classification for cancer of the ovary, fallopian tube, and peritoneum. International Journal of Gynecology & Obstetrics. 2014; 124: 1–5.
- [15] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. Journal of Chronic Diseases. 1987; 40: 373–383.
- [16] Aletti G, Santillan A, Eisenhauer E, Hu J, Aletti G, Podratz K, *et al.* A new frontier for quality of care in gynecologic oncology surgery: multiinstitutional assessment of short-term outcomes for ovarian cancer using a risk-adjusted model. Gynecologic Oncology. 2007; 107: 99–106.
- [17] Hawarden A, Russell B, Gee ME, Kayali F, Clamp A, Crosbie EJ, et al. Factors determining ultra-short-term survival and the commencement of active treatment in high-grade serous ovarian cancer: a case comparison study. BMC Cancer. 2021; 21: 378.
- [18] Schuurman MS, Kruitwagen RFPM, Portielje JEA, Roes EM, Lemmens VEPP, van der Aa MA. Treatment and outcome of elderly patients with advanced stage ovarian cancer: a nationwide analysis. Gynecologic Oncology. 2018; 149: 270–274.
- ^[19] Vergote I, Tropé CG, Amant F, Kristensen GB, Ehlen T, Johnson N, *et al.* Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. New England Journal of Medicine. 2010; 363: 943–953.
- [20] Ceccaroni M, D'Agostino G, Ferrandina G, Gadducci A, Di Vagno G, Pignata S, *et al.* Gynecological malignancies in elderly patients: is age 70 a limit to standard-dose chemotherapy? An Italian retrospective toxicity multicentric study. Gynecologic Oncology. 2002; 85: 445–450.
- ^[21] Falandry C, Savoye AM, Stefani L, Tinquaut F, Lorusso D, Herrstedt J, *et al.* EWOC-1: a randomized trial to evaluate the feasibility of three different first-line chemotherapy regimens for vulnerable elderly women with ovarian cancer (OC): a GCIG-ENGOT-GINECO study. Journal of Clinical Oncology. 2019; 37: 5508–5508.
- [22] Kim J, Hurria A. Determining chemotherapy tolerance in older patients with cancer. Journal of the National Comprehensive Cancer Network. 2013; 11: 1494–1502.
- [23] Nordin A, Sundar S, Nieto J, Eversfield C, Turner C, Knott C, et al. Ovarian cancer audit feasibility pilot, short-term mortality in ovarian, fallopian tube and primary peritoneal carcinomas across England. 2022. Available at: https://digital.nhs.uk/ndrs/data/dataoutputs/ovarian-cancer-audit-feasibility-pilotocafp---project-summary-report/short-term-mortalityacross-england (Accessed: 25 May 2024).
- ^[24] Wright JD, Chen L, Tergas AI, Patankar S, Burke WM, Hou JY, *et al.* Trends in relative survival for ovarian cancer from 1975 to 2011. Obstetrics & Gynecology. 2015; 125: 1345–1352.
- [25] Langstraat C, Aletti GD, Cliby WA. Morbidity, mortality and overall survival in elderly women undergoing primary surgical debulking for ovarian cancer: a delicate balance requiring individualization. Gynecologic Oncology. 2011; 123: 187–191.
- ^[26] Sbai M, Jasper E, Martin F, Rajkumar S, Montes A, Jeyarajah J, *et al.* Shared decision making in gynaecological oncology; a challenge in an ageing population. The Obstetrician & Gynaecologist. 2021; 23: 290– 294.

- [27] Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. The Lancet. 2013; 381: 752–762.
- ^[28] Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2001; 56: M146–M157.
- [29] Verweij NM, Schiphorst AHW, Pronk A, van den Bos F, Hamaker ME. Physical performance measures for predicting outcome in cancer patients: a systematic review. Acta Oncologica. 2016; 55: 1386–1391.
- [30] Cesari M, Cerullo F, Zamboni V, Di Palma R, Scambia G, Balducci L, et al. Functional status and mortality in older women with gynecological cancer. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2013; 68: 1129–1133.
- [31] Mohile SG, Dale W, Somerfield MR, Schonberg MA, Boyd CM, Burhenn PS, et al. Practical assessment and management of vulnerabilities in older

patients receiving chemotherapy: ASCO guideline for geriatric oncology. Journal of Clinical Oncology. 2018; 36: 2326–2347.

[32] Mohile SG, Mohamed MR, Xu H, Culakova E, Loh KP, Magnuson A, et al. Evaluation of geriatric assessment and management on the toxic effects of cancer treatment (GAP70+): a cluster-randomised study. The Lancet. 2021; 398: 1894–1904.

How to cite this article: Alistair Ward, Eleanor van der Zanden, Vangelis Mone, Stephen A. Bremner, Florian Drews. Management of advanced epithelial ovarian cancer in the older patient: an age stratified cohort study of a gynaecological cancer centre in Southern England. European Journal of Gynaecological Oncology. 2024; 45(4): 145-154. doi: 10.22514/ejgo.2024.080.