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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.

KEYWORDS

Ovarian cancer; Denominator; Survival; Surgery; Chemotherapy; Patient selection

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).

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.

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 175mg/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 (<1cm) (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 Figure 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.

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 less than 0.05 was regarded as being statistically significant. All tests were two-sided and a p-value of less than 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.

Results

Between 16th August 2007 and 3rd February 2014, 593 women diagnosed with advanced ovarian cancer (AOC) were identified from the database. Of these, 441 (74.4%) patients received either PDS (n=146) or IDS after NACT (n=295), and 152 (25.6%) patients received no cytoreductive surgery. The clinico-pathological data comparing those that did and did not undergo surgery is summarised in Table 1. Patients who did not undergo surgery were significantly older ($p<0.00001$), had a worse performance status ($p<0.00001$), a higher ACCI ($p<0.00001$), lived in more deprived regions ($p<0.00001$), presented with more advanced disease ($p=0.0001$) and were more likely not to have a histological diagnosis of their malignancy ($p<0.00001$).

Figure 1 summarises study population by treatment received. Of the 152 patients that did not receive any cytoreductive surgery, 25 were considered for palliation of symptoms only due to poor performance status that precluded any cancer treatment either with chemotherapy or cytoreductive surgery. NACT was recommended for 123 patients but only commenced in 104 patients due to 14 patients dying prior to NACT and five patients declining NACT. Thirteen patients did not complete all their NACT cycles due to either death or intolerance. The remaining 91 patients completed all their planned NACT cycles and were subsequently considered for IDS (but did not receive it). Failure to receive IDS was most commonly due to: poor performance status or co-morbidities (n= 30); progressive disease following NACT (n=24); no response to NACT (n=21); patient refusal of IDS (n=7); issues pertaining to disease distribution (n=7); dying prior to IDS (n=1); or, unknown (n=1).

Patients who did not receive cytoreductive surgery were considered in three groups: (1) all those who did not receive cytoreductive surgery (n=152); (2) those who were fit enough to undergo NACT (but did not necessarily receive it) (n=123); and (3) those who completed NACT and were considered for IDS (but did not undergo it) (n=91). The median OS of patients in group 1 was 11.3 months (95% CI 7.8-15.0). The corresponding value for patients in group 2 and 3 were 14.0 (95% CI 10.2-17.7) and 19.1 (95% CI 15.8-22.5) months respectively.

Five of the 123 patients that were fit enough to undergo NACT declined chemotherapy. Seven of the 91 patients that completed NACT and were considered for IDS declined surgery. The median OS for the former group of patients was 6.1 months (95% CI 0.9-11.4) whilst those patients in the latter group had not reached median OS by 33 months of follow up.

To illustrate the 'denominator effect', we analysed the median OS for the five groups of patients as described in Methods. OS progressively decreased from Group A patients (n=140) with the median OS 54.5 (35.7 – 73.3) months, Group B (n=441) with median OS 38.7 (34.9 – 42.4) months, Group C (n= 532) with median OS 35.4 (31.9 – 38.8) months, Group D (n=564) with median OS 33.3 (29.8 – 36.8) months and Group E, the total patient cohort 'Denominator' with AOC (n=593 with median OS of 30.2 (26.7 – 32.6) months (Table 2)

Comparison of median OS between Group A (patients receiving PDS) and Group E (the total patient cohort) demonstrated a highly statistically significant difference, p= 0.000586. There was a statistically significant difference between OS in Groups B and Group E, p = 0.000353 and between Groups C and E, p = 0.039180. (Table 2 and Figure 2).

Eighteen studies met the specified inclusion criteria(21-38) for the systematic search. Only two (11%) papers explicitly defined their total patient cohort(21, 27). Two additional papers (11%) used terms which were ambiguous in relation to the total patient population(34, 35). No papers presented OS for the total patient cohort although one(21) did include non-operated patients with their surgical study cohort. Two papers (11%) documented the number of patients who received any therapeutic treatment(21, 27) with two papers (11%) ambiguous in their descriptions(34, 35). Although twelve papers (67%) explicitly described all patients receiving surgery(21, 23-25, 27-30, 32, 34-36) only four papers (22.2%) published their OS of all surgically managed patients(24, 28-30). Table 3 presents this and any comment on survival data.

Discussion

In this study, we highlight the effect of the denominator on survival using our centre survival data and the sparse description of denominators in published literature in AOC. To our knowledge, this is the first study to explicitly define the denominator in AOC and describe its relevance. Our study, demonstrates a significant difference in OS based on the total patient cohort 'denominator'. Presenting denominator data would improve the understanding of the process of patient selection within any given Centre, standardise selection between centres and facilitate reducing selection bias which is inevitable in retrospective studies. Importantly it would also help in understanding the underlying factors that preclude patients from receiving therapy, thus potentially improving outcomes. OS for AOC internationally continues to be poor with a five year survival of 30%(39). Unless we focus our efforts on understanding the whole patient cohort of ovarian cancer, including those that do not receive any treatment, obtaining improvements in OS will remain challenging.

In our series, 25.6% of patients with AOC did not receive cytoreductive surgery, 4.9% of whom were too ill to receive any treatment beyond that of palliation (Figure 1). Such findings are consistent with the UKs National Cancer Data Repository which has on record that 44%

of patients diagnosed with AOC in the UK do not receive cytoreductive surgery and 25% do not receive any treatment beyond palliation(7). Such a high prevalence of undertreated patients is not unique to the UK with comparable corresponding figures from the American National Cancer Database (no surgery in 21% and no chemotherapy in 8.7%) and Surveillance, Epidemiology and End Results (SEER) Database (no surgery in 34.2% and no chemotherapy in 16.5%)(8, 9).

Whilst this manuscript demonstrated the impact on survival based on the category of patient investigated, it is reasonable to expect that this denominator effect would impact as well on morbidity of treatment and quality of life post treatment(40). An explicitly defined denominator is crucial to efforts to benchmark survival between centres worldwide. The European Society of Gynaecological Oncology should be applauded for incorporating total denominator data into their recent quality standards for ovarian cancer(41). Such data can be used for self-assessment, for institutional quality assurance programs, for governmental quality assessment and eventually to build a network of certified centres for ovarian cancer surgery that are transparent about the quality of care they deliver and the survival data that their approach achieves.

Unfortunately, such robust reporting is scant in the literature and potentially artificially inflates survival outcomes. Our data represents every single patient with AOC based on histology, cytology and/or radiology and tumour markers in a centre serving a population of 2.2 million. Patients in other health care systems may be triaged in different ways. It is likely that there will be variation in overall operating rates in nationalised healthcare systems compared to systems with significant patient and provider selection. The total patient denominator, may aid identification of those centres with an unselected patient cohort compared to those treating a predominantly triaged population with good fitness for surgery. The lack of total denominator data makes a fallacy of a centre's "cytoreduction rate" or "primary surgery rate".

The importance of the total patient denominator has been established in numerous nationwide cancer audits in the United Kingdom, such as the "National Bowel Cancer Audit Report"(42) and the "National Oesophago-Gastric Cancer Audit"(43). Such basic data has allowed trends in patients receiving treatment to be followed at a local, regional and national level. Both these registers collect data in not only those who receive surgery but also those that, either

due to patient or disease factors, do not. The importance of denominator data for ovarian cancer should be considered no different to these other high risk and aggressive cancers.

Even with the use of a denominator as simplistic as the total patient cohort there are still areas of contention. Firstly, is the issue of AOC being defined as stage 3 or 4 disease. It is possible that the true overall patient denominator may be underestimated in cases with inadequate retroperitoneal or extra-pelvic exploration performed. Equally, diagnosis based on radiology and tumour markers alone may increase the denominator with non-ovarian tumours mimicking that of epithelial ovarian tubal and primary peritoneal cancers. The result of this being that centres with suboptimal staging practice or who are less aggressive in obtaining histological diagnosis are potentially going to present a cohort with inferior OS relative to their peers. A potential solution would be to expand the denominator to include all stage distributions of patients with ovarian cancer and to declare the proportion who did not receive a histological diagnosis. The development of an outcomes "dataset" is beyond the remit of this paper but standardised reporting of denominator, stage, histological diagnosis as well as patient and disease descriptors would, we believe, be a tool to accurately categorise centres and allow greater interpretation of centres outcomes. The development of a "core outcome" set for ovarian cancer, as recommended by the COMET initiative would be a welcome development in this space(44, 45). Comparisons could then be made with centres with similar data distributions and thus allow their research findings to be appropriately implemented either more cautiously in centres with wider but more heterogenous patient group or more rapidly in similar centres.

As an important initial step, we suggest that to enable accurate interpretation of prospective or retrospective cohort surgical studies in AOC, the minimum denominator descriptors that should be provided should include the total number of patients as well as the total number of patients operated on. Indeed, the absence of such denominator data risks a disservice to studies that are innovative in their conclusions.

In conclusion, the denominator of advanced cancer cases in each centre is critical to understanding selection and survival. This is essential for benchmarking and quality assurance in gynaecological cancer and should be an integral part of any publication on outcomes from AOC.

Tables/Figures

Table 1: Clinicopathological data of the total patient cohort presented comparing patients who did not undergo surgery with those who underwent surgical management of AOC

Figure 1: Flowchart demonstrating patient outcomes for the total patient cohort 'denominator'.

Table 2: Impact on median OS by group of patients analysed demonstrating the 'Denominator effect'.

Figure 2: Kaplan-Meier curve comparing OS by patient groups A-E.

Table 3: Reporting of denominator data, surgical cohort data and survival data in included studies

Conflict of interest statement

The authors declare no conflicts of interest

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4. Table

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Table 1: Clinicopathological data of the total patient cohort presented comparing patients who did not undergo surgery with those who underwent surgical management of AOC

	Non-surgical cases n = 152		**Surgical cases** n = 441		***p***
Age	72.3 (95% CI 61.3 - 83.3)		63.27 (95% CI 51.46 - 75.08)		*<0.00001*
PS (Median IQR)	2 (1-2) (54 cases)		1 (0-1) (307 cases)		*<0.00001*
ACCI	4 (3-5) (70cases)		2 (0-3) (441 cases)		*<0.00001*
LSOA Deprivation Score	3 (2-5)		5 (2-7)		*<0.00001*
Stage					
3	92	60.5%	347	78.7%	*0.000011*
4	56	36.8%	94	21.3%	*0.000146*
Unstaged advanced	4	2.6%	0	0.0%	*0.00063*
Site of origin					
Ovary	124	81.6%	322	73.0%	*0.034988*
Peritoneal	28	18.4%	78	17.7%	*>0.05*
Tubal	0	0.0%	41	9.3%	*0.000098*
Histology					
Serous	107	70.4%	348	78.9%	*0.032121*
Serous low grade	3	2.0%	23	5.2%	*>0.05*
Mucinous	2	1.3%	3	0.7%	*>0.05*
MMMT	3	2.0%	22	5.0%	*>0.05*
Mixed Epithelial	1	0.7%	15	3.4%	*>0.05*
Psammomatous	1	0.7%	0	0.0%	*>0.05*
Clear Cell	2	1.3%	16	3.6%	*>0.05*
unknown	31	20.4%	3	0.7%	*<0.00001*
Mullerian	2	1.3%	2	0.5%	*>0.05*
Undifferentiated/Anaplastic	0	0.0%	4	0.9%	*>0.05*
Endometroid	0	0.0%	5	1.1%	>0.05

4. Table

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Table 2. Impact on median OS by group of patients analysed demonstrating the 'Denominator effect'.

Treatment group	**Median OS (months) (95% CI)**	***p***
A: Patients undergoing PDS	54.5 (35.7 – 73.3)	0.000586
B: Group A and patients undergoing IDS	38.7 (34.9 – 42.4)	0.000353
C: Group B and patients assessed for IDS	35.4 (31.9 – 38.8)	0.039180
D: All AOC patients receiving any treatment	33.3 (29.8 – 36.8)	0.393738
E: All advanced ovarian cancer patients	30.2 (26.7 – 32.6)	Reference

4. Table

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Table 3: Reporting of denominator data, surgical cohort data and survival data in included studies

Study	Journal	Stage	Total operated patients	Study group and number of patients on whom survival data is presented	OS in study group (Median OS +/-95% CI) months or 5-year survival	Denominator Data (Total patient number)	Total Cohort OS (Median +/- 95% CI) months or 5-year survival
Ataseven et al (1)	*Gynecol Oncol*	4	315	PDS:286	16 (12–20) - 50 (3–57)	355	PDS + No surgery: 30 (NACT patients excluded)
Bachmann et al (2)	*J Cancer*	3c -4	Not stated	R0/R1: 108	18.8 (9.7 – 27.9) - 30.5 (24.7 – 57.3)	Not stated	Not stated
Bian et al (3)	*Arch Gynecol Obstet*	3c -4	339	IDS: 114 PDS:225	IDS: 25 (21.7–28.3) PDS: 25 (22.1–27.9)	Not stated	Not stated
Feng et al (4)	*Gynecologic Oncology*	1 - 4	625	625	51.40%	Not stated	Not stated
Gadducci et al (5)	*Int J Gynecol Cancer*	3c-4	384	IDS: 64 PDS: 322	IDS: 41.8% PDS: 69.3%	Not stated	Not stated
Gill et al (6)	*Gynecol Oncol*	3c -4	Not stated	IDS (?R2): 45 PDS (R2): 45	IDS 28.2 PDS: 16.8	Not stated	Not stated
Heitz et al (7)	*Gynecol Oncol*	3b-4	663	PDS: 578	49 (42–55)	739	Not stated
Luo et al (8)	*Medicine*	3c-4	370	Overall: 341 PDS: 283 IDS: 58	Overall 50.0 (44.5–55.5) PDS: 51.0 IDS: 41.0	Not stated	Not stated

Medina-Franco et al (9)	*Ann Surg Oncol*	3c-4	105	Overall: 105 PDS: 42 IDS: 63	Overall: 38 PDS: 33.59 IDS: 56.4	Not stated	Not stated
Mueller et al (10)	*Gynecol Oncol*	3-4	581	581 IDS: 149 PDS: 432	Overall 63.2 (55.3–73.2) PDS 71.7(59.8-not reached) IDS (42.9 (37.1–56.3)	Not stated	Not stated
Munoz-Casares et al(11)	*Eur J Surg Oncol*	3c-4	Not stated	IDS + HIPEC: 124	49%	Not stated	Not stated
Oseledchyk et al(12)	*Int J Gynecol Cancer*	3-4	278	R1/R2: 96	19.5 - 32.9	Not stated	Not stated
Pereira et al(13)	*Surgical Oncology*	3-4	Not stated	116	If alive: 169.8 If dead: 34.9 months	Not stated	Not stated
Phillips et al		3-4	441	All surgery: 441 PDS: 140	All surgery: 38.7 (34.9-42.4). PDS: 54.5 (35.7-73.3)	593	30.2 (26.7-32.6)
Plotti et al(14)	*Eur J Surg Oncol*	3-4	337	PDS: 154	48-52%	Unclear	Not stated
Skof et al(15)	*Radiol Oncol.*	3c-4	160	PDS: 80 IDS 80	PDS: 31.6 IDS 24.8	Unclear	Not stated
Stewart et al(16)	*Can J Surg*	3-4	334	IDS: 156 PDS: 178	IDS: 33.4 PDS 69.5	Not stated	Not stated
Sun et al(17)	*Transl Oncol*	3c-4	Not stated	PDS + HIPEC: 46	74.0 (8.5-139.5)	Not stated	Not stated
Xu et al(18)	*J Ovarian Res*	3c - 4	Not stated	IDS: 160	32.1 (27.1–37.1)	Not stated	Not stated

Legend: PDS = Primary debuking surgery; IDS = Interval debulking surgery; R0= Complete cytoreduction; R1 = Optimal <1cm residual disease; R2= Suboptimal >1cm residual disease; HIPEC = Hyperthermic intraperitoneal chemotherapy

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5. Figure
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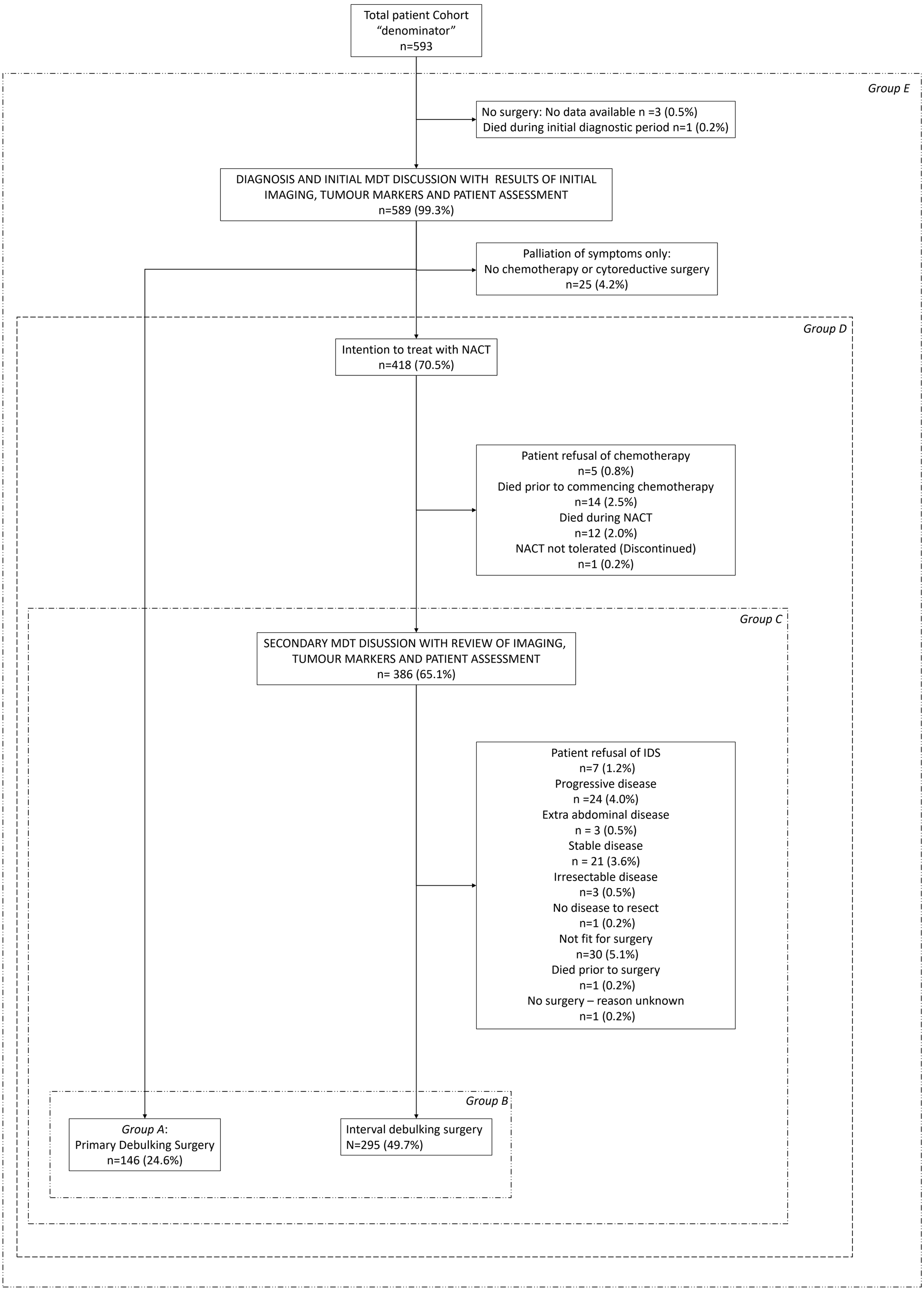
Figure 1: Flowchart demonstrating patient outcomes for the total patient cohort “denominator”



5. Figure

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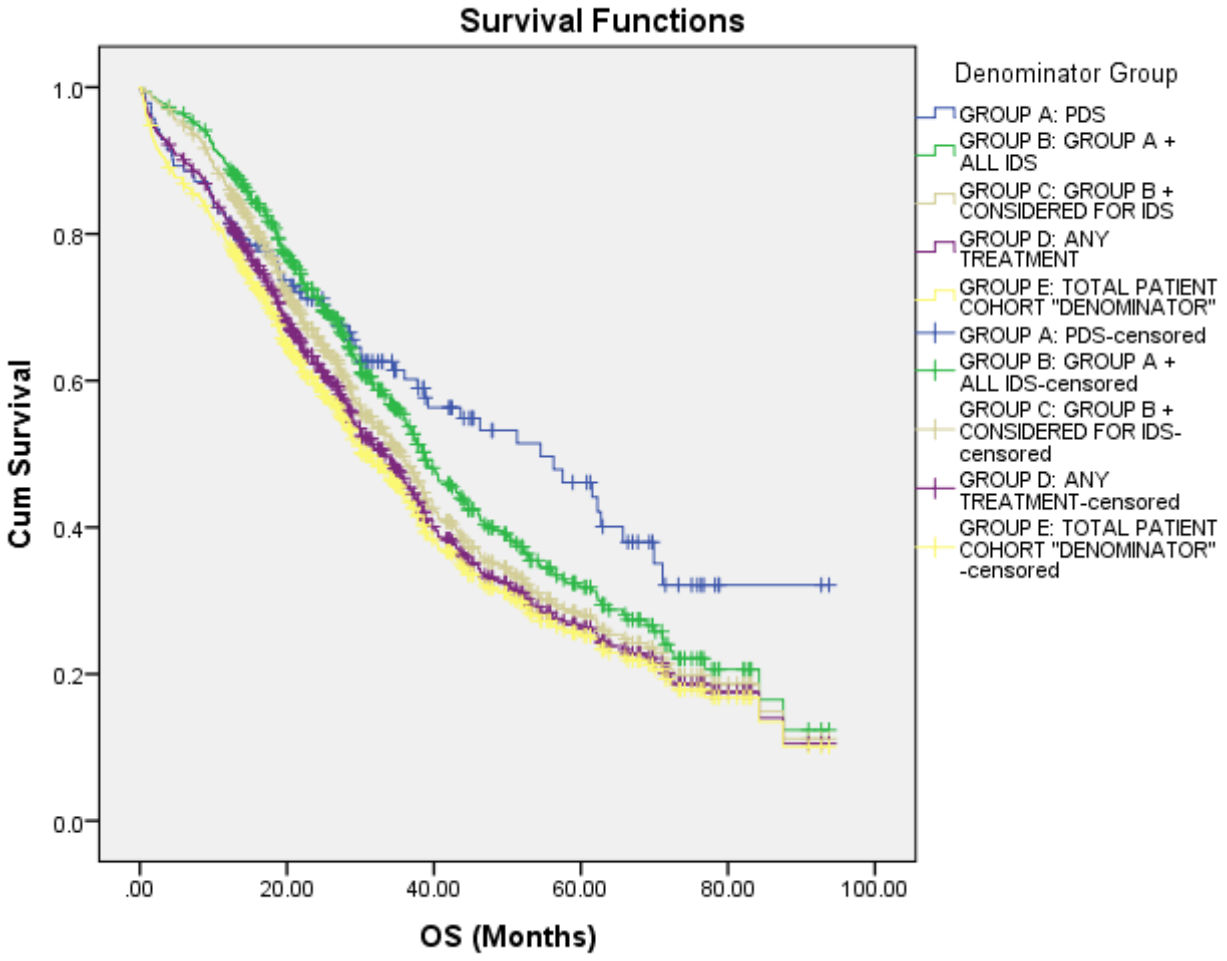
Figure 2: Kaplan-Meier curve comparing OS by patient groups A-E.



***7. Highlights (for review)**

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