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Outcomes of women not receiving treatment for advanced ovarian cancer in the West of Scotland: a retrospective analysis

W. MacNab[1], R.M. Glasspool[2], S. Shanbhag[1], A. H. Sadozye[2], K.A. Burton[1], I.A. McNeish[2], N.S. Reed[2], N. Siddiqui[1], M.K. Mehasseb[1]

[1] Department of Gynaecological Oncology, Glasgow Royal Infirmary, Glasgow
[2] Beatson West of Scotland Cancer Centre, Glasgow (United Kingdom)

Summary

Objective: There are very few published reports on the outcomes of women who receive no active treatment for advanced ovarian cancer. The present authors aimed to determine the proportion of women diagnosed with advanced ovarian cancer who do not receive active treatment, the factors that guide the decision not to offer treatment, and their survival duration without treatment. *Materials and Methods:* The authors conducted a retrospective analysis of all women diagnosed with ovarian cancer who were not given active treatment by the West of Scotland Cancer Network (WoSCAN) between 2009 and 2012. Data were collected on patient demographics, referral process and outcome. *Results:* Ten percent (n=110) of all ovarian cancers received no active treatment, 25.2% of those not treated declined active treatment, 70% presented for the first time as an emergency, and 28% of diagnoses were made on clinical-radiological grounds only. The median survival from diagnosis was 31 days. *Conclusion:* 10% of patients with ovarian cancer are not given any active treatment. The median survival in this cohort is less than one month.

Key words: Ovarian carcinoma; Prognosis; Treatment; Survival; Epidemiology.

Introduction

Ovarian cancer is the second commonest gynaecological malignancy in the United Kingdom with 7,116 new cases recorded in 2011 [1]. Approximately 46% of patients present with advanced (Stage 3 or 4) disease [2]. The incidence of ovarian cancer increases with age, with 50% of cancers diagnosed in women over 65 years of age [3]. Survival falls with age, which maybe due to a number of factors such as cancer biology and associated co-morbidities [4] and poor performance status, but may also include reluctance of attending oncologists to instigate treatment for fear of toxicity. As a result of a combination of these factors, a proportion of patients will not be considered suitable for any active treatment.

In the United Kingdom, women with suspected ovarian cancer are referred to, and are discussed at, regional Multi Disciplinary Team (MDT) meetings, where recommendations for treatment are made. In the West of Scotland, all ovarian cancers are managed by the West of Scotland Managed Cancer Network (WoSCAN), which is one of the largest Networks in the UK, covering a population of 2.8 million, 50% of the total population of Scotland.

There are few published data on patients who are not offered active treatment, as, by definition, they are not included in clinical trials looking at new interventions or appraisals of current treatment regimes. A review of the literature did not identify any studies that reported on this group exclusively. The present authors aimed to determine the proportion of women diagnosed with advanced ovarian cancer not receiving active treatment, the factors that may guide the decision not to offer treatment, and survival without active treatment in this cohort.

Materials and Methods

A retrospective analysis was undertaken of all ovarian and primary peritoneal cancers (also known as tubo-ovarian cancers) registered with the West of Scotland cancer registry between January 2009 and December 2012. This was approved by the West of Scotland Cancer Network clinical governance committee. This period allowed sufficient time following diagnosis for overall survival to be assessed reliably. Patients were excluded from analysis if they had any surgery or chemotherapy, including palliative regimes. Further exclusions were made if patients did not have a record on any of the electronic health record (eHR) systems used across the cancer network. Where records were incomplete despite cross-referencing multiple eHR systems, analysis was undertaken on the available data and acknowledged accordingly.

Health Deprivation was calculated using the Scottish Index of Multiple Deprivation (SIMD) [5], which is a validated tool for identifying deprivation by geographical location and has been described fully in other publications. This model uses "datazones" (an area of approximately 350 households), which are identified by postal (zip) code.

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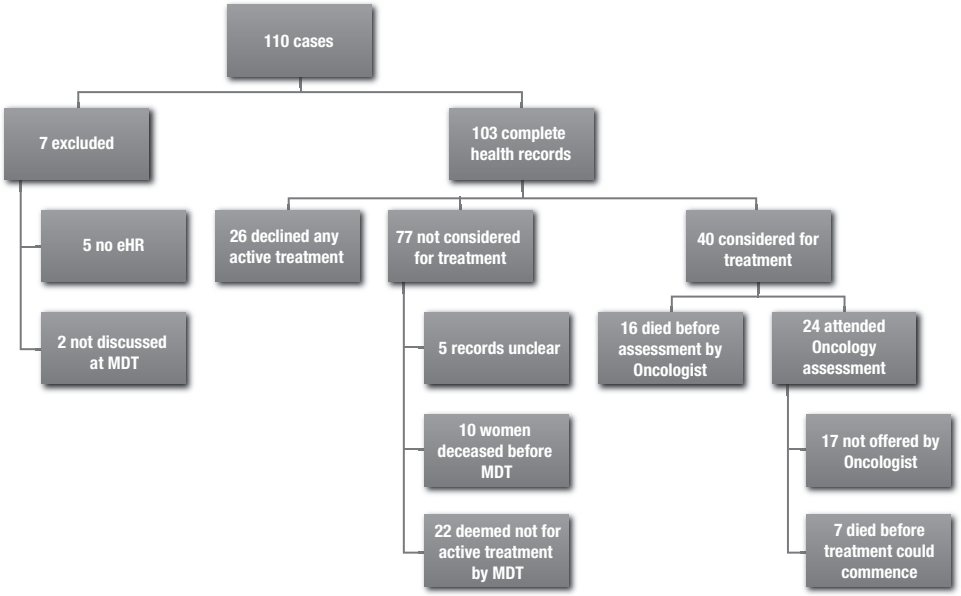

Figure 1. — Study population.

The diagnosis was established on ***pathological*** (histology or cytology report confirming ovarian or primary peritoneal cancer) or ***clinical-radiological*** grounds. The latter was based on clinical findings, imaging, and tumour markers, including CA125: CEA ratio (a ratio of greater than 25 supports the possible diagnosis of an ovarian primary) [6].

Referrals were categorized by urgency and specialty first referred to: ***urgent*** (primary care physician referral to secondary care as a suspected cancer), ***non-urgent*** (routine referrals to secondary care or specialist-to-specialist referrals), ***emergency*** (first presentation as an emergency admission), and ***undocumented***. Specialties referred to were recorded as gynaecology, general surgery, urology, and general (internal) medicine (GIM). The dates of referral, MDT discussion, and death were also recorded.

For the purposes of this study, the date of the MDT discussion, rather than the date of pathology result, was taken to be the date of diagnosis to allow direct comparison with clinical-radiological diagnoses. Survival was calculated as the number of days from MDT meeting to death.

The reason the patient did not receive active treatment was classified as: 1) ***Patient declined active treatment***: women whose records clearly stated that they did not want active treatment, regardless of the recommendation of the MDT. The referring physician counselled these women before making their decision. 2) ***Patient not offered active treatment***: women not offered active treatment by the MDT based on the information provided by the referring clinician, OR women considered as possible candidates for treatment but who either died before attending an appointment with an Oncologist or were not offered treatment following consultation with an Oncologist. 3) ***Patients deceased before active treatment commenced***: women who accepted treatment offered to them by an Oncologist but who died before it could commence.

Results

Over the period of the study (2009-2012), 1,100 cases of ovarian cancer were registered with the WoSCAN. Of these, 110 (10%) received no active treatment. Seven women were excluded from further analysis: five did not have electronic health records and two were not discussed at an MDT meeting. Of the remaining 103 women, 26 (25.2%) declined any treatment offered by the referring physician, and were discussed at the MDT for registration purposes only. Seventy-seven (74.8%) were considered for referral to the MDT: ten had died by the time of MDT discussion, 22 were not deemed fit for active treatment, and five had unclear records. The 40 remaining women were referred to an oncologist: 16 died before their appointment and 17 were deemed not fit for chemotherapy. Hence in summary, 70 (68.0%) women were not offered active treatment at any stage. The remaining seven (6.8%) women died before treatment could commence (Figure 1).

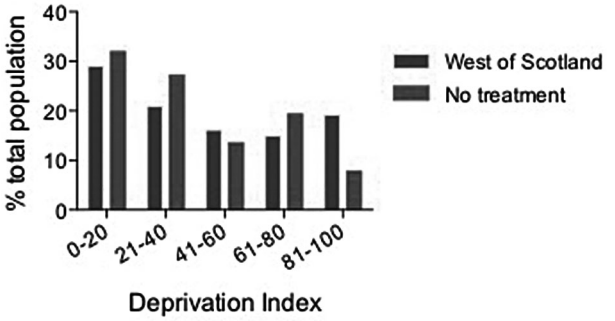

Figure 2. — Demographic characteristics of women not receiving active treatment (x-axis represents deprivation quintiles, y-axis represents percentage of population).

The median age of the study cohort was 78 years (range 44-93 years). In comparison, a cohort of women treated with chemotherapy for ovarian cancer within the same Network, had a median age of 64 years ($p = 0.0001$).

Health deprivation was calculated for all cases. Depriva-

Table 1. — *Referral type, specialty referred to, and referral intervals.*

	Emergency admission	Non-urgent admission	Urgent admission	Unknown
Gynaecology	3	2	6	-
General internal medicine	25	2	3	-
General surgery	16	2	5	-
Urology	1	1	0	-
Undocumented	3	0	0	-
Referral to diagnosis interval; median (range) (n=60)	22 days (4-103)	81 days (21 – 108)	33 days (16-104)	-
Treatment decision				
Declined active treatment	18	1	2	5
Active treatment not offered	29	6	10	25
Died before active treatment commenced	1	0	2	4

Table 2. — *Method of diagnosis, age, and treatment decision.*

	Clinical – radiological	Pathological	
		Cytology	Histology
Number (%)	29 (28.2%)	59 (57.3%)	15 (14.6%)
Median age (range)	83 (61-93)	77 (44-89) 7	4 (58-89)
Survival days (range)	29 (0 – 946)	24 (3 – 324)	32 (16 - 174)
Declined	8	13	5
Not offered	21	42	7
Died before treatment commenced	0	4	3

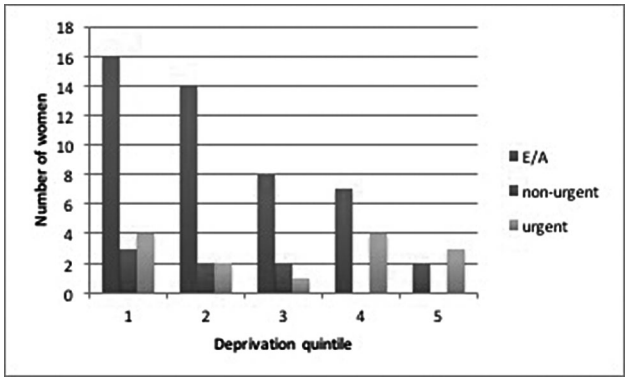

Figure 3. — Effect of deprivation on referral type.

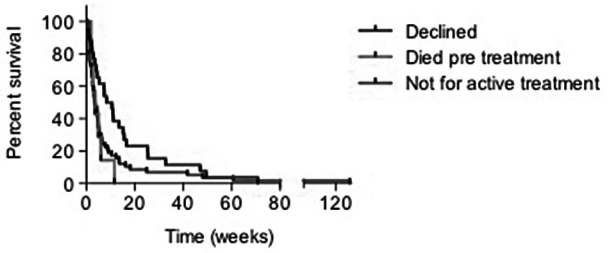

Figure 4. — Survival per decision category.

tion scores were divided into quintiles (1 being the most deprived and 5 being the least) and the three groups were compared to each other. In comparison the West of Scotland population as a whole, there was a significant difference in the proportion of women from the least deprived quintile (19.1% *vs.* 7.8%) $p \leq 0.05$ (Figure 2).

The type of referral was recorded in 69 cases only. Emergency admissions accounted for 48 (69.7%) cases, urgent referrals for 14 (20.2%) cases , and non-urgent referrals for seven (10.1%) cases. Table 1 shows distribution of referrals by type and initial specialty. In three cases the specialty referred to was not documented (emergency admissions group).

Overall, only 15.9% of referrals were initially made to gynaecology services. Notably, a low number of emergency referrals were made to gynaecology (6.3%), in contrast to 42.9% of urgent referrals. The referral date as well as referral type was recorded for 60 of the 103 women. For these women, the median referral to diagnosis interval was 25 (range 4-103) days. Women who died before treatment commenced had the shortest median referral to treatment interval at 15 (range 5 to 55) days versus 20 (range 2 to 108 days) for those not offered treatment and declined treatment 21 days (range five to 104 days). There was a reduction in the number of emergency admissions (E/A) with decreasing deprivation (Figure 3).

The diagnosis was established on histological or cytological grounds in 74 (71.8%) women: 52 from ascitic fluid cytology, seven from pleural fluid cytology, and only 15 from histology gained from image guided biopsies. The diagnosis was made on clinical-radiological grounds in the remaining 29 (28.2%) women. A 101 women had a serum CA125 result recorded. In the clinical-radiological group,

nine did not have a CA215:CEA ratio calculated, and of those that did, four women had a ratio of less than 25. All patients offered treatment had a pathological diagnosis, as well as 69.2% of women declining treatment (Table 2).

The median overall survival for all women was 31 (range 0 to 946) days. Women who declined treatment had the longest median survival (67 days, range 6-341) (declined versus all other women $p = 0.0232$) (Figure 4).

Discussion

The present study examined the proportion of women with advanced ovarian cancer who were not offered any active treatment at one of the UK's largest regional gynaecological cancer networks. There is a paucity of data on this specific cohort of women. Extrapolation from studies reporting on the optimal treatment of ovarian cancer and adherence to guidelines would estimate non-treatment rates of 3.3–10% [7-9]. The present study population is comparable to the population in McNally's study as they were both managed by Scottish Cancer Networks. It known that older women are less likely to receive standard treatment [10-13] and the present results reflect this.

Public Heath England (PHE) has published data on the incidence of ovarian cancer in England [14], which shows no significant variation by degree of deprivation. However, deprivation has been shown to be an independent variable associated with not receiving optimal treatment for ovarian malignancy [9] and a predictor of poorer survival [15]. Although not directly comparable to the PHE data, the present findings show that 60% of the women were in the two lowest quintiles for health deprivation. This might explain the access to healthcare systems, referral patterns, and possibly treatment decisions subsequently made.

A quarter of patients (25.2%) declined active treatment following initial counselling by the referring clinician and it was not possible to ascertain what information was provided to the patient, specifically about treatment options, outcomes, and toxicities, for them to have based their decision on. This group had the longest median survival, which suggests that some women may have been medically fit enough for active treatment, and had they been counselled by medical, clinical or gynaecological oncologist their decision might have been different. A study by Seifert *et al.* [16] looking at urgent in-patient chemotherapy for women with a poor performance status found that treatment is feasible and does result in good survival for some, so appropriate counselling particularly of apparently poor performance status patients is essential.

The diagnosis of ovarian cancer was made on clinical-radiological grounds in 28% of women in the present study. This is higher than the 10% rate observed by Freedman *et al,* [17] in their study comparing the performance of pathological versus clinical diagnosis of ovarian cancer, whereby the clinical-radiological diagnosis was approximately 87% accurate (where final pathology was available to confirm). This may explain the long survival of some women in the present study, in particular the two women who had a clinical–radiological diagnosis without a supporting CA125: ratio, who lived for more than six months, for whom the absence of histological proof, may have led to the incorrect diagnosis of ovarian cancer.

A pathological diagnosis is required, in all but exceptional circumstances, before commencing chemotherapy [18] and in the present study, a histological diagnosis was less likely in older women which may reflect the perception that older women are less likely to be offered treatment and therefore pursing a histological diagnosis is unnecessary.

The present study found that 20% of women were referred as "urgent" and 70% presented for the first time as an emergency. The National Cancer Intelligence Network (NCIN) published audit figures for all ovarian cancers (including those receiving treatment) [19] and found that 23% of referrals were "urgent" suspected cancer and 33% were emergency referrals. It likely that the higher emergency presentation rate in women who ultimately received no active treatment reflects poorer awareness of ovarian cancer symptoms, delayed or no presentation to primary care and thus poorer performance status at presentation. Within the group referred as an emergency, only 6.3% were directed to gynaecology. It is well recognized that ovarian cancer presents with vague symptoms that can mimic a number of other conditions. Thus, initial referral, and diagnosis, are often delayed or initiated by the non-gynaecological specialties. Education of clinicians may reduce diagnostic delays and increase the number of women fit for treatment at presentation to the gynaecology services. A study by Lim *et al.* [20] investigating time from referral to diagnosis for ovarian cancer, found that the median interval for urgent referrals was similar to the present study at 1.4 months and non-urgent referrals at 2.6 months. This suggests that the present referral to diagnosis intervals are in keeping with other cancer networks, but improving this might increase the proportion of women are offered active treatment.

The median survival in the present population was one month. This is comparable to other studies [21, 22]. Mortality is particularly high in the first one to two months following diagnosis in all women, even those who receive treatment. Advanced age, emergency presentation, and tumour morphology have the greatest effect on survival to one year and these variable have a cumulative adverse effect on survival [21]. It is reasonable to conclude that the factors identified have a similar effect on the decision not to treat as well.

In the present study, positively identifying the factors that determined not receiving active treatment was difficult, beyond those cases where treatment was declined. Significant co-morbidities were recorded in the majority of patients and these may have been instrumental in the decision not to treat. It is likely that rapid disease progression rather than diagnos-

tic delays explains the death of the seven women who were offered treatment but died before commencing chemotherapy.

To the best of the present authors' knowledge, this is the first study exclusively to examine women not receiving active treatment for ovarian cancer. The present study has the strength of accessing a large population treated by a single cancer network, ensuring consistency of diagnosis, management, and record keeping.

There are some potential weaknesses to the present study. Firstly, this was a retrospective analysis and as such, it was not possible to consider patients who died without being registered with the Network or discussed in the MDT. Secondly, it is possible that the clinical-radiological diagnosis was not completely accurate and some of these women did not have ovarian cancer. Last, the SIMD is a validated tool for health deprivation, but is accepted that it can only be a marker for an individual's risk of health deprivation and some patients may have been inaccurately categorized.

Conclusion

Ten percent of women with advanced ovarian cancer receive no active treatment. These women are usually older, mostly from a less privileged social background, and present mainly to non-gynaecology services with poor performance status. A quarter decline treatment at presentation. Rapid disease progression rather than diagnostic or therapeutic delays accounts for the inability to commence treatment in those women deemed fit.

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References

[1] CRUK: "Cancer Research UK Ovarian Cancer Statistics 2014". Available at: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/ovarian-cancer

[2] McPhail S., Johnson S., Greenberg D., Peake M., Rous B.: "Stage at diagnosis and early mortality from cancer in England". Br. J. Cancer, 2015, *112*, S108.

[3] Tew W.P., Fleming G.F.: "Treatment of ovarian cancer in the older woman". *Gynecol. Oncol.*, 2015, *136*, 136.

[4] Freyer G., Tew W.P., Moore K.N.: "Treatment and trials: ovarian cancer in older women". *Am. Soc. Clin. Oncol. Educ. Book*, 2013, 227.

[5] SIMD: "Scottish Index of Multiple Deprivation 2012". Available at: http://simd.scotland.gov.uk/publication-2012

[6] Sørensen S.S., Mosgaard B.J.: "Combination of cancer antigen 125 and carcinoembryonic antigen can improve ovarian cancer diagnosis". Dan. Med. Bull., 2011, *58*, A4331.

[7] Fagö-Olsen C.L., Ottesen B., Kehlet H., Antonsen S.L., Christensen I.J., Markauskas A., *et al.*: "Differences in regional diagnostic strategies and in intended versus actual first-line treatment of patients with advanced ovarian cancer in Denmark". *Int. J. Gynecol. Cancer*, 2014, *24*, 1195.

[8] McNally O.M., Delaney E., Petty R.D., Cruickshank M.E., Hutcheon A.W., Parkin D.E.: "Is optimal first-line chemotherapy deliverable in all newly diagnosed ovarian cancers? A population-based study". *Br. J. Cancer*, 2003, *89*, 966.

[9] Long B., Chang J., Ziogas A., Tewari K.S., Anton-Culver H., Bristow R.E.: "Impact of race, socioeconomic status, and the health care system on the treatment of advanced-stage ovarian cancer in California". *Am. J. Obstet. Gynecol.*, 2015, *212*, 468 e1.

[10] Efstathiou E., Dimopoulos M.A., Bozas G., Kastritis E., Moulopoulos L.A., Rodolakis A., *et al.*: "Advanced epithelial ovarian cancer in the elderly: chemotherapy tolerance and outcome". *Anticancer Res.*, 2007, *27*, 611.

[11] Jorgensen T.L., Teiblum S., Paludan M., Poulsen L.O., Jorgensen A.Y., Bruun K.H., *et al.*: "Significance of age and comorbidity on treatment modality, treatment adherence, and prognosis in elderly ovarian cancer patients". *Gynecol. Oncol.*, 2012, *127*, 367.

[12] Thrall M.M., Gray H.J., Symons R.G., Weiss N.S., Flum D.R., Goff B.A.: "Trends in treatment of advanced epithelial ovarian cancer in the Medicare population". *Gynecol. Oncol.*, 2011, *122*, 100.

[13] van Altena A.M., Karim-Kos H.E., de Vries E., Kruitwagen R.F., Massuger L.F., Kiemeney L.A.: "Trends in therapy and survival of advanced stage epithelial ovarian cancer patients in the Netherlands". Gynecol. Oncol., 2012, *125*, 649.

[14] NCIN: "National Cancer Intelligence Network: A Profile of Ovarian Cancer in England 2012". Available at: http://www.ncin.org.uk/publications/data_briefings/a_profile_of_ovarian_cancer_in_england

[15] Abdel-Rahman M.E., Butler J., Sydes M.R., Parmar M.K., Gordon E., Harper P., *et al.*: "No socioeconomic inequalities in ovarian cancer survival within two randomised clinical trials". *Br. J. Cancer*, 2014, *111*, 589.

[16] Seifert H., Georgiou A., Alexander H., McLachlan J., Bodla S., Kaye S., *et al.*: "Poor performance status (PS) is an indication for an aggressive approach to neoadjuvant chemotherapy in patients with advanced epithelial ovarian cancer (EOC)". *Gynecol. Oncol.*, 2015, *139*, 216.

[17] Freedman O.C., Dodge J., Shaw P., Oza A.M., Bernadini M., Klachook S., *et al.*: "Diagnosis of epithelial ovarian carcinoma prior to neoadjuvant chemotherapy". *Gynecol. Oncol.*, 2010, *119*, 22.

[18] NICE: "NICE (National Institute of Health and Care Excelence) guideline (CG122). Ovarian cancer: recognition and initial management 2011". Available at: http://www.nice.org.uk/guidance/cg122

[19] NCIN National Cancer Intelligence Network: "Route to Diagnosis 2016". Available at: http://www.ncin.org.uk/publications/routes_ to_ diagnosis.

[20] Lim A., Mesher D.: "Time to diagnosis of Type I or II invasive epithelial ovarian cancers: a multicentre observational study using patient questionnaire and primary care records". BJOG, 2016, *123*, 1012.

[21] Barclay M., Gildea C., Poole J., Hirschowitz L., Menon U., Nordin A.: "Factors Affecting Short-term Mortality in Women With Ovarian, Tubal, or Primary Peritoneal Cancer: Population-Based Cohort Analysis of English National Cancer Registration Data". *Int. J. Gynecol. Cancer*, 2016, *26*, 56.

[22] Maringe C., Walters S., Butler J., Coleman M.P., Hacker N., Hanna L., *et al.*: "Stage at diagnosis and ovarian cancer survival: evidence from the International Cancer Benchmarking Partnership". *Gynecol. Oncol.*, 2012, *127*, 75.

Corresponding Author:
M.K. MEHASSEB, MBBCh, MSc, MD, MRCOG, PhD
Department of Gynaecological Oncology
Glasgow Royal Infirmary - Queen Elizabeth Building
16 Alexandra Parade
Glasgow, G31 2ER (United Kingdom)
e-mail: mohamed.mehasseb@ggc.scot.nhs.uk