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Reporting 'Denominator' data is essential for benchmarking and quality standards in ovarian cancer

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HIGHLIGHTS

- Survival from AOC is influenced by the total patient cohort 'denominator'.
- Literature on outcomes after surgery contain denominator descriptors infrequently.
- Denominator data is essential for benchmarking in gynaeoncology.
- Denominator data should be described in surgical studies.

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ABSTRACT

Objective. Combined surgery and platinum-based chemotherapy is the internationally agreed standard therapy for advanced ovarian cancer (AOC). However international cancer registry datasets demonstrate a significant proportion of patients do not receive both or either therapies. Our objective was to evaluate the effect of total patient cohort data ('Denominator') on median overall survival (OS) and determine how frequently this was reported in literature.

Methods. We retrospectively reviewed OS outcomes for 593 patients diagnosed with AOC for 77 months at a regional cancer centre. Patients were stratified into five progressively overlapping categories based on treatment received - Primary debulking surgery (PDS), PDS or Interval debulking (IDS), all surgery and those considered for IDS, patients receiving any treatment and total patient cohort. A systematic search of literature was performed.

Results. Median OS progressively decreased from 54.5 months in patients receiving PDS, 38.7 months in the PDS + IDS group, 35.4 months in the PDS/IDS + patients considered for IDS, 33.3 months in patients receiving any treatment and 30.2 months in the total patient cohort. OS in the surgically treated group was statistically significantly different from the OS in the total patient cohort (Denominator)($p = 0.000353$). Denominator descriptors were identified in 11% of studies.

Conclusions. Denominator data is critical to understanding selection and OS in AOC. Published outcomes of selected cohorts should routinely incorporate outcomes for all women managed within the reporting Centre. This is essential for benchmarking and quality assurance in gynaecological cancer and should be an integral part of any publication on outcomes from AOC.

1. Introduction

Disease burden with cytoreductive outcomes following debulking surgery and platinum sensitivity are two of the strongest predictors of survival in advanced ovarian cancer (AOC) [1–3]. As such, the importance of surgery is reflected in published international guidelines [4,5]. However, both the United States SEER data and the United Kingdom Cancer registry datasets demonstrate that up to 44% of patients with AOC do not receive optimum therapy [6,7]. Explanations for such deviations in care include: elderly patients; emergency presentations; unclear histology; significant co-morbidities; as well as patient choice [7–9]. Investigating the underlying factors for this under-treated group has been difficult with limited data recorded in national databases in these patients compared to their counterparts who receive treatment [9].

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In contrast, there are numerous publications, mainly single centre based, on the success associated with primary cytoreductive surgery where attempted [10–16]. In this latter group, survival data is often presented without reference to the population from which they are derived. This makes it impossible to ascertain the selection processes which resulted in the reported patient cohort. Patient selection in AOC between centres can vary by: i) by the proportion of patients selected at each centre to receive any treatment; ii) those managed by primary surgery vs neoadjuvant chemotherapy and; iii) finally by the proportion who following neoadjuvant chemotherapy have debulking surgery. All of these variables may render the population reported showing an excellent outcome (e.g. by selecting only those with a high chance of complete cytoreduction) or a poorer outcome (by a policy that all patients are exposed to primary surgery). Failure to report the proportion of patients receiving each treatment modality therefore risks bias, with centres that routinely operate on patients with more disseminated disease potentially reporting inferior survival data in their surgical arm compared to centres that would routinely manage similar patients with the same tumour load with chemotherapy or palliation. The more aggressive centres may however have superior overall survival (OS) data because they are operating on a greater proportion of patients. We define the denominator as the total number of advanced ovarian cancer cases presenting referred to a specific cancer centre or within the catchment area of a cancer centre and describe the survival shift as the 'denominator effect'.

In this study, we evaluate the effect of the denominator on the survival of the total AOC cases in a systematic literature search of published literature and data from our cancer centre.

2. Methods

We undertook a retrospective review of all patients diagnosed with stage 3 or 4 AOC between 16th August 2007 and 3rd February 2014. All patients were managed by subspecialty trained gynaecological oncologists at the Pan-Birmingham Gynaecological Cancer Centre (PBGCC), Birmingham, United Kingdom, which serves a population of 2.2 million people. All patients were discussed at the Centre Multi-disciplinary team meeting (MDT) and prospectively recorded in an electronic database. The UK system of healthcare necessitates the management of every ovarian cancer patient within this population to be discussed at the PBGCC MDT. Approval for this study was obtained from the hospital clinical effectiveness department.

All consecutive patients diagnosed with stage 3 or 4 epithelial ovarian, tubal or peritoneal cancer were identified from the database, along with those lacking a histological confirmation but diagnosed based on imaging and biochemical findings and agreed as AOC by the MDT. All women with suspected AOC underwent a clinical examination, transvaginal ultrasound scan, serum CA125 assay and CT scan of the thorax, abdomen and pelvis, with imaging reviewed by specialist gynaecological cancer radiologists. Following discussion at the MDT meeting, women either underwent: primary debulking surgery (PDS), 3–4 cycles carboplatin AUC 6 ± paclitaxel 175 mg/m^2 based neoadjuvant chemotherapy (NACT) with an intention to consider interval debulking surgery (IDS), or palliation of symptoms alone (no cytoreductive surgery or chemotherapy). Our standard approach to advanced ovarian cancer is PDS followed by 6 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 3 cycles of platinum based NACT to enhance their feasibility to radical surgery with 3–5 further cycles of adjuvant chemotherapy. This is in-keeping with international guidelines of practice [17,18]. Contraindications for IDS consist of progressive disease on NACT, worsening performance status, severe cardiovascular disease and patient choice. All patients with a response on CT/CA125 or clinical indicators are considered for IDS. The PBGCC was an early adopter of advanced upper abdominal surgical procedures in the UK with complete (R0) and optimal (<1 cm) (R1) cytoreduction rates of 62.2% and 14.3% respectively in AOC. Detailed surgical outcomes have been previously published [19].

Gynaecological cancer care in the UK National Health Service (NHS) is delivered at designated regional cancer centres that are responsible for the care of all women with gynaecological malignancies within a specific catchment population. For illustration, the PBGCC manages all patients with gynaecological cancer within a 2.2 million catchment population. Although patient-initiated referrals to other providers are achievable, the NHS system focuses referrals to named providers within a gynaecological cancer centre. Referrals for private care are relatively uncommon and still necessitate discussion at, and notification to, the MDT of the regional cancer centre. Referrals to other cancer centres are uncommon and usually occur when a specific second opinion is required often after initial treatment has been implemented. As such, within the UK NHS all women with ovarian cancer within a designated region are likely to be registered with a specified cancer centre.

The following data were analysed: age; performance status (PS); age-adjusted Charleston co-morbidity index (ACCI); Deprivation score (LSOA) [20]; stage; organ of origin; histology; treatment received; cytoreduction rate; surgical complexity score (SCS) [12]; and survival data. We classified our total patient cohort by mode of treatment received into five progressively overlapping groups: group A comprised patients who underwent PDS; group B comprised patients in group A and also included all patients who underwent IDS; group C comprised patients in group B and also included patients who underwent assessment for IDS but who did not eventually undergo surgery; group D included patients in group C and also included all patients treated with chemotherapy alone; and group E included all patients in group D and also included all patients who did not receive any treatment. Group E therefore represents the total patient cohort 'denominator' and consists of all patients managed by our cancer centre. These groups are illustrated in Fig. 1. We investigated whether survival and other variables differed between these five groups.

We performed a systematic search of EMBASE databases between 1996 to Week 03 2017 using a combination of text words "ovarian ca*" and Medical Subject Headings "surgery" or "ovary cancer" to generate a subset of citations relevant to the research question. Search was limited to studies involving human subjects, published in the English language, between 1.1.16 and 31.12.16. Duplicate papers were removed, as were commentaries, narrative reviews and letters. Additional papers were identified from reference lists and previously identified studies. Inclusion criteria consisted of: prospective or retrospective, single centre, cohort studies of surgically treated stage 3–4 AOC that presented OS data. Exclusion criteria consisted of: multicentre studies, randomised controlled trials of chemotherapy or papers where OS data could not be extracted. Papers were selected from their abstracts by one author (AP) with a second review by another (SS) where inclusion or exclusion was unclear. The EMBASE database was last interrogated on 18/1/17.

2.1. Statistical analysis

Categorical variables were compared with the chi-squared test and parametric and non-parametric continuous variables were compared with the ANOVA or Kruskal-Wallis test respectively. All tests were two-sided and a p-value of <0.05 was regarded as being statistically significant. All tests were two-sided and a p-value of <0.05 was regarded as statistically significant. The Kaplan-Meier method was used to estimate survival with survival compared using the Log rank method with IBM SPSS version 20.

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