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Mode of Referral of Ovarian Cancer Patients: Does it Alter Treatment and Survival?

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Abstract. *Background/Aim: Some studies have shown that ovarian cancer patients admitted after referral to the emergency department had a worse prognosis than those referred through non-emergency pathways. We believe that our study is the first in the UK to explore this difference and aimed to compare the 1-year, 3-year, and 5-year overall survival rates of ovarian cancer patients referred non-urgently from the general practitioner (GP) vs. patients referred urgently to the emergency department (ED). Patients and Methods: This was a retrospective cohort study conducted at the University Hospitals of Leicester (UHL) from 1st January 2015 to 31st December 2019 involving 298 ovarian cancer patients: 197 referred non-urgently from the GP and 101 patients referred to the ED. Results: There was no significant difference in the 1-year, 3-year, and 5-year overall survival in ovarian cancer patients referred from the GP compared to patients referred to the ED, 84.8%, 62.2%, and 48.4% versus 80.2%, 64.8%, and 43.5%, respectively (p=0.732). Conclusion: The mode of referral for ovarian cancer patients may not affect their prognosis. Prompt referral to the gynaecological oncology multidisciplinary team, a good acute oncology service, early imaging and image-guided diagnostic pathways, timely appointment, and timely initiation of treatment in our centre may have minimized the difference in outcome in the two groups.*

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Worldwide, ovarian cancer is the most lethal gynaecologic cancer. Currently, it is well established that ovarian cancer has a five-year survival of less than 45% (1). Indeed, around one-fifth of advanced ovarian cancer patients can survive beyond one year if treated (2).

Ovarian cancer has been associated with a poor prognosis. Most ovarian cancer patients have no symptoms in the early stages. Presenting symptoms, are non-specific and related to gastrointestinal pathologies (3). This has been correlated to late presentation, late diagnosis, and delay in management (4). Furthermore, recent studies suggest that epithelial ovarian cancer might present late as it originates from other pelvic organs such as the fallopian tube (5). Ovarian cancer may initiate in the fallopian tube or the peritoneum and then spread to the ovaries (6).

Prognostic factors for ovarian cancer, known as phenotypes, are associated with overall survival. The well-known prognostic factors for ovarian cancer include age, stage, grade, histology, the extent of ascites, performance status, the residual tumour size after cytoreductive surgery, and taxane-based chemotherapy (7, 8).

Current literature does not conclusively show that the mode of referral affects cancer survival rates. A Canadian study observed that ovarian cancer patients referred from the emergency department (ED) had a poorer prognosis than those referred from any other healthcare setting (9). Another study in Milan, noted that ED patients had more advanced symptoms and inferior complete cytoreduction rates than those referred through non-emergency pathways (10). Delay in referral from the primary care is also known to be a poor prognostic factor in many types of cancer (11, 12). However, delay in GP referral of ovarian cancer patients has not been shown to affect overall survival (13).

Patients and Methods

We conducted a retrospective cohort study of ovarian cancer patients presenting to the University Hospitals of Leicester (UHL) between January 1, 2015, and December 31, 2019. Our study involved a total of 298 patients with ovarian cancer: 197 were

Table I. *Comparison of patient characteristics in ovarian patients referred from the general practitioner (GP) and emergency department (ED).*

Variables	GP (n=197)	ED (n=101)	*p*-Value
Age (years)			
Min. – Max.	18-92	21-87	0.976
Mean±SD	63.13±14.12	63.18±13.93	
Median (IQR)	65 (54-74)	65 (55-73)	
CA125 (At diagnosis)			
Min. – Max.	5-58,290	5-10,406	0.350
Mean±SD	1,156±4,771.36	867.75±1,635.14	
Median (IQR)	181 (47-558)	220.5 (55-984.5)	
Ethnicity			
Asian	20 (10.2%)	15 (14.9%)	0.488
British	164 (83.2%)	80 (79.2%)	
Other	13 (6.6%)	6 (5.9%)	
Main symptoms			
Abdominal pain	84 (42.6%)	40 (39.6%)	<0.001*
Abdominal bloating	27 (13.7%)	12 (11.6%)	
Change in bowel habits	18 (9.1%)	8 (7.9%)	
Incidental findings	14 (7.1%)	24 (23.8%)	
PMB	20 (10.2%)	3 (3%)	
Weight loss	19 (9.6%)	2 (2%)	
Others	15 (7.6%)	12 (11.9%)	
Mode of referral			
Urgent/2WW	192 (97.5%)	101 (100%)	0.17
Routine	5 (2.5%)	0	
Investigations by GP/ED			
USS/CA125	115 (58.4%)	9 (8.9%)	<0.001*
CT/MRI	18 (9.1%)	4 (4%)	
None	64 (32.5%)	88 (87.1%)	
Stages			
1	68 (34.5%)	29 (28.7%)	0.341
2	17 (8.6%)	10 (9.9%)	
3	81 (41.1%)	38 (37.6%)	
4	31 (15.7%)	24 (23.8%)	
Type of ovarian cancer			
HGSC	112 (56.9%)	61 (60.4%)	0.784
LGSC	9 (4.6%)	3 (3%)	
Endometroid	20 (10.2%)	11 (10.9%)	
Mucinous	27 (13.7%)	10 (9.9%)	
CCC	13 (6.6%)	4 (4%)	
Sex cord stromal tumor	4 (2%)	4 (4%)	
Germ cell tumor	2 (1%)	2 (2%)	
Carcinosarcoma	4 (2%)	1 (1%)	
Poorly differentiated adenocarcinoma	3 (1.5%)	2 (2%)	
Others	3(1.5%)	3 (3%)	
Mode of diagnosis			
US guided biopsy	59 (29.9%)	33 (32.7%)	0.143
Histology after surgery	114 (57.9%)	57 (56.4%)	
Radiological	1 (0.5%)	3 (3%)	
Biopsy of cervical node	1 (0.5%)	0	
Laparoscopy/laparotomy	16 (8.1%)	4 (4%)	
Cytology of pleural fluid	0	2 (2%)	
Ascitic drainage	3 (1.5%)	2 (2%)	
Endoscopy and Biopsy	3 (1.5%)	0	
Treatment			
PDS	120 (60.9%)	60 (59.4%)	0.777
USO	2 (1%)	0	
NACT	43 (21.8%)	20 (19.8%)	
Palliative chemotherapy	19 (9.6%)	14 (13.9%)	
Adjuvant chemotherapy	123 (62.4%)	55 (54.5%)	
No Treatment	13 (6.6%)	7 (6.9%)	

IQR: Inter quartile range; SD: standard deviation; CA125: cancer antigen 125; PMB: postmenopausal bleeding; 2WW: two-week wait; USS: ultrasound scan; CT: computed tomography; MRI: magnetic resonance imaging; HGSC: high-grade serous carcinoma; LGSC: low grade serous carcinoma; CCC: clear cell carcinoma; PDS; primary debulking surgery: USO: unilateral salpingo-oophorectomy; NACT: neoadjuvant chemotherapy; *p*: *p*-Value for comparison between the studied groups.

referred non-urgently from the General Practice (GP), and 101 were referred urgently to the ED. The primary objective of the study was to determine the effect of the mode of referral of ovarian cancer patients on the 1-year, 3-year, and 5-year overall survival rates. The secondary objective was to compare the overall survival rates of ovarian cancer patients in the UHL to the overall East Midlands, UK, and to similar Organisation for Economic Co-operation and Development (OECD) countries with published data.

Patients were identified using the gynaecological oncology multidisciplinary team (MDT) database and a histopathology database using the code 'ovary'. Data were collected using the Integrated Care Environment, which is an electronic platform containing pathology reports. Somerset Cancer Register was used, which is a digital platform designed for healthcare professionals to manage cancer patient care. Dictated letters, Chemocare (containing patients' electronic medical and clinical oncology notes), and radiology report platforms were accessed.

Inclusion criteria were females 18 years and above diagnosed with primary ovarian cancer, peritoneal cancer, and fallopian tube cancer at all stages. Exclusion criteria were females less than 18 years of age, benign ovarian tumours, borderline tumours, recurrent ovarian cancer, and Krukenburg tumours.

Our data registry included the following: age, CA125, ethnicity, primary symptoms, source of referral, investigations done before referral, stage of ovarian cancer, type of ovarian cancer, method of histological diagnosis, median follow up, and overall survival rates. Median follow-up was calculated as the median time (months) between diagnosis of ovarian cancer to the time when the patient was last seen alive.

Ethical approval was sought from the Research and Innovation Committee at the University Hospitals of Leicester; however, approval was not required as the study was retrospective. Patients' identifiable data were anonymized. No patient consents were required.

Data were analysed using IBM SPSS software version 20.0 (Armonk, NY, USA: IBM Corp). Qualitative data were described using numbers and percentages. The Kolmogorov-Smirnov test was used to verify the normality of distribution. Quantitative data were described using range (minimum and maximum), mean, standard deviation, median, and interquartile range (IQR). The significance of the obtained results was judged at the 5% level.

Chi-squared test was used for categorial variables to compare between the groups. Fisher's Exact test or the Monte Carlo test was used for correction of chi-square when more than 20% of the cells had an expected count less than 5. Student *t*-test was used for correction of chi-square when more than 20% of the cells had an expected count less than 5. Student *t*-test was used for normally distributed quantitative variable to compare between the two studied groups. Furthermore, Mann-Whitney test was used for abnormally distributed quantitative variables to compare between the two studied groups. Kaplan-Meier Curves were performed to compare the 1-year, 3-year, and 5-year overall survivals in both the groups.

Results

There was a total of 298 ovarian cancer patients in the study: 197 were referred from the GP non-urgently and 101 were referred to the ED. On comparison of the patients' characteristics, no significant difference was noted in age, CA125 level, ethnicity, mode of referral, stage of ovarian cancer, type of ovarian cancer, and treatment provided in both the groups (Table I). The median follow-up of the patients referred from the GP and to the ED was 38.5 (0.2-84.8) months and 35.4(0.3-85.4) months, respectively.

There was no statistical difference between the histological sub-type of ovarian cancer between the two groups. High-grade serous carcinoma (HGSC) was the most common type of ovarian cancer seen in patients referred in both groups. In ovarian cancer patients referred from the GP, HGSC was the most common histological sub-type (56.9%) followed by mucinous (13.7%), endometrioid ovarian cancer (10.2%), clear cell carcinoma (CCC) (6.6%), low grade serous carcinoma (LGSC) (4.6%), sex cord-stromal tumour (2%), and carcinosarcoma (2%). In ovarian cancer patients referred to the ED, a similar pattern was seen: HGSC (60.4%), endometroid ovarian cancer (10.9%), mucinous (9.9%), CCC (4.0%), cord-stromal tumour (4.0%), germ cell tumour (2%), and poorly differentiated carcinoma (2%).

There was no significant difference in the mode of diagnosis (Table I). In the GP group, the diagnosis was made mainly through histology after surgery (56.4%) followed by ultrasound-guided biopsy (32.7%), compared to 57.9% and 29.9% in the ED group.

Mode of management was not statistically different between the two groups as shown in Table I. Patients referred from the GP underwent primary debulking surgery (PDS) (60.9%), neoadjuvant chemotherapy (NACT) (21.8%), palliative chemotherapy (9.6%), and unilateral salpingo-oophorectomy (USO) (1.0%). Furthermore, 59.4%, 19.8%, and 13.9% patients referred to the ED underwent PDS, NACT, and palliative chemotherapy, respectively. No treatment was noted in 6.6% of patients referred from the GP *vs*. 6.9% of patients referred to the ED.

The mean interval from the decision to treat to the date of commencement of treatment was 27.95±33.65 days in the GP group *vs*. 27.15±29.50 days in the ED group (p=0.42). The interval from the date of surgery to the date of starting adjuvant chemotherapy was 48.11±19.21 days in the GP group and 56.61±33.07 days in the ED group (p=0.07). (Table II).

Table II. *Comparison between the two studied groups according to interval from decision to treat to date of commencing treatment and interval from date of surgery to date of starting adjuvant.*

Variables	GP (n=197)	ED (n=101)	*p*-Value
Interval from decision to treat to date of commencing treatment			
Min. – Max.	0.0-342.0	0.0-232.0	0.424
Mean±SD	27.95±33.63	27.15±29.50	
Median (IQR)	23 (14-32)	22 (12.5-34)	
Interval from date of surgery to date of starting adjuvant chemotherapy			
Min. – Max.	21-129	19-218	0.072
Mean±SD	48.11±19.21	56.61±33.07	
Median (IQR)	43 (35-54)	49 (38-63)	

GP: General practitioner; ED: emergency department; IQR: inter quartile range; SD: standard deviation; *p*: *p*-Value for comparison between the studied groups.

The 1-year, 3-year, and 5-year overall survival of stage 3 ovarian cancer patients showed no significant difference between the two groups (p=0.542). Likewise, the 1-year, 3-year, and 5-year overall survival of stage 4 ovarian cancer patients showed no significant difference between the two groups (p=0.085) (Figure 1).

The 1-year, 3-year, and 5-year overall survival rates of early-stage ovarian cancer patients (stage 1 and stage 2) referred from the GP were 95.3%, 88.0%, and 79.4%, respectively. The 1-year, 3-year, and 5-year overall survival rates of early-stage ovarian cancer patients referred to the ED were 100%, 91.9%, and 70.7%, respectively (p=0.68) (Figure 2).

The 1-year, 3-year, and 5-year overall survival of stage 3 & 4 ovarian cancer patients referred from the GP was 76.8%, 40.9%, and 22.2% *vs*. 69.4%, 47.6%, and 25.2% in the ED group (p=0.833), respectively (Figure 2). There was no statistical difference between 1-year, 3-year, and 5-year overall survival of patients with stage 3c and 4 in the two groups (p=0.565).

In ovarian cancer patients across all stages (stage 1-stage 4) referred from the GP, the 1-year, 3-year, and 5-year overall survival rates were 84.8%, 62.2%, and 48.4%, respectively. The 1-year, 3-year, and 5-year overall survival rates of ovarian cancer patients referred to the ED were 80.2%, 64.8%, and 43.5%, respectively (p=0.732) (Figure 2).

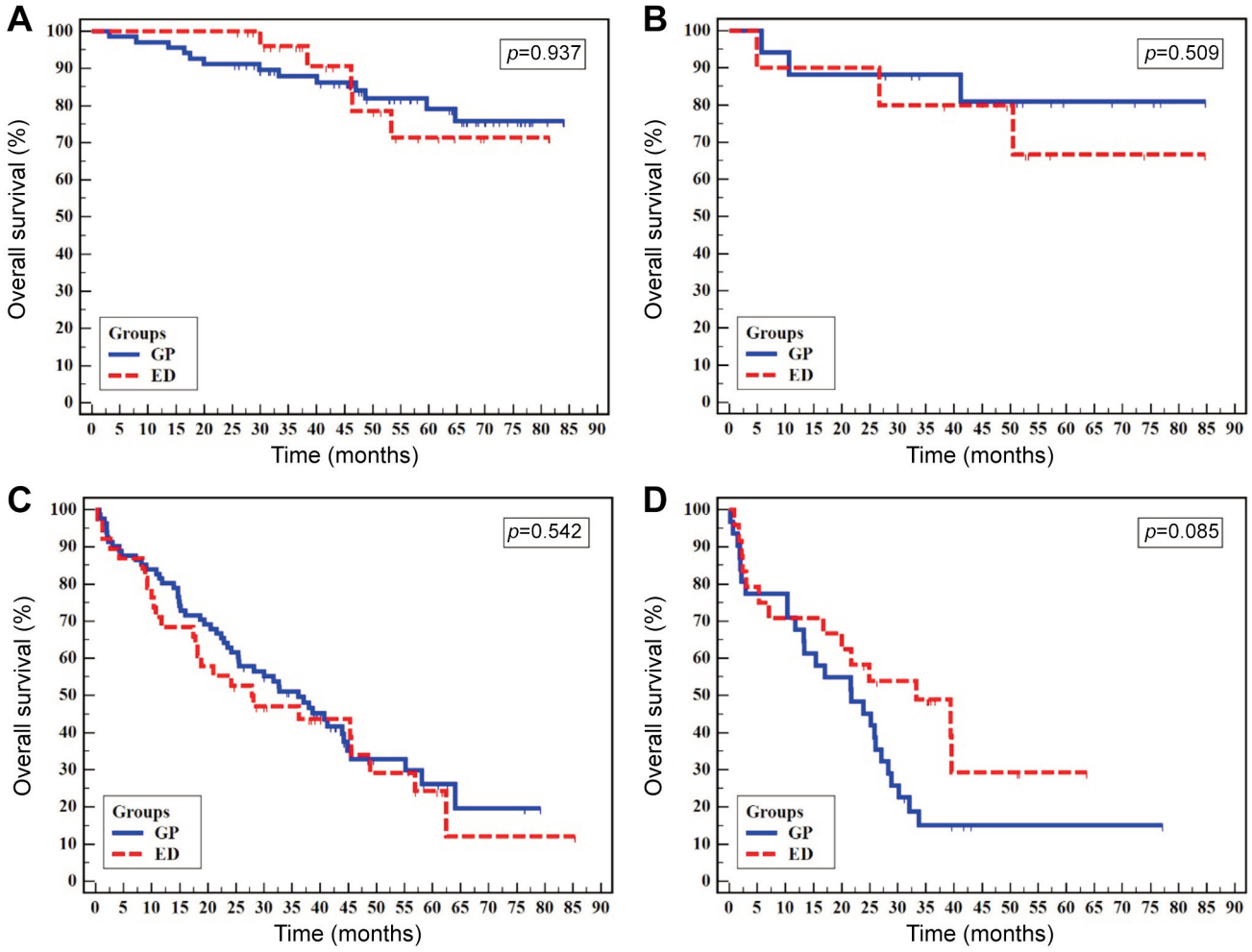

Figure 1. *Kaplan-Meier overall survival curve for patients referred with ovarian cancer from the general practitioner and emergency department in stages 1 (A), 2 (B), 3 (C) and 4 (D).*

Discussion

The cause-and-effect relationship between the mode of referral of ovarian cancer patients and disease prognosis is poorly understood (13). There is paucity of data in the literature regarding mode of referral as a prognostic factor in ovarian cancer. Since ovarian cancer has a poor prognosis, understanding potential prognostic factors are vitally important (14).

A large retrospective study (n=601) had observed that patients presenting to the ED had a significantly lower overall survival in contrast to ovarian cancer patients presenting elsewhere. The study showed that ovarian cancer patients presenting to the ED had more severe symptoms with more abdominal pain and chest symptoms. Patients in the ED underwent more investigations, had shorter referral intervals and diagnostic intervals than patients presenting elsewhere. Despite shorter referral intervals, patients referred to the ED presented in latter stages and had poorer survival rates than those presenting elsewhere (9). Similarly, an Italian study noted that advanced ovarian cancer patients referred to the ED were associated with lower complete cytoreduction rates than those referred from non-emergency settings (10).

Data from another retrospective study (n=135) showed that delays in presenting to the primary care and delays in referral by the GP did not significantly affect the 18-month survival rate (13). Another retrospective study (n=72) showed that there is no significant difference in the survival between patients referred urgently and non-urgently (15).

Our data showed that there was no significant difference between the main symptoms in patients presenting with ovarian cancer referred from the GP *vs.* patients admitted to the ED. Patients referred from the GP had more abdominal pain (42.6% *vs.* 39.6%), abdominal bloating (13.7% *vs.* 11.9%), change in bowel habits (9.1% *vs.* 7.9%), PMB (10.2% *vs.* 3%), and

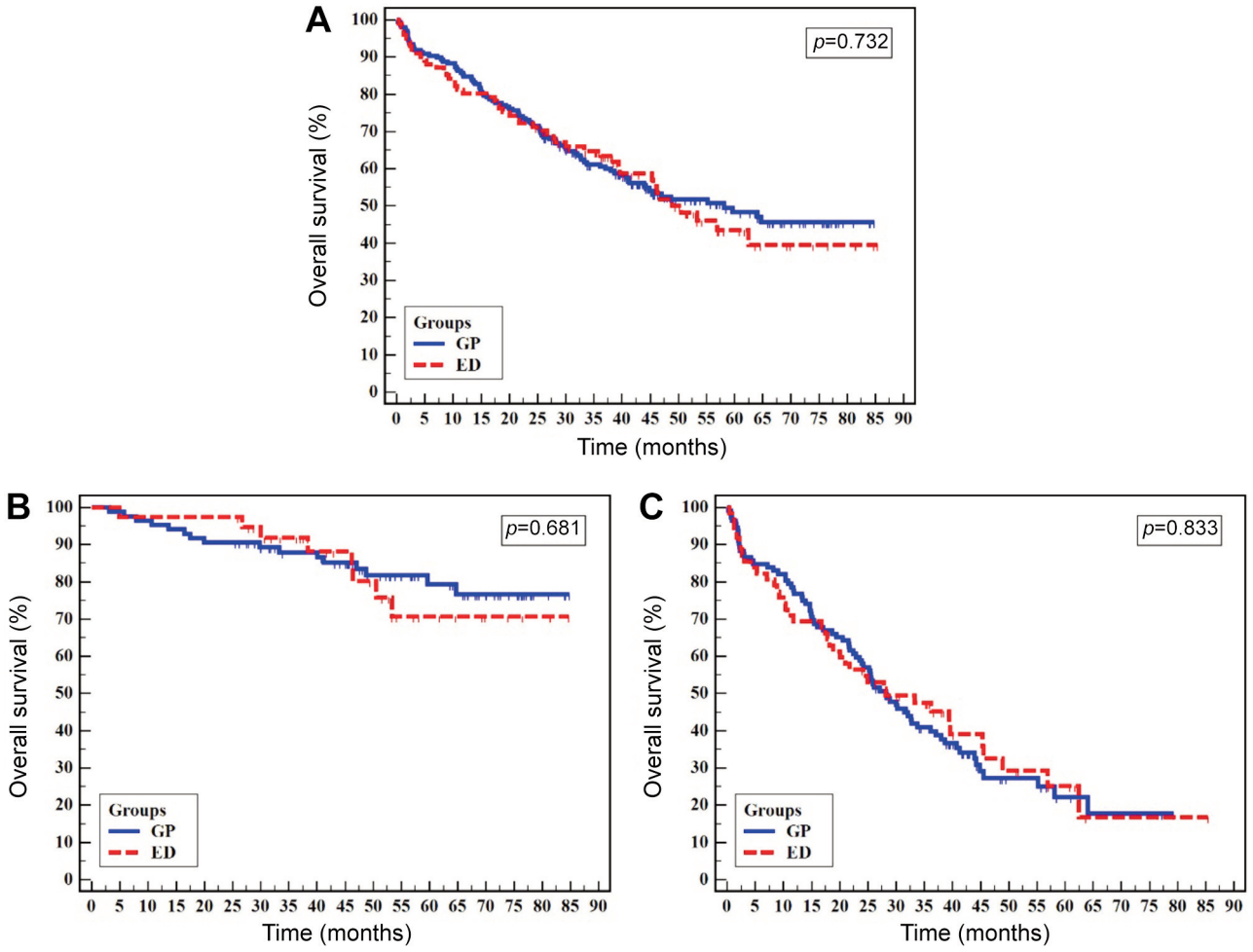

Figure 2. *Kaplan-Meier overall survival curve for patients referred with ovarian cancer from the general practitioner and emergency department. A: all stages; B: early stages (1 and 2); C: advanced stages (3 and 4).*

weight loss (9.6% *vs*. 2%) (p<0.001) than those admitted to ED. However, there was no significant difference between ovarian cancer patients referred by the GP non-urgently compared to patients referred to the ED urgently regarding the stage of the disease (p=0.34) and management (p=0.78).

A cohort study (n=215,284) including different types of cancer revealed that there was a positive association between the use of urgent referrals in patients with suspected cancer and their survival rates. It encouraged GPs to have a lower threshold in using the urgent referral pathways to improve survival rates (16).

Our survival data were comparable to the rest of the UK. We compared our findings with the 1-year and 3-year overall survival of ovarian cancer patients in the UK between 2010 and 2014 (nearest comparable period) with follow-up until 2015 (17). The 1-year and 3-year overall survival rates of ovarian cancer patients in our data were 83.2% and 46.8% compared to those in the UK data; 70.4% and 47.3%.

We also compared our 1-year and 3-year overall survival with that of six other similar OECD countries between 2010 and 2014 (18). In Australia, the 1-year and 3-year overall survival rates of ovarian cancer patients were 78.6% and 56.4%. In Canada, the 1-year and 3-year overall survival rates of ovarian cancer patients were 72.9% and 50.1%. In Denmark, the 1-year and 3-year overall survival rates were 77.6% and 53.6%. In Ireland, the 1-year and 3-year overall survival rates were 69.2% and 44.8%. In New Zealand, the 1-year and 3-year overall survival rates were 71.4% and 45.5%. In Norway, the 1-year and 3-year overall survival rates were 77.7% and 57.2% (17).

We compared the overall survival of advanced ovarian cancer in the UK as a whole. In the UHL, the 1-year and 3-year overall survival rates of stage 3 were 76.5% and 49.6%; moreover, the 1-year and 3-year overall survival rates of stage 4 were 69.1% and 29.2%. In the UK, the 1-year and 3-year

overall survival rates of stage 3 ovarian cancer were 69.7% and 39.2%; whereas, the 1-year and 3-year overall survival of stage 4 ovarian cancer was 52.0% and 22.2% (17).

More recent survival data were made available from the Ovarian Cancer Audit Feasibility Pilot (2013-2017). The 1-year and 5-year overall survival for ovarian cancer, fallopian tube, and primary peritoneal carcinoma patients in the East Midlands (as a whole) was 63% and 31% *vs.* 83.2% and 46.8% in the UHL (19).

We wanted to explore the rationale behind no significant difference in the survival rates of patients referred from the GP non-urgently to those of patients referred to the ED. We believe that the same referral pathways and guidelines were adhered to in both the groups. The GPs and ED teams were able to identify the red flags for suspected ovarian cancer in patients presenting with different stages of cancer, do appropriate investigations and refer them *via* the 2-week wait pathway to the gynaecology and the gynaecological oncology departments (20).

Furthermore, the patients referred from the GP as well as the patients admitted to ED received comparable prompt management. Our study underlines the importance of the 2-week wait referral pathway in not only improving the diagnosis and survival rates, but it ensures consistency of the service provided for all cancers within the NHS (21).

Patients may have presented to the GP several times before being referred to the gynaecological oncology service. Our study did not have the remit to explore this part of the patient journey. One can hypothesize that by the time patients are referred, they may be at a more advanced stage, and, therefore, may be more symptomatic. We do not know how much of an impact this may have had on the treatment and survival of our patients, and hence on the survival figures in the two groups.

This hypothesis is supported by a previous study that observed that most of the patients presenting to the GP with ovarian cancer may not be initially referred to the gynecology department. Ovarian cancer patients often have non-specific symptoms that mimic gastrointestinal disease (22). Around half of patients presenting to the GP were not initially referred to gynecology clinics as shown in one study (23). In a Danish study, 90% of ovarian cancer patients presented to the GPs with symptoms of ovarian cancer; however, only one-third of these patients were directly referred to the gynaecology services (24). One study concluded that women with ovarian cancer presented with persistent abdominal distension compared to women with other intestinal pathologies who had more fluctuating symptoms (25).

We believe that our study, although retrospective, is the first in the UK to investigate the impact of the mode of referral in ovarian cancer on treatment and prognosis. Both groups were similar in terms of age, CA125, ethnicity, stage of cancer, type of cancer, mode of diagnosis, and treatment, which reduced the selection bias. However, one significant limitation of the study was the discrepancy in the number of patients between the two groups. Another limitation was the comparison of our survival rates with those of the rest of the UK and similar OECD countries. However, these were the best available data in the nearest time periods.

Between 2015 and 2019, there has been a significant change in the surgical approach to advanced ovarian cancer in our institution. A more comprehensive approach in cytoreductive surgery, more training and upskilling of the gynaecological oncology surgeons has led to this change. As a result, our recent analysis has shown that complete cytoreduction (R0) was achieved in 84.4% of advanced ovarian cancer patients undergoing PDS *vs.* 77.2% of women who had interval debulking surgery (IDS). Our survival rates between 2015 and 2019 have markedly increased when compared to the previous four years, 2011 to 2014. The 3-year survival rates were 43.8% and 31.3% in advanced ovarian cancer patients undergoing PDS and IDS between 2011 and 2014, whereas they were 62.3% and 50.1% in advanced ovarian cancer patients who underwent PDS and IDS between 2015 and 2019.

The mode of referral for ovarian cancer patients may not affect their prognosis. Further prospective data are needed to corroborate and consolidate our findings. Our overall survival figures are comparable to those of the UK and similar OECD countries, and better than the overall East Midlands survival data. Delay in diagnosis can be investigated by further studies in the UK with a focus on patient reported data on self-referral to the GP surgery, in women who are eventually diagnosed with ovarian cancer.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

AB was involved in the conceptualization, validation, formal analysis, investigation, data curation, and writing of the manuscript. AI edited the manuscript. QD edited the manuscript. SC was involved in the conceptualisation, reviewing, and editing of the manuscript. All Authors read and approved the final manuscript.

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