Trends in surgical complexity and treatment modalities utilized in the management of ovarian cancer in an era of neoadjuvant chemotherapy

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HIGHLIGHTS

- The utilization of NACT increased from 7.7% in 2004 to 27.8% in 2015.
- High complexity surgeries increased from 26.3% to 30% from 2004 to 2015.
- During the same time period, overall 30- and 90-day mortality decreased.
- During the same time period, 5-year survival increased.

ARTICLE INFO

ABSTRACT

Objectives. To investigate the impact of the increased use of neoadjuvant chemotherapy on the complexity of cytoreductive surgeries for ovarian cancer.

Methods. Using the National Cancer Database, we performed a retrospective cohort study of women diagnosed between 2004 and 2015 with stage III or IV epithelial ovarian cancer who underwent either primary cytoreductive surgery (PDS) followed by adjuvant chemotherapy, neoadjuvant chemotherapy (NACT) followed by interval debulking surgery. Cases were assigned a surgical complexity category as 1) Inadequate, 2) Low, 3) Moderate and, 4) High complexity. The primary outcome was the trend in surgical complexity over time. Secondary outcomes included temporal trends in treatment modality, perioperative mortality, and survival.

Results. At total of 52,582 (76.3%) underwent PDS and 16,307 (23.7%) underwent NACT. The utilization of NACT increased from 7.7% in 2004 to 27.8% in 2015 (p-trend < 0.001). Patients undergoing moderate complexity surgeries increased from 28.9% to 33.5% and high complexity surgeries from 26.3% to 30% (p-trend < 0.001, for both). Trends in increasing surgical complexity were seen in both NACT and PDS cohorts. This increase in surgical complexity was seen most profoundly at the high-volume centers. Overall 30-day mortality decreased from 3.4% in 2004 to 1.4% in 2015; and 90-day mortality decreased from 7.6% to 4%. During the same time, 5-year survival increased from 39.7% to 49%.

Conclusions. Increase in the utilization of NACT is associated with decreased 30- and 90-day mortality and increase in five-year survival. Moreover, the overall complexity of ovarian cancer surgery has increased in both PDS and NACT cohorts.

1. Introduction

Neoadjuvant chemotherapy (NACT) followed by interval cytoreductive surgery has always been an alternative treatment modality for those patients with ovarian cancer who were poor surgical candidates or those in whom optimal debulking at time of primary debulking surgery (PDS) was unlikely [1,2]. For new diagnosis stage III ovarian cancer patients, the clinical decision of proceeding with NACT versus PDS and the impact on patient outcomes has been long disputed in the literature. In early reports, maximal primary cytoreduction to no visible residual disease was shown to be a significant predictor of survival among these patients [3]. Achieving no residual disease may require aggressive surgical efforts and has been shown to improve survival [4]. In contrast, randomized controlled trials show that NACT results in reduction in operative time, fewer operative complications, and fewer organ resections [5]. Additional randomized control trials demonstrate that when compared to PDS, NACT has similar efficacy, decreased morbidity, and is cost-effective [6–9]. From 2003 to 2011, there has been an increasing trend in utilization of NACT followed by interval cytoreductive

surgery from 16% to 34% for stage IIIC and from 41% to 62% for stage IV ovarian carcinomas [2]. However, there are concerns that the increasing utilization of NACT compromises the complexity of cytoreductive surgeries, and specifically, the quality of training of future gynecologic oncologists [10].

The primary objective of the current study is to investigate the impact of the increased use of NACT on the complexity of cytoreductive surgeries for ovarian cancer. The secondary objectives were to evaluate temporal trends in treatment modalities used, perioperative mortality, and survival for ovarian cancer in the United States during the same time period.

2. Methods

We used the National Cancer Database to perform a retrospective cohort study of women diagnosed with stage III or IV epithelial ovarian cancer between 2004 and 2015 undergoing either primary debulking surgery followed by adjuvant chemotherapy or neoadjuvant chemotherapy followed by interval cytoreductive surgery. This database (herein referred to as the database) is a joint program between the American Cancer Society and the Commission on Cancer of the American College of Surgeons. This database uses a hospital-based registry, and the Commission on Cancer requires approved programs to abstract and follow all malignant tumors diagnosed or treated at the hospital [11]. Currently, approximately 70% of the ovarian cancer cases in the United States are reported to the database [12]. In order to ensure confidentiality, reported data are de-identified and therefore exempt per the University of Michigan Institutional Review Board policies.

Cases were selected using the diagnostic code C56.9 (Malignant neoplasm of ovary). We restricted our analyses to patients with epithelial ovarian cancer and advanced stage (defined as International Federation of Gynecologists and Obstetricians (FIGO) stages III and IV), who underwent surgery and/or chemotherapy within 6 months of their diagnosis. Exclusion criteria were the following: stage I/II disease, non-epithelial histology, treatment with palliative intent, and no treatment within the first 6 months after diagnosis. Initially, all patients who received treatment were included for trend analysis, and then for the subsequent analyses of surgical complexity, only those who received both chemotherapy and surgery (in either sequence) were included.

The primary outcome was the trend in surgical complexity over time. The database guidelines require the data abstractors to review the operative procedures and assign the procedure codes listed in the registry manual, instead of using the Common Procedural Terminology (CPT) codes. Surgical cases were designated as inadequate or adequate, and then adequate surgeries were categorized as either low complexity, moderate complexity, or high complexity. Descriptions of the adequacy

of surgery and surgical complexity categories are detailed in Table 1. Additional variables collected included the following patient characteristics: age (categorized as ≤40, 41–50, 51–60, 61–70, 71–80, and > 80 years), Charlson comorbidity index (the database provides a score of 0, 1, or 2 or more) [13], race and ethnicity (categorized as a mutually exclusive race-ethnicity variable — non-Hispanic White, non-Hispanic Black, Hispanic, other or unknown), median household income from ZIP code of residence, insurance status, and distance travelled. Additional hospital characteristics were collected including facility type (as categorized by the national cancer database — community cancer program, comprehensive community cancer, academic or research program, integrated network cancer program) and mean hospital volume of epithelial ovarian cancer cases. The mean hospital volume was calculated by dividing the total number of cases reported by the hospital by the time interval over which the hospital reported the cases to the database. The mean hospital volume was then divided into four categories of annualized hospital volume (≤10 cases-per-year, 11–20 cases-per-year, 21–30 cases-per-year and ≥ 31 cases-per-year). These cutoffs were chosen based on previous reports denoting [1] hospitals performing >20 cases as high volume [14,15] and [2] those with ultra-high volume (≥31 cases-per-year) have the lowest 30-day and 90-day complications [16]. Secondary outcomes included 30-day and 90-day mortality, and overall five-year survival.

Data management and analyses were performed using STATA version 15 (Stata-Corp, College Station, TX). Categorical variables were compared with chi-squared tests; continuous variables were compared with student's t-tests. Linear changes in study variables over the timeframe of the study were assessed using a non-parametric trend test (Stata, nptrends) [17]. All tests were two-tailed, and alpha was set at 0.05.
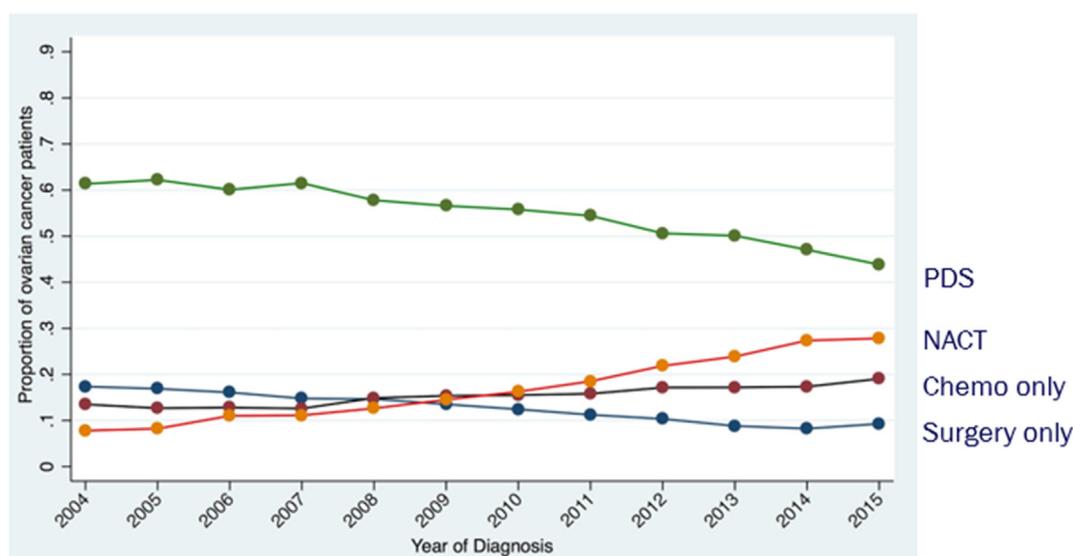
3. Results

3.1. Trends of treatment modalities

A total of 95,785 cases met inclusion criteria. A detailed flowchart of our cohort development is shown in Supplementary Fig. 1. Of those who met inclusion criteria, 14,752 (15.4%) underwent chemotherapy only, 12,144 (12.7%) underwent surgery only, and 68,889 (71.9%) underwent both chemotherapy and surgery. This cohort of patients was used to generate the trend in treatment modalities utilized for ovarian cancer patients from 2004 to 2015. The percentage of patients undergoing surgery only (with no chemotherapy prior to or after surgery) went from 17.4% (95% CI 17.1–17.6) to 9.3% (95% CI 9.1–9.4) (p-trend <0.001). Similarly, there was a decline in patients undergoing primary debulking surgery followed by adjuvant chemotherapy from 61.4% (95% CI 61–61.7) to 43.8% (95% CI 43.5–44.2) (p-trend <0.001). There was increase in patients undergoing chemotherapy only (no surgical management) from 13.5 (95% CI 13.2–13.7) to 19.1% (95% CI 18.8–19.3) (p-trend <0.001). Finally, the percentage of neoadjuvant chemotherapy increased from 7.7% (95% CI 7.6–7.9) to 27.8% (95% CI 27.5–28.1) (p-trend <0.001). These results are summarized in Fig. 1.

3.2. Surgical complexity

For this analysis, patients who underwent both chemotherapy and surgery were retained. From a total of 68,889 patients, 52,582 (76.3%) underwent primary debulking surgery followed by chemotherapy and 16,307 (23.7%) underwent neoadjuvant chemotherapy and interval debulking (Supplementary Fig. 1). Complete demographic characteristics of the two cohorts used for surgical complexity analysis is presented in Table 2.

A number of clinically significant differences between the two groups were noted. Patients undergoing neoadjuvant chemotherapy (median age 65, IQR 57–72) were significantly older than those undergoing primary debulking surgery (median age 61, IQR 52–70) (p <

Table 1
Description of surgical complexity.

	Procedures Included
Inadequate surgery	Total removal of tumor or (single) ovary only, resection of ovary (wedge, subtotal, or partial) only, or unilateral salpingo-oophorectomy, with or without hysterectomy. Excludes patients undergoing omentectomy.
Low complexity surgery	Unilateral or bilateral (salpingo-)oophorectomy with omentectomy, partial or total, with or without hysterectomy
Moderate complexity surgery	Ovarian debulking[a]/cytoreductive surgery
High complexity	Ovarian debulking[a]/cytoreductive surgery with colon (including appendix) or small intestine resection or partial resection of urinary tract (not incidental) or anterior, posterior, total, or extended pelvic exenteration

[a] Debulking is defined by the database as a partial or total removal of the tumor mass and can involve the removal of multiple organ sites. It may include removal of ovaries and/or the uterus (a hysterectomy). The pathology report may or may not identify ovarian tissue. A debulking is usually followed by another treatment modality such as chemotherapy.

Fig. 1. Trends in treatment modality from 2004 to 2015. Utilization of neoadjuvant chemotherapy has increased significantly over this time period. (p < 0.001 for all four trend analysis presented in this figure).

0.001). Patients undergoing neoadjuvant chemotherapy were more likely to have stage IV disease (42%) vs. primary debulking patients (20%) (p < 0.001). Other factors such as race, Charlson score, insurance status, income, facility type, distance to hospital were noted to demonstrate statistically significant differences between the groups due to large sample size, but the absolute differences in the groups were very small (Table 2). In centers performing 11–20 cases per year, 78.2% of patients underwent PDS while 21.8% were treated with NACT. Similarly, in centers performing 21–30 and > 30 cases per year, 76.3% and 74.2% of patients under PDS while 23.6% and 25.7% are treated with NACT, respectively (p < 0.001).

From 2004 to 2015, the rate of inadequate surgeries decreased from 13.5% (95% CI 13.3–13.8) to 10.5% (95% CI 10.2–10.8) (p-trend <0.001) and the rate of low complexity surgery dropped from 31.2% (95% CI 30.8–31.5) to 26.1% (95% CI 25.7–26.4) (p-trend <0.001). Conversely, the rates of moderate complexity surgeries increased from 28.9% (95% CI 28.6–29.3) to 33.5% (95% CI 33.1–33.8) and high complexity surgeries went from 26.3% (95% CI 26–26.6) to 30% (95% CI 29.7–30.4) (p-trend <0.001, for both) (Fig. 2). These trends in increasing surgical complexity were seen in both NACT and PDS cohorts. This increase in surgical complexity was seen most profoundly at the high-volume centers. (Fig. 3).

3.3. 30- and 90-day mortality and 5-year survival

In patients undergoing both chemotherapy and surgery, the 30-day mortality decreased from 3.4% to 1.4% and 90-day mortality decreased from 7.6% to 4% over the interval from 2004 to 2015 (p-trend <0.001). The overall five-year survival increased from 39.7% (95% CI 38.2–41) in 2004 to 49% (47.8–50.4) in 2012 (p-trend <0.001). Survival data from 2013 to 2015 was unavailable in this release of NCDB (Fig. 4).

4. Discussion

In this cohort, there was an increase in utilization of NACT from 7.7% in 2004 to 11% in 2004 to 38% in 2015, similar to trends found by other investigators [1,2,9]. Despite the increased utilization of NACT, surgical complexity did not decrease. On the contrary, the complexity of surgery increased both in PDS and NACT patient cohorts from 2004 to 2013, particularly at high-volume centers. We also observed a reduction in both 30-day and 90-day mortality and an increase in five-year survival during the same time period.

Previous findings showed the use of NACT was associated with a reduction in operative time, fewer operative complications, and fewer organ resections [5]. One might infer that the increased use of NACT would compromise the complexity of cytoreductive surgeries, however, our study demonstrates that surgical complexity has not decreased despite the increasing utilization of NACT. In our cohort, overall surgical complexity trends were similar between the low versus high volume centers and between the NACT and PDS groups. There were downward trends in inadequate and low complexity surgeries. Conversely, there was an increase in both moderate and high complexity surgeries in both PDS and NACT cohorts. We hypothesize that the increase in surgical complexity is seen in both groups because there have been studies published showing the survival benefit of optimal debulking to no visible residual disease [3,4,18]. We believe that this has led to more aggressive surgical practices in the attempt to resect all visible disease. Although NACT has been associated with intraoperative and postoperative benefits, we find that interval debulking surgery is not necessarily less complex. It has been previously shown that NACT when compared to PDS did not result in lower complexity scores or decreased aggressiveness of surgery (upper abdominal or exenterative procedures or ostomies) [2]. Our study suggests the complexity of interval debulking procedures has increased most significantly in high surgical volume hospitals. These high volume environments are where gynecologic oncology fellowships are located, and therefore, we believe surgical training is not compromised. However, we still encourage ACGME to monitor data over time to ensure fellows are getting adequate surgical training in the setting of changes in chemotherapy utilization.

Traditionally, PDS has been the preferred treatment in the United States for ovarian cancer, however, there have been conflicting reports comparing survival outcomes between NACT and PDS. There have been two randomized controlled trials outside of the United States that showed NACT as noninferior to PDS with similar overall survival and lower operative morbidity [7,9]. However, these trials reported lower overall survival and lower rates of optimal debulking which lead to questions about generalizability given more aggressive cytoreductive practices in the United States [19–21]. A retrospective cohort study performed in the United States using data from six NCCN centers showed decreased survival in patients with stage IIIC ovarian cancer who were treated first with NACT versus upfront debulking surgery [2]. Given its retrospective design, these results might be confounded by NACT being administered to very frail patients or patients with the most advanced disease leading to shorter survival. Additionally, NCCN centers are more

Table 2
Characteristics of women with Stage III or IV epithelial ovarian cancer between 2004 and 2015 who received primary debulking surgery followed by adjuvant chemotherapy versus neo-adjuvant chemotherapy followed by interval debulking surgery in the National Cancer Database.

Variable	Categories	Overall	Primary debulking surgery	Interval debulking surgery after neoadjuvant chemotherapy	P-Value
		N = 68,889	N = 52,582	N = 16,307	
Age (years)	<40	2283 (3%)	2035 (4%)	248 (2%)	<0.001
	40–49	8695 (13%)	7328 (14%)	1367 (8%)	
	50–59	18,069 (26%)	14,410 (27%)	3659 (22%)	
	60–69	21,179 (31%)	15,608 (30%)	5571 (34%)	
	70–79	14,512 (21%)	10,257 (20%)	4255 (26%)	
	≥80	4151 (6%)	2944 (6%)	1207 (7%)	
Race	Non-Hispanic white	57,197 (83%)	43,947 (84%)	13,250 (81%)	<0.001
	Non-Hispanic black	4821 (7%)	3499 (7%)	1322 (8%)	
	Hispanic	3714 (5%)	2768 (5%)	946 (6%)	
	Other	3157 (5%)	2368 (5%)	789 (5%)	
Charlson score	0	56,489 (82%)	43,464 (83%)	13,025 (80%)	<0.001
	1	10,178 (15%)	7548 (14%)	2630 (16%)	
	≥2	2222 (3%)	1570 (3%)	652 (4%)	
Insurance	Uninsured	2567 (4%)	2032 (4%)	535 (3%)	<0.001
	Private	33,674 (49%)	27,090 (52%)	6584 (40%)	
	Medicaid	4201 (6%)	3044 (6%)	1157 (7%)	
	Medicare	26,836 (39%)	19,190 (36%)	7646 (47%)	
	Other	1611 (2%)	1226 (2%)	385 (2%)	
Income	<$38,000	10,057 (15%)	7671 (15%)	2386 (15%)	0.103
	$38,000–$47,999	15,313 (23%)	11,627 (22%)	3686 (23%)	
	$48,000–$62,999	18,597 (27%)	14,114 (27%)	4483 (28%)	
	$63,000+	23,852 (35%)	18,319 (35%)	5533 (34%)	
Facility type	Community Cancer Program	2830 (4%)	2210 (4%)	620 (4%)	<0.001
	Comprehensive Community Cancer	26,148 (39%)	20,051 (40%)	6097 (38%)	
	Academic/Research Program	29,890 (45%)	22,378 (44%)	7512 (47%)	
	Integrated Network Cancer Program	7738 (12%)	5908 (12%)	1830 (11%)	
Distance to the hospital	Ist Quartile (<4.9 miles)	14,402 (21%)	11,150 (22%)	3252 (20%)	<0.001
	2nd Quartile (5–11 miles)	16,325 (24%)	12,593 (24%)	3732 (23%)	
	3rd Quartile (11.1–29 miles)	17,934 (26%)	13,674 (26%)	4260 (26%)	
	4th Quartile (>30 miles)	19,164 (28%)	14,321 (28%)	4843 (30%)	
Hospital volume	≤10 cases/year	12,518 (18%)	9624 (18%)	2894 (18%)	<0.001
	11–20 cases/year	17,484 (25%)	13,680 (26%)	3804 (23%)	
	21–30 cases/year	18,793 (27%)	14,353 (27%)	4440 (27%)	
	≥30 cases/year	20,094 (29%)	14,925 (28%)	5169 (32%)	
Grade	Well differentiated, differentiated	2091 (3%)	1894 (4%)	197 (1%)	<0.001
	Moderately differentiated, moderate	6829 (10%)	5961 (11%)	868 (5%)	
	Poorly differentiated	36,863 (54%)	29,260 (56%)	7603 (47%)	
	Undifferentiated, anaplastic	10,722 (16%)	8113 (15%)	2609 (16%)	
	Call type not determined/not stated	12,384 (18%)	7354 (14%)	5030 (31%)	
Stage	III	51,591 (75%)	42,102 (80%)	9489 (58%)	<0.001
	IV	17,298 (25%)	10,480 (20%)	6818 (42%)	
Histology	Serous	51,330 (75%)	39,214 (75%)	12,116 (74%)	<0.001
	Mucinous	1279 (2%)	1149 (2%)	130 (1%)	
	Endometrioid	3005 (4%)	2747 (5%)	258 (2%)	
	Clear	2219 (3%)	1884 (4%)	335 (2%)	
	Other	11,056 (16%)	7588 (14%)	3468 (21%)	

likely to perform more aggressive cytoreductive surgeries that result in optimal debulking, thus skewing data in favor of PDS [2].

Similar to the previous NCCN centers study, we found an increasing trend in the 5-year survival in our cohort from 39% to 45% between 2004 and 2012 [2]. In contrast to the database of NCCN center outcomes, the National Cancer Database includes a mix of academic and community hospitals with varying case volume, surgical practices, and use of NACT. Therefore, our results may be more generalizable. Other factors that could contribute to improved survival include more aggressive debulking efforts and improved treatment modalities such as intraperitoneal chemotherapy and development of newer therapeutics.

We found a decrease in both 30- and 90-day mortality from 2004 to 2015 (Fig. 3). These findings may be due to the increased utilization of NACT. It has been shown previously that NACT followed by interval debulking surgery reduces postoperative complications and increases the probability of optimal debulking [1,8,22]. Furthermore, optimal PDS often requires aggressive procedures that have the potential to result in postoperative complications that may delay chemotherapy [8,23,24]. In patients with multiple co-morbidities or with advanced disease, NACT may reduce the risk of perioperative morbidity, delay in chemotherapy

secondary to postoperative complications, and perioperative mortality. While the increased frequency of NACT may explain our findings of decreased 30- and 90-day mortality, there are also other potential reasons that may have changed over the time interval of our study, including improvements in preoperative patient optimization, enhanced perioperative management, and advancements surgical technique.

We believe that our findings of decreased postoperative mortality and increased overall survival rates in our cohort even in the setting of increased adoption of NACT suggests that utilization of NACT is not adversely affecting patient outcomes. Maximum cytoreduction to no visible residual disease at the time of PDS has been shown to be a significant predictor of survival among patients with stage III or IV ovarian carcinoma [25]. However, there is likely a subgroup of patients in whom the benefits of aggressive PDS would not outweigh the risks. It has been discussed that in patients over 75 years of age with high tumor dissemination, stage IV disease, or poor performance status (ASA ≥3) or poor nutritional status (preoperative albumin <3.0 g/dL), NACT would be a more appropriate treatment modality [26]. In another approach to choose the most appropriate treatment modality for a specific patient is using the Leuven Criteria when considering NACT versus PDS in stage
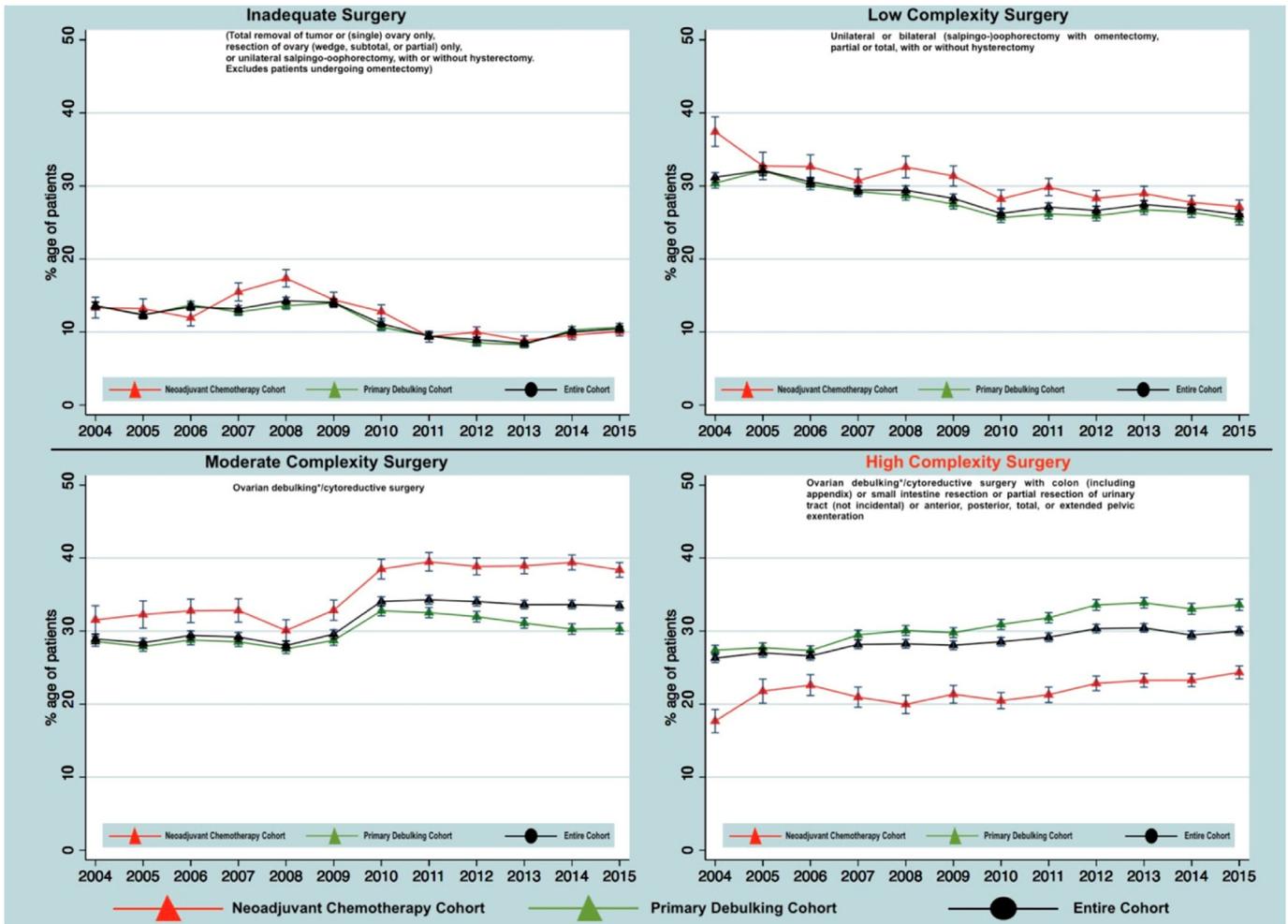
Fig. 2. Trends in surgical complexity from 2004 to 2015. Inadequate and low complexity surgeries have decreased while moderate and high complexity surgeries have increased. Trends were similar between the PDS and NACT cohorts.
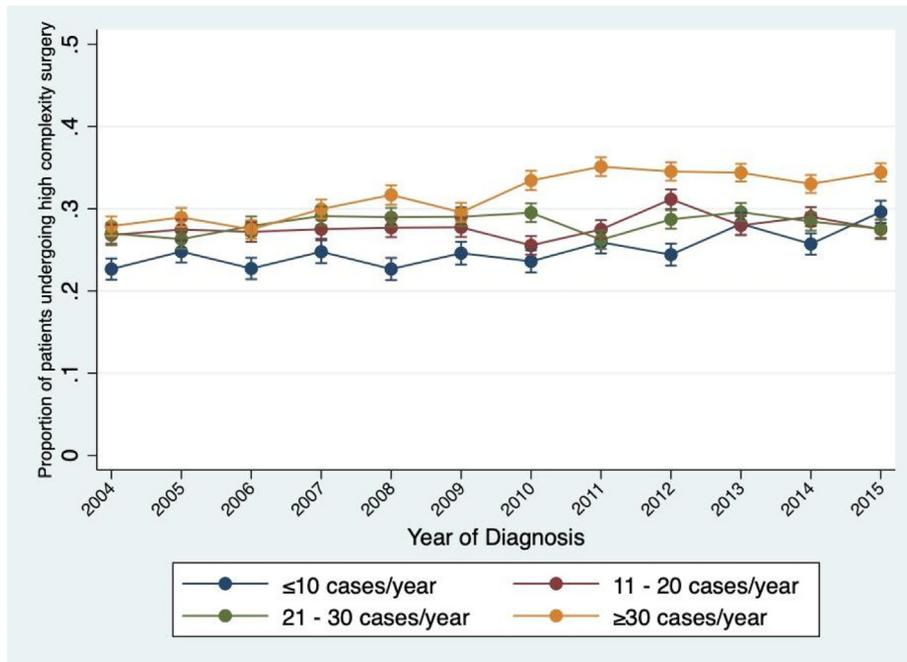

Fig. 3. Proportion of patients undergoing high complexity surgery based on yearly case volume of the hospital.
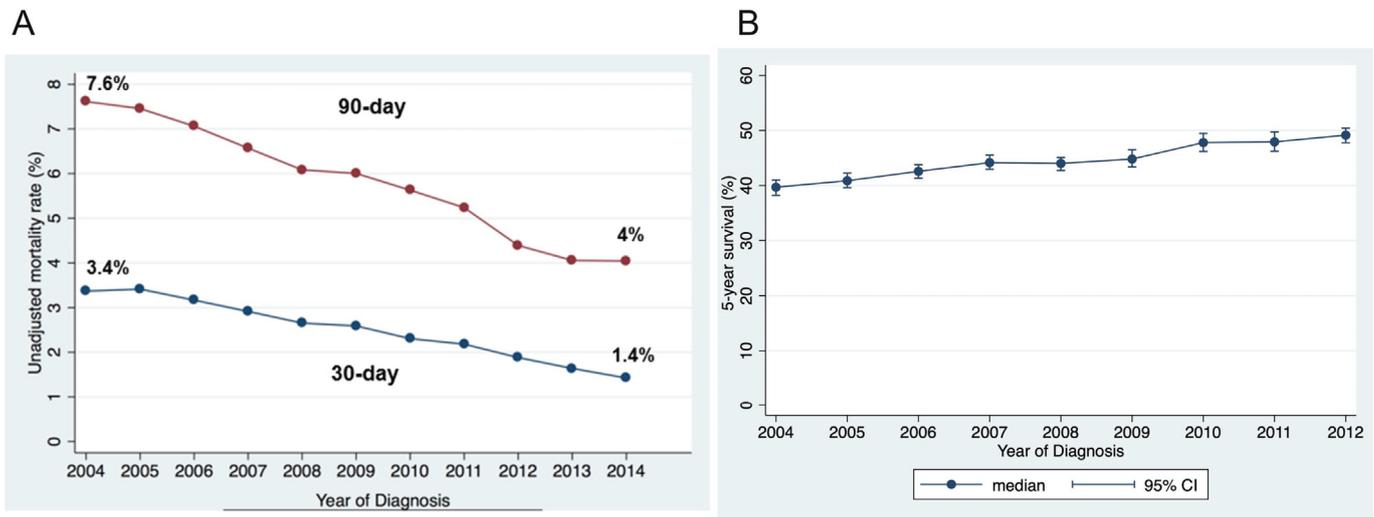
A

B

Fig. 4. (A) 30-day and 90-day mortality trend from 2004 to 2014. (B) Five-year survival between 2004 and 2012. (5-year survival data was not yet available for 2013–2015).

IIIC and IV ovarian carcinoma [27]. Although our study shows improved mortality and survival trends during the same timeframe as increasing use of NACT, we are not suggesting routine use of NACT. Instead, we advocate an individualized approach by selecting the treatment modality most beneficial for the patient based on their perioperative risk factors and extent of disease.

Strengths of this study include the ability to evaluate the trend of surgical complexity in relation to the increasing utilization of neoadjuvant chemotherapy across multiple hospitals with varying patient volumes. Information bias is minimized as the database requires certified tumor registrars enter information resulting in reliable data. Lastly, the database makes short-term outcomes data (30- and 90- day mortality, readmission) available at a nationwide level.

Our study has several limitations. First, the database only includes treatment that was used in the first six months after diagnosis. Therefore this limits our assessment of patients who may have received care outside of this time-frame. There is a possibility of confounding given the inability to determine residual disease status or details of adjuvant therapy received. Selection bias is also a possibility as different surgeons and centers likely vary in regards to aggressiveness of cytoreductive surgery and the practice of neoadjuvant chemotherapy administration. Furthermore, the complexity of the surgery included in our analysis is limited to the most definitive intervention. For example, if a unilateral oophorectomy is performed prior to a debulking surgery, only the debulking surgery is reported in the database. Lastly, it is possible that the definition, and therefore complexity, of the procedures have changed over time. For example, earlier data abstraction could have been less rigorous, and procedures considered low complexity at the beginning of the study periods could be more recently considered moderate complexity. However, according to the National Cancer Database, the data abstraction has been consistent over the study period.

During the study period, the utilization of NACT has increased. During the same time, 30- and 90-day mortality have decreased, and overall five-year survival has increased. Moreover, the overall trend of complexity of ovarian cancer surgery has increased in both PDS and NACT cohorts. These results should be reassuring for fellowship training programs and applicants for gynecologic oncology fellowship amidst concerns that increasing NACT proportion would negatively affect the exposure to high complexity surgery case-volumes.

Author contribution statement

Shitanshu Uppal designed and directed the project. Melissa Brackmann assisted with the computational framework and analysed the data along with Shitanshu Uppal. Whitney Horner took the lead in writing the manuscript with assistance from Katherine Peng, Versha Pleasant, Melissa Brackmann, Jasmine Ebott, and Rachel Gutfreund. Kevin Reynolds and Karen McLean provided critical feedback and helped shape the research, analysis and manuscript.

Declaration of Competing Interest

The authors whose names are listed immediately below certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

The following is the supplementary data related to this article.Supplementary Fig. 1. Cohort development.Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2019.05.023.

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