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GENERAL GYNECOLOGY

Socioeconomic differences impact overall survival in advanced ovarian cancer (AOC) prior to achievement of standard therapy

Andrew Phillips[1,2] · Sean Kehoe[2,3] · Kavita Singh[2] · Ahmed Elattar[2] · James Nevin[2] · Janos Balega[2] · Rachel Pounds[2] · Ahmed Elmodir[4] · Jennifer Pascoe[4] · Indrajit Fernando[4] · Sudha Sundar[2,3]

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Abstract

Purpose Survival difference between socioeconomic groups with ovarian cancer has persisted in the United Kingdom despite efforts to reduce disparities in care. Our aim was to delineate critical episodes in the patient journey, where deprivation has most impact on survival.

Methods A retrospective review of 834 patients with advanced ovarian cancer (AOC) between 16/8/07–16/2/17 at a large cancer centre serving one of the most deprived areas of the UK. Using the Index of Multiple Deprivation (IMD), patients were categorised into five groups.

Results Surgery was more common in less deprived patients ($p < 0.00001$). Across IMD groups, there were no differences in complete (R0) cytoreduction rate ($r = 0.18$, $p > 0.05$), age, or comorbidity. The R0/total cohort rate increased with increasing IMD group ($p < 0.0001$). Patients refusing any intervention belonged exclusively to the three most deprived groups; 5/7 patients who refused surgery belonged to the most deprived IMD group. Overall survival in the total patient group was less in IMD group 1–2 compared to 9–10 ($p = 0.002$). On multivariate analysis, IMD group was not an independent predictor of survival ($p > 0.05$).

Conclusions Socioeconomic differences in survival manifest in patients not receiving surgical treatment for AOC and are not purely explained by comorbidity, age, stage, or histological factors.

Keywords Deprivation · Ovarian · Cancer · Cytoreduction · Charlson

Introduction

The cornerstone of management of advanced (stages 3 and 4) ovarian cancer (AOC) consists of both cytoreductive surgery [1–3] and platinum-based chemotherapy. The importance of these has been reflected in published international guidelines [4–6]. Despite this, both Surveillance, Epidemiology, and End Results Program (SEER) data from the United States and NCRAS cancer registry data sets from the United Kingdom (UK) demonstrate that up to 44% of patients with AOC do not receive optimum therapy [7, 8]. Numerous explanations have been suggested for these deviations from standard treatment including: advanced age; emergency presentation; unclear histology; significant comorbidities; as well as patient choice [7–9]. Investigating the causative factors for this under-treated group is difficult due to the limited data recorded in national databases for these patients compared to their counterparts who receive treatment [10].

Socioeconomic differences in survival exist for many different cancers across many different geographical areas [11–14]. In ovarian cancer, socioeconomic differences in 1-year survival between the most and least affluent have remained relatively stable at 7–9% in the UK between 1971 and 2013 [15–17]. These differences have persisted despite the introduction of specific policies aiming to reduce cancer inequalities such as the NHS cancer plan that was introduced in 2000 [18]. Despite the persistent socioeconomic

✉ Andrew Phillips
Andrew.phillips6@nhs.net

1 Department of Obstetrics and Gynaecology, Royal Derby Hospital, Uttoxeter Road, Derby DE22 3NE, UK

2 Pan-Birmingham Gynaecological Cancer Centre, City Hospital, Dudley Rd, Birmingham B18 7QH, UK

3 Institute of Cancer and Genomic Sciences, University of Birmingham, Vincent Drive, Birmingham B15 2TT, UK

4 The Cancer Centre, Queen Elizabeth Hospital, Mindelsohn Way, Edgbaston, Birmingham B15 2GW, UK

differences in 1-year survival, no socioeconomic differences have been observed in 5-year survival since the year 2000 [prior to the mid-1990s, there was, however, a deprivation gap of 2–3%] [19].

An analysis of pooled results of two randomised trials (ICON2 and ICON3) investigated whether socioeconomic differences persisted in an environment with a structured treatment and follow up regime [19]. This showed that under trial conditions, in such a patient group, no socioeconomic differences in survival were identified. The author, Abdel-Rahman, thus postulated that deprivation differences in AOC in the wider population may be due to access to treatment and differing standards of care; factors that are inherently controlled for in participants of randomised trials.

As only 6.3% of women with gynaecological cancers are enrolled in clinical trials [20], they may not be representative of the total population from which they are derived in key determinants such as performance status, comorbidities, and disease burden. Equally epidemiological studies may not accurately record subjective variables such as those who declined or opt not to have treatment [19].

We have previously reported on how it is crucial to report the denominator of patients in a centre rather than reporting survival in patients undergoing optimum therapy [21]. Our aim in this study was to delineate points of interaction with the health system or critical episodes in the patient journey with AOC, where deprivation has the most impact on survival.

Materials and methods

The Pan-Birmingham Gynaecological Cancer Centre (PBGCC), Birmingham, serves a population of 2.2 million people purely within the National Health Service (NHS). As per data derived from Birmingham city council, 40% of its catchment population lives in areas considered to be of the most deprived in the UK. Birmingham is the 6th most deprived local government authority in the UK by this measure [22]. The NHS delivers care that is free at the point of delivery, on the basis of need, not on the ability to pay [23]. The diagnostic and treatment pathways for suspected cancer patients are governed centrally with hospitals that do not achieve a required level of adherence to these target times being penalised. All patients referred via their General [family] Practitioner with a suspected diagnosis of cancer need to be treated within 62 days from the date of the initial referral. Each of these patients will have access to a named clinical nurse specialist who provides support during diagnosis and treatment. Apart from free care at the point of delivery, patients with cancer have access to various financial packages of support both on a means tested and non-means tested basis. Prima facia all patients, irrespective of income, should have equal access to timely and appropriate treatment.

We investigated patient pathways for all women diagnosed with AOC between 16th August 2007 and 16th February 2017. Only patients with advanced [stage 3 or 4] epithelial ovarian/peritoneal or fallopian tubal cancer were included. Peritoneal non-serous histologies were excluded from the analysis. All patients were managed by subspecialty trained gynaecological oncologists at the PBGCC. As per national standards, all patients with AOC were discussed at the multi-disciplinary team meeting (MDT) and prospectively recorded in an electronic database. Approval for this study was obtained from the hospital clinical effectiveness department. The standard diagnostic and treatment policy for AOC and outcomes at our centre have previously been published [24]. Our standard approach for AOC is primary debulking surgery (PDS) followed by six cycles of platinum-based adjuvant chemotherapy. However, patients with stage 4 disease, poor performance status (ECOG/WHO 3–4), obvious porta hepatis involvement on scan, small bowel mesenteric or extensive serosal involvement on diagnostic laparoscopy, or with large amount of ascites/pleural effusions with low albumin level are offered three cycles of platinum-based neoadjuvant chemotherapy (NACT) to enhance their feasibility to radical surgery with 3–5 further cycles of adjuvant chemotherapy. Contraindications for interval debulking surgery (IDS) consist of progressive disease on NACT, worsening performance status, severe cardiovascular disease, and patient choice. All patients demonstrating a response on radiological, serological, or clinical parameters are considered for IDS [24–27].

Deprivation was assessed by a standard method using the Index of Multiple Deprivation [IMD], a deprivation index used in England and Wales to describe small regions (lower layer super output areas (LSOA) of approximately 1500 people) in terms of income, employment, health and disability, education, skills and training, barriers to housing and services, living environment, and crime. Scores from the IMD deciles were categorised into five deprivation groups. Patients with an IMD score of 1–2 incorporate the most deprived patients and patients with an IMD score of 9–10 incorporate the most affluent.

Where available, patient comorbidities were assessed according to the age-adjusted Charlson Comorbidity Index (ACCI) [28, 29]. The following data were analysed: IMD deprivation group; age, ACCI, organ of origin; histological subtype; grade; stage; surgical approach (PDS, IDS, no surgery); surgical complexity score (SCS) as per Aletti [30]; cytoreductive outcome (complete (R0), optimal (<1 cm) (R1) and suboptimal (>1 cm) (R2); and survival (months).

We assessed the potential impact of the different deprivation quintiles on overall survival (OS) in two different measures of the patients' pathway. First, we analysed survival

with regard to the overall patient (denominator) cohort and second with regard to those that did or did not receive surgical therapy.

Statistical analysis

Statistical analysis was performed using SPSS 21 (Statistical Package for Social Sciences; IBM. Chicago, IL). Categorical variables were compared using the Chi-squared test and parametric and non-parametric continuous variables were compared using the ANOVA or Kruskal–Wallis test, respectively. All tests were two-sided and a p value of less than 0.05 was regarded as being statistically significant. The Kaplan–Meier method was used to estimate survival with survival compared using the log-rank method.

Results

Between 16th August 2007 and 16th February 2017, 859 women diagnosed with AOC were identified from the PBGCC MDT database. Two women were excluded due to no IMD decile data being available and 23 patients were excluded; although they were undergoing NACT with an intention for subsequent IDS, they had not undergone surgery at the time of analysis. Of the remaining 834 patients, 608 (72.9%) underwent standard therapy with surgery and chemotherapy and the remaining 226 (27.1%) patients received no cytoreductive surgery and only received chemotherapy or palliation. Of those that underwent surgery, 205 had PDS, 397 had IDS after NACT, and in six, there was no record of the type of primary surgical treatment involved.

As expected from an area of the UK with higher than average levels of deprivation, significantly, more patients lived in more deprived areas compared to less deprived areas ($p < 0.00001$): IMD group 1–2 (33.8%); IMD group 3–4 (19.9%); IMD group 5–6 (19.5%); IMD group 7–8 (14.4%); and IMD group 9–10 (12.4%). Despite the imbalance of the distribution of deprivation in our cohort, there were no significant differences seen between age at diagnosis, histological subtype or grade of cancer, stage of diagnosis or, if surgery was undertaken, whether PDS or IDS was performed.

In patients undergoing surgery, there was no significant difference in the complexity of surgery that patients received, although patients in IMD groups 9–10 received high complexity surgery (SCS ≥ 8) more often than those in IMD groups 1–2 (15.6% and 7.6%), respectively ($p > 0.05$). However, the rate of patients undergoing surgery was significantly different across all five IMD groups ($p < 0.00001$) with the rate of surgery increasing from 66.3% in deprivation IMD groups 1–2 to 89.4% in IMD groups 9–10. The complete cytoreduction rate, when calculated as a percentage of the total patient denominator (i.e., the true R0 rate), ranged from 41.1% in the most deprived (IMD groups 1–2) to 67.0% in the least deprived groups (IMD groups 9–10) and the difference between deprivation groups was significant ($p < 0.0001$) (Table 1). The proportion of patients undergoing surgery strongly correlated with increasing IMD group ($r = 0.94$), and whilst the complete (R0) cytoreduction rate only weakly correlated with increasing IMD group ($r = 0.18$), the true R0 rate strongly correlated with increasing IMD group ($r = 0.73$).

The reasons for deviation from the standard treatment are listed in Table 2. Patients who refused intervention (either chemotherapy or surgery) belonged to IMD groups 1–2, 3–4, and 5–6. With specific with regard to surgery, of the seven patients who refused surgery, five came from the most deprived IMD group (1–2).

Comorbidity data allowing for calculation of the ACCI were available in 535 patients [of whom 440 (82.2%) underwent surgery and 95 (17.8%) did not]. As expected, a significant difference was seen overall between all patients who did receive surgery and who did not receive standard treatment with regard to the ACCI ($p < 0.00001$). There was, however, no significant difference across the five IMD groups with regard to ACCI when analysed by whether they underwent surgery or not (Fig. 1). In addition, no significant difference was seen across the five IMD groups when all patients were included irrespective of their treatment outcome.

The OS for the entire cohort was 36.5 (95% CI 32.7–40.3) months. Median OS increased with increasing IMD group ranging from 33.4 (95% CI 26.3–40.5) months in IMD group 1–2, to 50.9 (95% CI 22.9–78.8) months in IMD group 9–10. This difference was found to be statistically significant ($p = 0.002$) (Fig. 2).

When the patients who did not undergo surgery were removed from the analysis, the median OS was 48.2 (95% CI 40.7–55.7) months and there was no significant difference between IMD groups, although there was a trend towards greater OS in the least deprived patients (IMD group 9–10) (Fig. 3).

The median OS of the 226 patients that did not undergo surgery was 11.7 (95% CI 8.3–15.1) months, and again, no significant difference was seen between the IMD groups (Fig. 4).

On multivariate analysis adjusting for stage, grade, histological subtype, and cytoreductive outcome, the IMD group did not remain as an independent predictor of survival ($p > 0.05$).

Discussion

To our knowledge, this is the largest study with patient level data that addresses the impact of deprivation on survival in patients with AOC. It includes patients that both did and did

Table 1 Clinico-pathologico-surgical data according to deprivation group

IMD group	1 and 2	%	3 and 4	%	5 and 6	%	7 and 8	%	9 and 10	%	*p*	Total	%
N	282		166		163		120		103			834	
Age (years) (95% CI)	65.8 (41.8–78.7)		66.4 (44.4–91.4)		65.5 (40.9–90.1)		67.0 (44.4–89.8)		67.4 (44.9–89.9)		> 0.05		
Organ													
Ovary	204	72.3%	122	73.5%	115	70.6%	82	68.3%	67	65.0%	> 0.05	590	70.7%
Fallopian tube	31	11.0%	15	9.0%	19	11.7%	18	15.0%	18	17.5%		101	12.1%
Peritoneal	47	16.7%	29	17.5%	29	17.8%	20	16.7%	18	17.5%		143	17.1%
Histology													
Serous	235	83.3%	142	85.5%	140	85.9%	107	89.2%	86	83.5%	> 0.05	650	77.9%
Non-serous/unknown	47	16.7%	24	14.5%	23	14.1%	13	10.8%	17	16.5%		184	22.1%
Grade													
High	225	79.8%	132	79.5%	138	84.7%	105	87.5%	88	85.4%	> 0.05	688	82.5%
Low	13	4.6%	6	3.6%	8	4.9%	4	3.3%	7	6.8%		34	4.1%
Unknown	44	15.6%	28	16.9%	17	10.4%	11	9.2%	8	7.8%		112	13.4%
Stage													
3	192	68.1%	118	71.1%	120	73.6%	80	66.7%	84	81.6%	> 0.05	594	71.2%
4	68	24.1%	40	24.1%	32	19.6%	31	25.8%	11	10.7%		182	21.8%
Unstaged advanced	22	7.8%	8	4.8%	11	6.7%	9	7.5%	8	7.8%		58	7.0%
Surgery													
PDS	53	18.8%	45	27.1%	43	26.4%	32	26.7%	32	31.1%	> 0.05	205	24.6%
IDS	134	47.5%	63	38.0%	78	47.9%	64	53.3%	58	56.3%		397	47.6%
Unknown	0	0.0%	1	0.6%	1	0.6%	2	1.7%	2	1.9%		6	0.7%
Treatment variations													
Operated	187	66.3%	109	65.7%	122	74.8%	98	81.7%	92	89.3%	< 0.00001	608	72.9%
Non-operated	95	33.7%	57	34.3%	41	25.2%	22	18.3%	11	10.7%		226	27.1%
SCS													
Median	2 IQR 2–5		2 IQR 2–5		2 IQR 1–3		3 IQR 2–5		2 IQR 2–5		> 0.05		
Low	128	69.2%	67	62.0%	90	74.4%	55	57.3%	57	63.3%	> 0.05	397	66.2%
Intermediate	43	23.2%	25	23.1%	21	17.4%	28	29.2%	19	21.1%		136	22.7%
High	14	7.6%	16	14.8%	10	8.3%	13	13.5%	14	15.6%		67	11.2%
Cytoreduction													
R0	116	62.0%	76	69.7%	67	54.9%	63	64.3%	69	75.0%	> 0.05	391	64.3%
R1	25	13.4%	11	10.1%	23	18.9%	17	17.3%	9	9.8%		85	14.0%
R2	46	24.6%	22	20.2%	32	26.2%	17	17.3%	13	14.1%		130	21.4%
Unknown	0	0.0%	0	0.0%	0	0.0%	1	1.0%	1	1.1%		2	0.3%
Total cohort R0		41.1%		45.8%		41.1%		52.5%		67.0%	0.000071		46.9%

Table 2 Reasons for deviation from standard treatment protocols

	Deprivation group											
	1 and 2	%	3 and 4	%	5 and 6	%	7 and 8	%	9 and 10	%
No data	3	3.2%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Died during investigation or prior to commencing NACT	6	6.3%	6	10.5%	7	17.1%	3	13.6%	0	0.0%
Best Supportive care only	22	23.2%	14	24.6%	3	7.3%	4	18.2%	2	18.2%
Primary chemotherapy alone with no surgical treatment (reason unspecified)	15	15.8%	8	14.0%	5	12.2%	5	22.7%	2	18.2%
Died during NACT or prior to surgery	7	7.4%	3	5.3%	6	14.6%	1	4.5%	1	9.1%
Unsuitable for IDS	35	36.8%	24	42.1%	17	41.5%	9	40.9%	6	54.5%
Patient declined treatment (Chemotherapy or surgery)	7	7.4%	2	3.5%	3	7.3%	0	0.0%	0	0.0%

not undergo surgery, i.e., the denominator or total patient cohort. We demonstrate that although a deprivation gap exists between the most and least deprived patients, this can be explained by differences in the uptake, or the utilisation, of surgery and the cytoreductive outcomes obtained. Deprivation, therefore, appears to be a surrogate marker of the failure to achieve standard treatment. The hypothesis postulated by Abdel-Rahman, that deprivation differences in AOC may be driven by patients not receiving standard treatment, is, therefore, confirmed by our study [19]. Our findings are similar to the previous studies that have identified no socioeconomic differences in survival when only considering the operated patient cohort [31], but our study goes one step further and demonstrates a survival difference between the least and most deprived groups when both the operated and non-operated patient populations are combined. Our data agree with findings seen at the epidemiological level that those who are less deprived are more likely to receive standard treatment [32].

Although it is generally acknowledged that more deprived patients carry a higher burden of associated medical comorbidities [33], in our cohort, across the different deprivation groups, the median ACCI scores in both operated and non-operated patients were similar. As expected, the ACCI differed significantly between patients that did and did not undergo surgery. Whilst it could be argued that the difference in survival between the least and most deprived groups was due to a greater number of more comorbid patients remaining in the unoperated cohort of the most deprived patients who would never be fit for standard treatment, we suggest that this is not the case, as there was no significant difference in ACCI or CCI when both surgically treated and non-surgically treated patients were combined across all IMD groups. This implies that there is no significant excess morbidity, as judged by the ACCI, in those from a more deprived areas, and thus, we suggest that differences in age and comorbidities are not sufficient in themselves to explain the deprivation gap.

One of the limitations of this study is that the ACCI as categorical descriptors of morbidity may miss prognostically relevant fine graduations in severity of individual comorbidities and hence may not accurately describe the impact of diseases on that individual patient [34]. This could result in identically scoring conditions being more detrimental to patient health and performance in the more deprived patients compared to the more affluent patients. For example, myocardial infarction scores 1 point but that does not address the burden of that specific myocardial infarction on that specific patient. As such, although there is no difference in ACCI across deprivation groups, the manifestations and impact of comorbidity may still be different and could be a contributor to variable standards of care.

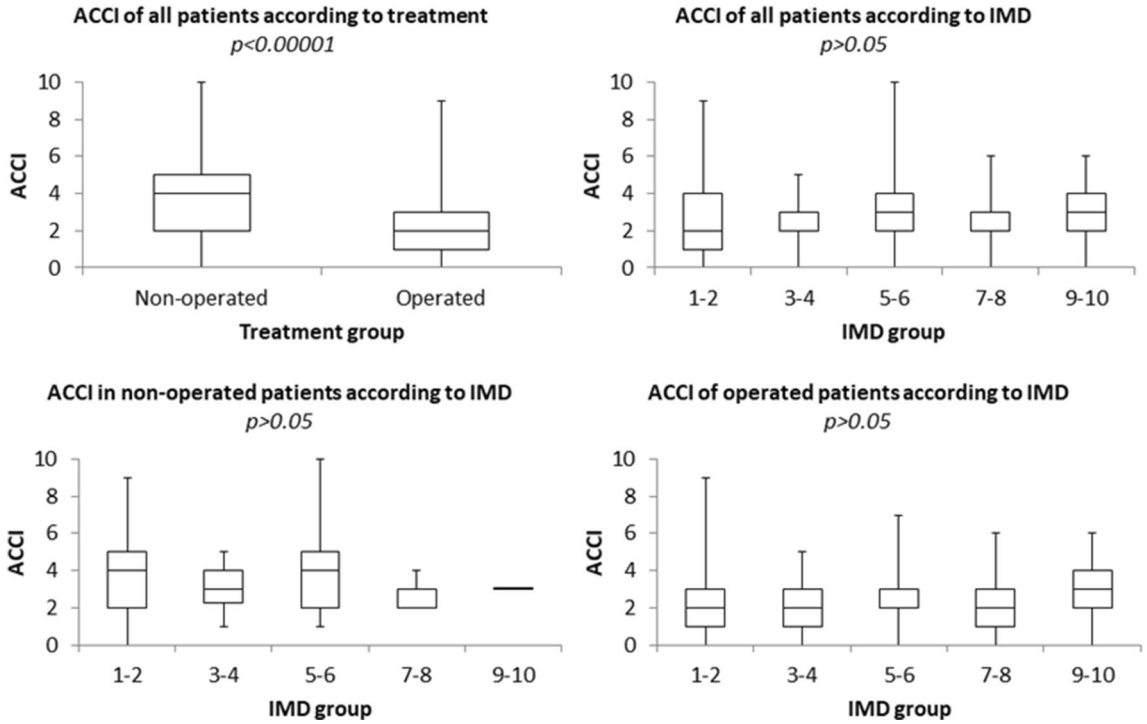

Fig. 1 ACCI scores by treatment and IMD group

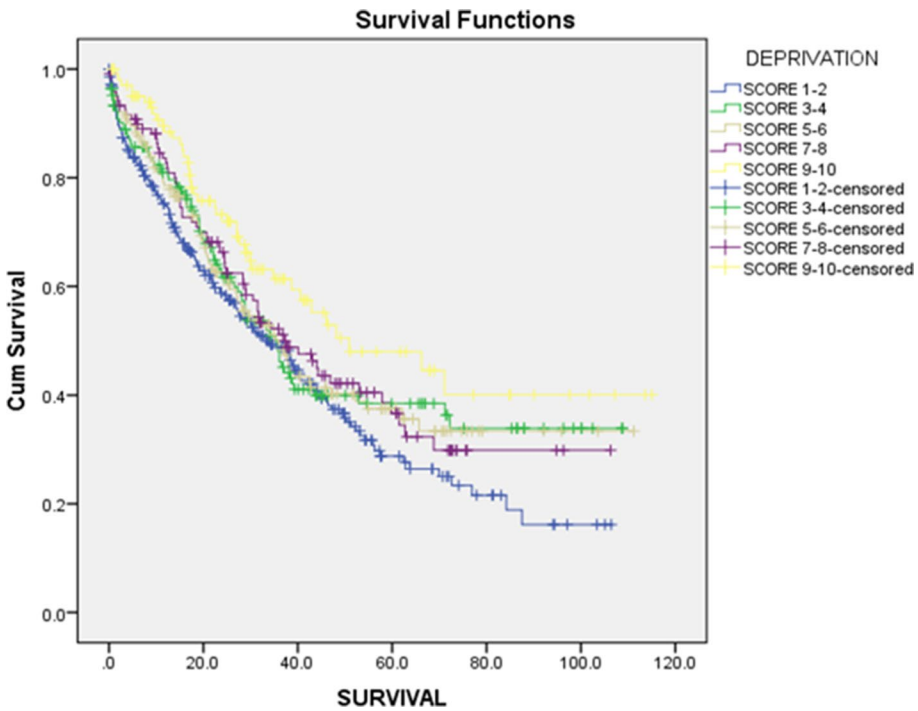

Fig. 2 Kaplan–Meier curve of total cohort overall survival analysed by IMD group

The majority of patients who declined standard treatment, and surgery in particular, arose from the most deprived group. Such findings are consistent with other studies demonstrating that those from more deprived backgrounds not only have poorer health behaviours [such as diet, smoking, and exercise], but also significant psychosocial risks [such as more perceived stress, less optimism for the future, and less social support] than their more affluent counterparts [35]. Indeed, more affluent patients not only have better access to health care, but equally have better access to sources

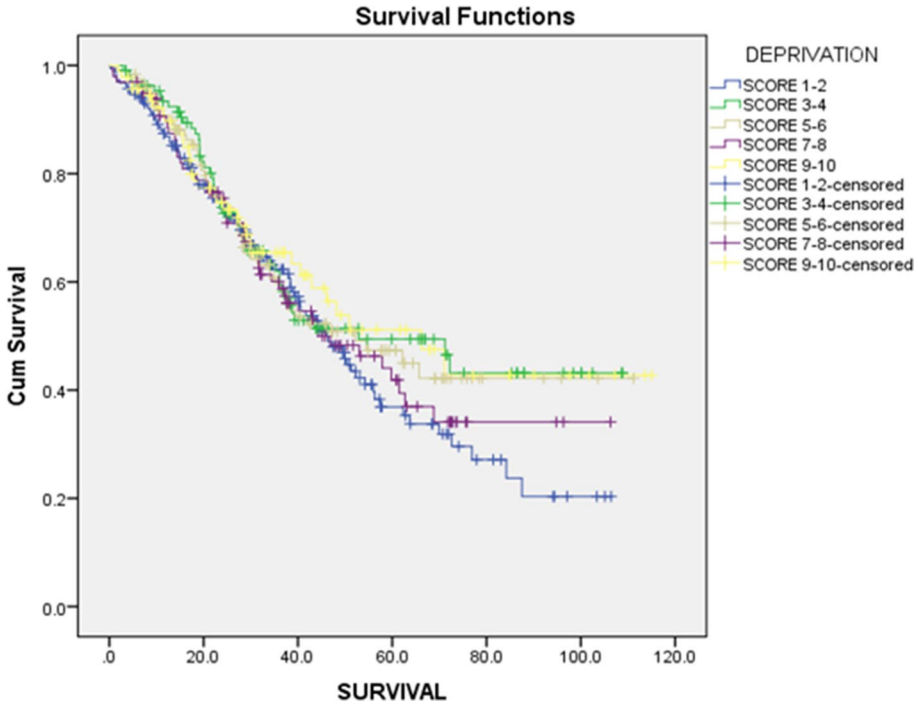

Fig. 3 Kaplan–Meier curve of the overall survival of all surgically treated patients analysed by IMD group

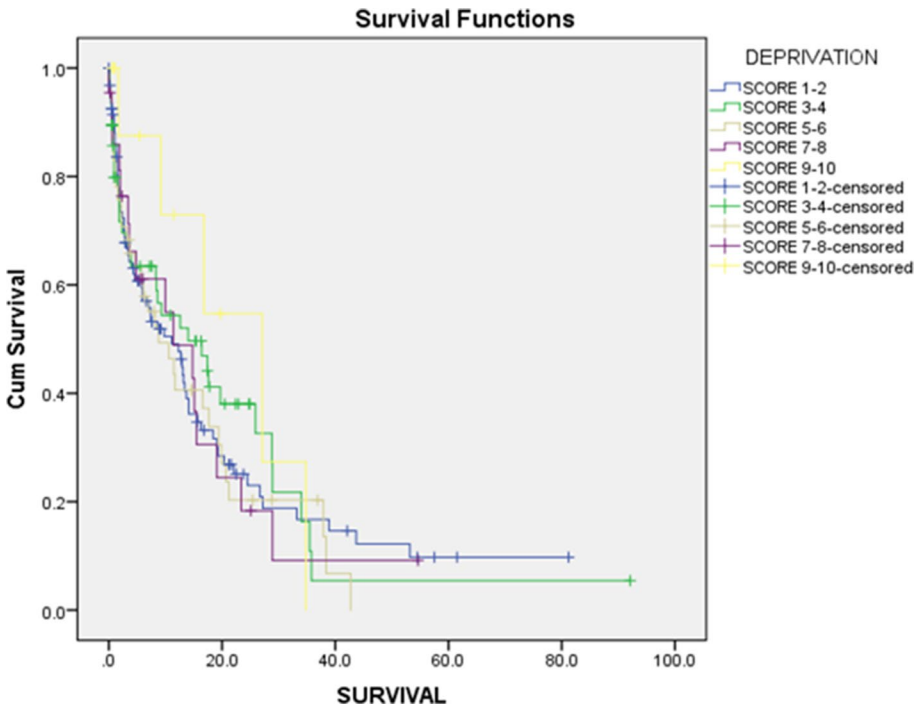

Fig. 4 Kaplan–Meier curve of the overall survival of all non-surgically treated patients analysed by IMD group

of health-related information and the potential for a more knowledgeable support network [36]. We suggest that the rejection of standard treatment highlights issues around communication, social support, and expectations of care and only by addressing all these issues will such deviations from standard care be reduced and outcomes improve in the most deprived groups.

Despite there being no difference in the stage or histological subtype between the various deprivation groups, less deprived patients were significantly more likely to undergo surgery and there was a non-significant trend towards a better surgical outcome, i.e., complete cytoreduction, than more deprived patients. Both the proportion of patients receiving surgery and the true R0 rate strongly correlated with and

increasing IMD group. However, no significant differences were seen between the complexity of surgery undertaken across all deprivation groups and even between IMD groups 1–2 and IMD groups 9–10; no significant difference was seen in surgical complexity despite more patients in IMD groups 9–10 undergoing high complexity surgery. One possible reason for this, beyond the limitations of comorbidity assessment and patient expectations, may be the idiosyncrasies of the stage 3 and 4 FIGO ovarian cancer stage classification. A solitary 2 cm omental nodule and wide spread abdominal carcinomatosis will both stage as 3c, equally an isolated para-cardiac or an inguinal node as well as widespread extra-abdominal metastasis will be staged as 4B. The FIGO staging for AOC is so broad in its scope that the potential for more deprived patients to be presenting with more advanced disease within the same FIGO stage cannot be discounted [37]. It is thus not surprising that deprivation is known to be associated with stage, grade, and suboptimal cytoreduction at surgery [38].

Abdel-Rahman [19] demonstrated no effect of deprivation on survival in participants of a randomised controlled trial with strict treatment and follow-up protocols. Our results expand on this to demonstrate no effect of deprivation on survival in patients that are able to receive standard treatment and who are followed up according to a generic programme. As such, they confirm the hypothesis postulated by Abdel-Rahman that deprivation differences in survival in AOC occur prior to attainment of standard treatment. To mitigate deprivation effects on survival, it is imperative that standard treatment is not readily discounted without due consideration in all patients.

Another limitation in our study is the lack of disease and patient data beyond that of comorbidity, FIGO stage, and histological details. It is possible, and indeed likely, that decisions to not perform standard treatment are influenced by biochemical factors such as albumin and nutrition as well as patient factors such as performance status. Furthermore, there are a lack of data concerning presentation which is important, since emergency admissions have inferior survival to elective [8]. A second consideration is that in our study, the proportion of patients undergoing surgery is higher than the UK average (73% versus 56%) [8] as well as a complete cytoreduction rate of 64.3% which is elevated compared to other UK centric studies such as CHORUS [27%] [39]. A final consideration is that our data regarding the ACCI are not complete in our data set with records available in only 535 out of 834 patients.

A significant driver of the increased cytoreduction rate will be due to the 34% of patients who required intermediate or high complexity surgery to treat their disease. Our results, therefore, may not be comparable to centres with a lower cytoreduction rate especially where advanced surgical procedures are rarely utilised. Further publication of deprivation linked data should be encouraged by cancer centres to investigate whether the deprivation gap we are witnessing is due in part by excellent treatment outcomes achieved in the least deprived cohort.

We have demonstrated that socioeconomic differences in survival manifest in patients not receiving surgical treatment for AOC. The PBGCC based in the West Midlands is a good region to demonstrate these socioeconomic differences, as there is a high level of deprivation [22], yet the gynaecological cancer centre has persistently achieved excellent survival rates in comparison with national and international peers [21]. However, even within a centre with excellent survival rates operating in a health system that supplies treatment free at the point of delivery on the basis of need, not on the ability to pay, there remains an imbalance in survival between the most and least deprived patients. This deprivation gap is illustrated by the difference in the proportion of patients undergoing surgery who achieve R0 and is not explained by differences in morbidity as judged by the ACCI or histopathological or staging discrepancies. Identifying these barriers to/impediments to standard treatment is the first step to eliminating the deprivation gap in AOC and providing optimal care for all.

The gynaecological cancer community has been traditionally focussed on improving outcomes through increasing the radicality of surgery and by improving targeted therapies. Whilst these innovations are important, we point out that the greatest improvements in survival outcomes are likely to be achieved by increasing parity of access to care in the most deprived communities, increasing the percentage of patients in the denominator (total patient cohort) undergoing both modalities of treatment (surgery and chemotherapy) as well as ensuring that patients are diagnosed at a performance status conducive to receiving treatment (i.e., earlier diagnosis).

Socioeconomic differences in survival occur in patients who do not receive standard treatment. Efforts to improve such inequalities need to focus upon facilitating standard treatment through earlier diagnosis, greater support for patients and better management of both patient expectations and fitness. Patient level studies examining the impact of deprivation prior to and after the introduction of advanced surgical procedures should be encouraged.

Compliance with ethical standards

Conflict of interest Sean Kehoe has received fees for lecturing for Astra Zeneca and Roche. Janos Balega has received personal fees from Astra Zeneca and Roche. Jennifer Pascoe has received personal fees from Tesaro. All other authors declare that we have no conflict of interest.

Ethical approval Approval for this retrospective study with no patient intervention was obtained from the hospitals research and development

department. (Sandwell and West Birmingham Hospitals NHS Trust Research and Development department).

Informed consent No identifiable patient details were included in this study.

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