Published in final edited form as:

Gynecol Oncol. 2017 June ; 145(3): 500–507. doi:10.1016/j.ygyno.2017.03.014.

Variation in Neoadjuvant Chemotherapy Utilization for Epithelial Ovarian Cancer at High Volume Hospitals in the United States and Associated Survival

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Abstract

Objective—To estimate variation in the use of neoadjuvant chemotherapy by high volume hospitals and to determine the association between hospital utilization of neoadjuvant chemotherapy and survival.

Methods—We identified incident cases of stage IIIC or IV epithelial ovarian cancer in the National Cancer Database from 2006–2012. Inclusion criteria were treatment at a high volume hospital (>20 cases/yr) and treatment with both chemotherapy and surgery. A logistic regression

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ADDITIONAL DISCLOSURE STATEMENT: The data used in the study are derived from a deidentified National Cancer Database file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology used, or the conclusions drawn from these data by the investigators.

CONFLICT OF INTEREST STATEMENT: We have no conflicts of interest to declare.

model was used to predict receipt of neoadjuvant chemotherapy based on case-mix predictors (age, comorbidities, stage etc). Hospitals were categorized by the observed-to-expected ratio for neoadjuvant chemotherapy use as low, average, or high utilization hospitals. Survival analysis was performed.

Results—We identified 11,574 patients treated at 55 high volume hospitals. Neoadjuvant chemotherapy was used for 21.6% (n=2494) of patients and use varied widely by hospital, from 5%–55%. High utilization hospitals (n=1910, 10 hospitals) had a median neoadjuvant chemotherapy rate of 39% (range 23–55%), while low utilization hospitals (n=2671, 14 hospitals) had a median rate of 10% (range 5–17%). For all ovarian cancer patients adjusting for clinical and socio-demographic factors, treatment at a hospital with average or high neoadjuvant chemotherapy utilization was associated with a decreased rate of death compared to treatment at a low utilization hospital (HR 0.90 95%CI 0.83–0.97 and HR 0.85 95%CI 0.75–0.95).

Conclusions—Wide variation exists in the utilization of neoadjuvant chemotherapy to treat stage IIIC and IV epithelial ovarian cancer even among high volume hospitals. Patients treated at hospitals with low rates of neoadjuvant chemotherapy utilization experience decreased survival.

INTRODUCTION

Primary debulking surgery followed by adjuvant platinum-based chemotherapy has long been the standard of care for ovarian cancer. Neoadjuvant chemotherapy followed by interval debulking surgery has recently emerged as an alternative strategy. Two large randomized trials found non-inferior survival for neoadjuvant chemotherapy compared with upfront cytoreductive surgery (1, 2). However, both of these trials were conducted in Europe and many have argued that the results may not be generalizable to the United States given the trials' low rate of optimal cytoreductive surgery and the low relative overall survival (3).

Rather than formulaically using neoadjuvant chemotherapy or primary debulking surgery for all newly diagnosed ovarian cancer patients, recent recommendations suggest tailoring initial therapy to the patient (4). Patients who undergo primary cytoreductive surgery to no gross residual disease have the best outcomes (5, 6). However, neoadjuvant chemotherapy can be used for patients who are older, have comorbid conditions, or a high disease burden in which an optimal resection is unlikely (4, 7). In these patients, the harms of upfront radical surgery may outweigh the benefits and neoadjuvant chemotherapy can be used to decrease surgical morbidity and rates of suboptimal primary debulking surgery. However, the criteria used to triage patients to either neoadjuvant chemotherapy or primary debulking surgery are subjective. A patient who may be perceived as too poor a surgical candidate or as having too high a disease burden at one hospital or by one provider may be considered a candidate for primary debulking surgery at another.

Ovarian cancer patients treated at high volume hospitals experience both increased rates of optimal cytoreductive surgery and improved survival (8–10). The extent to which high volume hospitals in the United States have adopted neoadjuvant chemotherapy and the variation by institution is unknown. However, single institution series suggest wide variation in practice patterns (11–13). This variation in the use of neoadjuvant chemotherapy by

institution provides a natural experiment to examine if a practice pattern of liberal use or restrictive use of neoadjuvant chemotherapy is associated with differences in survival.

In this study, our objectives were (1) to characterize the variation in utilization of neoadjuvant chemotherapy at high volume hospitals in the United States and (2) to determine the association between being treated at a hospital with a low, average, or high utilization of neoadjuvant chemotherapy and overall survival.

METHODS

Data Source

The National Cancer Database (NCDB) was used to identify incident cases of epithelial ovarian cancer. The NCDB is a hospital-based cancer registry and participating hospitals are those with Commission on Cancer (COC) accreditation. The NCDB captures approximately 70% of incident invasive cancer cases diagnosed in the United States each year (14). As this data source contains de-identified patient data, the Institutional Review Board at the University of North Carolina at Chapel Hill reviewed this study and declared it exempt from formal review.

Study Cohort

Our study cohort included all patients with a new diagnosis of stage IIIC or stage IV invasive epithelial ovarian cancer diagnosed in 2006–2012 (Figure 1). Only stage IIIC and IV patients were included as this is the population eligible for either neoadjuvant chemotherapy or primary debulking surgery and a survival benefit of resection to no gross residual disease has been demonstrated for both populations (6, 15, 16). Further inclusion criteria were treatment with both chemotherapy and surgery and treatment at a high volume hospital. Patients who received surgery or chemotherapy alone or had unknown receipt of chemotherapy or surgery were excluded. Following prior studies, high volume hospitals were defined as treating greater than 20 stage IIIC/IV patients per year averaged over the study period with both chemotherapy and surgery (17, 18).

Predictive Model Creation

Our primary outcome for the predictive model was receipt of neoadjuvant chemotherapy defined using the systemic therapy surgery sequence recorded in the NCDB. Patients receiving neoadjuvant chemotherapy followed by cytoreductive surgery were compared to those receiving upfront cytoreductive surgery followed by adjuvant chemotherapy. Examined predictors included the independent variables age, race, ethnicity, insurance, Charlson comorbidity index score, stage, histology, grade, year of diagnosis and hospital volume. Charlson comorbidity index score was reported using the Deyo classification and is categorized as 0, 1, and 2 in the NCDB. Hospital volume was further categorized in tertiles based on the annual average of stage IIIC/IV epithelial ovarian cancer cases treated at these already high volume hospitals over the study period. Data regarding residual disease at the conclusion of surgery or disease burden prior to surgery are not available in the NCDB.

A multivariable logistic regression model was estimated using the above listed independent variables in a random sample of 25% of the cohort (the test population). The calibration of the model was tested in the remaining 75% (the validation population) using the Hosmer-Lemeshow goodness-of-fit test, and the discrimination was tested using the area under the receiver operating characteristic curve (AUROC) (19–21).

Case-Mix Adjustment

Given that hospitals care for populations that differ from one another with respect to age, stage of disease and other factors that influence the decision to proceed with neoadjuvant chemotherapy, we calculated the case-mix adjusted rate of neoadjuvant chemotherapy utilization for each hospital to adjust for these differences. The above predictive logistic regression model was used to calculate the probability of receipt of neoadjuvant chemotherapy for each patient. The expected rate of neoadjuvant chemotherapy use for each hospital was calculated by averaging the predicted probability for each individual patient within that hospital. Each hospital's observed rate to expected rate ratio with a corresponding 95% confidence interval was calculated to determine if each hospital's observed neoadjuvant chemotherapy rate was above, below or within its expected rate (22). Hospitals were categorized as high-, average-, or low-utilization hospitals depending on whether their observed neoadjuvant chemotherapy rate was significantly above, within or below the 95% confidence interval around the predicted rate respectively. Individuals were then classified as receiving care at a high, average, or low neoadjuvant chemotherapy utilization hospital.

Survival Analysis

For our survival analysis, our primary outcome was overall survival defined as the time from diagnosis to death or last contact with the patient. Patients alive at last contact were censored. The primary independent variable for the survival analysis was receipt of care at a case-mix adjusted low-, average- or highneoadjuvant utilization hospital. Covariates examined as additional independent variables included age, race, ethnicity, insurance, Charlson comorbidity index score, stage, histology, year of diagnosis and hospital volume. The proportional hazards assumption was tested using Schoenfeld's residuals and log-log plots. Both confirmed the assumption was not violated. The log rank test was used to calculate the difference in median overall survival for the three groups. An adjusted Kaplan Meier plot was used to graphically represent overall survival. A multi-level mixed effects parametric survival regression was used to examine the association between case-mix adjusted neoadjuvant chemotherapy utilization and overall survival adjusting for the covariates noted previously. We used this multilevel model to account for the fact that patients were clustered within hospitals. A two-sided $p < 0.05$ was considered statistically significant. All analyses were complete using Stata version 14.0 (StataCorp LP, College Station, TX).

Sensitivity Analyses

As the use of upfront cytoreductive surgery is more controversial for stage IV patients, we repeated our analysis among only stage IIIC patients. We also repeated the survival analyses excluding the unknown grade patients and patients with epithelial histology not further

classified. We also entertained the possibility that neoadjuvant chemotherapy utilization rates could just be a marker for incorporating new treatments and thus be reflecting the overall quality of care delivered by the hospital. To address this possibility, we examined another marker of quality of care recorded in NCDB, 30-day hospital readmission, as a negative control to see if readmission rates differed between low, average and high utilization hospitals in the same pattern as survival.

Given that the use of neoadjuvant chemotherapy increased over time, we examined if low-, average- or high utilizers incorporated the use of neoadjuvant chemotherapy at different rates using generalized estimating equations (GEE) analysis. Additionally, we examined if certain hospitals changed their utilization category over the time period of the study. We did not have the statistical power to examine this question for each individual year and so divided the time period in half and repeated the case-mix adjustment as described above for each time period to re-categorize the hospitals. We then examined survival, again as described above, by the divided time period-defined utilization groups.

RESULTS

A total of 11,574 patients met inclusion criteria for the study (Figure 1). The majority of patients were treated with upfront cytoreductive surgery followed by adjuvant chemotherapy (78.4%, n=9080). The remainder were treated with neoadjuvant chemotherapy followed by cytoreductive surgery (21.6%, n=2494). There was an increase in the use of neoadjuvant chemotherapy over the study period, from 17.2% in 2006 to 30.1% in 2012. Patients who received neoadjuvant chemotherapy were also more likely to have stage IV disease, serous or unknown histology and higher grade tumors (Table 1). Patients treated at hospitals with higher median case volume were also more likely to have received neoadjuvant chemotherapy.

Our final predictive model for receipt of neoadjuvant chemotherapy contained all predictors listed in Table 1. The Hosmer Lemeshow calibration test failed to reject the null hypothesis that there was a significant difference between observed and predicted estimates ($p=0.45$) meaning that the observed and predicted estimates are similar and the model is predictive. The AUROC in the development cohort was 0.74 (95%CI 0.72–0.76) and the AUROC in the test cohort was 0.72 (95%CI 0.71–0.73) showing fair discrimination. This model was then used to case-mix adjust the neoadjuvant chemotherapy rates for each hospital.

Patients were treated at 55 high-volume (>20 cases/yr) hospitals. Of these 55 hospitals, 14 had lower than predicted neoadjuvant chemotherapy rates (low utilization), 10 had higher than expected neoadjuvant chemotherapy rates (high utilization) and 31 had neoadjuvant chemotherapy rates within the predicted range (average utilization) (Table 2). Median observed neoadjuvant chemotherapy rates were 39% for high utilization hospitals, 20% for average utilization hospitals and 10% for low utilization hospitals ($p<0.001$). Although the observed neoadjuvant chemotherapy rates differed between high, average and low utilization hospitals, median predicted neoadjuvant chemotherapy rates based on hospital case-mix were 22%, 21% and 22% ($p=0.87$) and did not differ, suggesting that differences in hospital

populations did not account for the difference in utilization of neoadjuvant chemotherapy between the groups.

When hospitals were categorized by case-mix adjusted neoadjuvant chemotherapy rates, there were significant differences in demographic, clinical and facility characteristics between the groups (Table 3). Patients treated at high utilization hospitals were less likely to have stage IV disease (26%) than those at average utilization hospitals (27%), but were more likely to have stage IV disease than those treated at low utilization hospitals (24%). Hospital case volume also differed. Average utilization hospitals were more likely to be in the highest volume tertile (57%) compared to low (30%) or high (28%) utilization hospitals. There were also small, but statistically different socio-demographic differences between high and low utilization hospitals. High utilization hospitals were more likely to have patients with private insurance (53%) compared to low utilization hospitals (49%) while low utilization hospitals were more likely to have patients with Medicare (42%) compared to high utilization hospitals (39%). Low utilization hospitals were also more likely to have patients of black race compared to high utilization hospitals (7.6% versus 4.8%). There was no significant difference in Charlson comorbidity index scores and age between low, average and high utilization hospitals.

Survival curves for the study cohort are shown in Figure 2. The median overall survival for patients treated at low neoadjuvant chemotherapy utilization hospitals was 42.5 months compared to 47.6 months at average utilization hospitals and 48.4 months at high utilization hospitals ($p < 0.001$). After adjustment for age, race, ethnicity, insurance, stage, histology, grade, Charlson comorbidity index score and hospital volume tertile, receipt of care at a hospital with an average or high neoadjuvant chemotherapy use rate was associated with a decreased rate of death compared to care at a low utilization hospitals (HR 0.90 95%CI 0.83–0.97 and HR 0.85 95%CI 0.75–0.95, respectively). There was no significant difference in overall survival rates between average and high utilization hospitals ($p = 0.29$).

Additionally, there were no significant changes in survival over time at low, average or high utilization hospitals (data not shown).

Sensitivity analysis

Given that neoadjuvant chemotherapy is more commonly used for stage IV disease, we performed an analysis of only patients with stage IIIC disease and found our results remained unchanged (Appendix Table A1). Additionally, among stage IIIC and IV patients, the survival difference between patients treated at high and low utilization hospitals also persisted when patients with unknown grade and unspecified epithelial histologies were excluded.

We also examined hospital readmission rates as a negative control to ensure that neoadjuvant chemotherapy utilization rates were not simply measuring the quality of care the hospital delivered more broadly. We found no difference between high utilization hospitals and low utilization hospitals with respect to 30-day unplanned readmission (7.1% versus 7.9% $p = 0.29$, aOR 0.88 95%CI 0.70–1.11).

Finally, we examined whether neoadjuvant chemotherapy use changed over time depending on utilization group and found no significant difference in the rate of incorporation of neoadjuvant chemotherapy ($p=0.71$, Supplementary Figure 1). We also examined if hospitals changed utilization categories over time by examining the time periods prior to and including 2009 and after 2009. We found that there was minimal re-categorization of hospitals and no hospitals changed categories from low utilizers to high utilizers or from high utilizers to low utilizers. In the survival analysis based on the new groupings we found that the association between decreased survival at low utilization hospitals compared with high utilization hospitals persisted (2009 HR 0.88 95%CI 0.80–0.96 and >2009 HR 0.83 95%CI 0.72–0.97).

DISCUSSION

Wide variation exists in the use of neoadjuvant chemotherapy to treat ovarian cancer among high volume hospitals in the United States. This wide variation suggests an opportunity to improve quality of care by improving our selection criteria for primary treatment with either neoadjuvant chemotherapy or primary debulking surgery. All hospitals we studied used both neoadjuvant chemotherapy and primary debulking surgery to care for newly diagnosed ovarian cancer, suggesting consensus across high volume hospitals in the United States that both forms of initial treatment have a role to play in the primary treatment of stage IIIC and IV ovarian cancer. However, we found differences in how the treatments were allocated. Patients cared for at hospitals that utilized lower than expected rates of neoadjuvant chemotherapy experienced decreased survival.

This study's methodology is different from previous studies, including one in the NCDB, which examined the patient level survival differences between neoadjuvant chemotherapy and primary debulking surgery (23, 24). Both studies found that primary debulking surgery leads to improved survival for patients with stage IIIC disease. Our study is novel in that we are not analyzing which treatment the patient received as our primary exposure, but instead are analyzing the practice pattern of the hospital in which they received care. This allows for minimization of the selection bias of the provider assigning the treatment to the individual patient and instead allows us to examine practice patterns more broadly to evaluate whether a more liberal or more restrictive use of neoadjuvant chemotherapy is associated with differences in survival.

We also found that among all high volume hospitals, utilization of neoadjuvant chemotherapy is increasing, from 17% in 2006 to 30% in 2012. Furthermore, within our already high volume hospital cohort, those hospitals with higher median case volume were more likely to use neoadjuvant chemotherapy than those with the lowest volume. This is in contrast to previous work which examined patients prior to 2005 and found higher volume hospitals were more likely to use primary debulking surgery compared to lower volume hospitals (17).

In this study, lower than expected neoadjuvant chemotherapy utilization was associated with a decreased median survival of approximately 6 months. For advanced stage ovarian cancer, which has a 5-year survival of 17–39%, a survival benefit of 6 months is tangible (25).

Rather than a new drug or procedure, our analysis suggests that the way physicians make decisions and assign primary treatment may affect survival. The decision to pursue upfront cytoreductive surgery in a poor surgical candidate or in a patient with unresectable disease plausibly impacts survival. Additionally, we restricted our analysis to high volume centers, as this is the setting in which the highest quality surgery is performed. The fact that even in this setting, we found low utilization of neoadjuvant chemotherapy is associated with decreased survival is thought-provoking. This inferior survival also persisted among only stage IIIC patients, a cohort in which the benefits of upfront cytoreductive surgery at a high volume center should be the highest.

The finding that patients treated at hospitals with high utilization of neoadjuvant chemotherapy have improved survival is particularly notable. This and prior studies have found that patients treated with neoadjuvant chemotherapy are more likely to be older, have higher disease burden, comorbidities or other factors that led their physician to select neoadjuvant chemotherapy as the primary treatment (12, 23). Although we were able to adjust for some of these, it is possible that residual unmeasured confounding remains, especially due to our inability to adjust for disease burden/location and functional status. Assuming this residual confounding is present, hospitals that care for a higher percentage of patients who received neoadjuvant chemotherapy are more likely to have a population with more aggressive cancer biology and poorer health than those with a lower percentage receiving neoadjuvant chemotherapy in ways we cannot measure and adjust for. This makes our results, that patients at these higher utilization hospitals actually lived longer, more remarkable.

We found decreased survival among patients treated at hospitals with low utilization of neoadjuvant chemotherapy. The underlying reasons for this relationship are unknown and cannot be answered in this observational study. However, optimal cytoreductive surgery either upfront or after neoadjuvant chemotherapy is a strong predictor of survival and a prospective study found 35% of presenting stage III and IV ovarian cancer patients have disease that is known to be unresectable prior to surgery (26, 27). Centers with very low utilization of neoadjuvant chemotherapy, such as those with a rate of 5%, are using primary debulking surgery for 95% of their stage IIIC and IV ovarian cancer patients. If the percentage of patients presenting with upfront unresectable disease is greater than 5%, this strategy could result in higher rates of suboptimal cytoreduction. Additionally, major postoperative complications that arise from primary radical debulking can cause chemotherapy delays that lead to decreased survival (28). Centers with low utilization of neoadjuvant chemotherapy may have lower survival due to increased suboptimal debulking rates and higher rates of surgical morbidity. Further research is needed to inform the decision that providers make to begin with surgery or neoadjuvant chemotherapy as our data suggests that improving our ability to triage patients appropriately has the potential to improve survival.

Our study is subject to several limitations including those inherent to its observational design, specifically, unmeasured confounding. It is possible that high and low utilization hospitals differ from one another in ways that we are unable to measure and that these differences account for the observed differences in survival. However, our sensitivity

analysis using readmission within 30 days of surgery as a negative control for quality of care did not support this explanation. Additionally, the NCDB lacks information about certain cancer-specific processes and outcomes that are known to impact ovarian cancer survival, such as residual disease, receipt of intraperitoneal chemotherapy, clinical trial enrollment, BRCA mutation status, performance status, and preoperative disease burden/location. Addition of these variables could further inform our results. Finally, the possibility of classification bias exists as we categorized hospitals into groups based on the 95% confidence interval around the observed to expected ratio. The number of patients treated at each hospital affects the width of the confidence interval and thus hospitals with lower volumes are more likely to be categorized as average utilizers.

In the United States, utilization of neoadjuvant chemotherapy to treat stage IIIC and IV epithelial ovarian cancer varies widely among high volume hospitals and over the study period, neoadjuvant chemotherapy utilization increased in each of the three hospital groups. Patients treated at hospitals that have lower than expected utilization of neoadjuvant chemotherapy experience decreased survival. The reasons underlying this decreased survival at the hospital-level are unknown. However, it is plausible that low utilization of neoadjuvant chemotherapy is associated with increased suboptimal primary cytoreductive surgery rates and increased major postoperative complications with adjuvant treatment delays, both leading to decreased survival. Improved standardization of indications for either primary surgery or neoadjuvant chemotherapy will help decrease variation, improve our ability to assign patients to the correct treatment, and potentially improve survival.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

FINANCIAL SUPPORT: Dr Barber is supported by NIH T32 HD040672-15.

Appendix

Appendix Table A1

Sensitivity Analyses

Neoadjuvant Chemotherapy Utilization ¹	Unadjusted Median Survival (months)	p-value ²	Unadjusted HR (95% CI)	Adjusted HR (95% CI) ³
Stage IIIC patients only (n= 8534)				
Low utilization	47.0	<0.001	1.0	1.0
Average utilization	52.4		0.86 (0.80–0.93)	0.89 (0.83–0.96)
High utilization	52.3		0.84 (0.76–0.93)	0.87 (0.79–0.96)
Epithelial histology NOS excluded (n=10697)				
Low utilization	42.7	<0.001	1.0	1.0
Average utilization	47.4		0.88 (0.83–0.94)	0.91 (0.86–0.97)

Neoadjuvant Chemotherapy Utilization ¹	Unadjusted Median Survival (months)	p-value ²	Unadjusted HR (95% CI)	Adjusted HR (95% CI) ³
High utilization	47.8		0.86 (0.78–0.93)	0.88 (0.81–0.96)
Unknown grade excluded (n=9932)				
Low utilization	43.8	<0.001	1.0	1.0
Average utilization	47.6		0.90 (0.84–0.96)	0.91 (0.85–0.98)
High utilization	49.4		0.84 (0.77–0.92)	0.86 (0.78–0.94)

¹ Low utilization hospitals are those with an observed neoadjuvant chemotherapy rate below predicted, average utilization are those with a rate within predicted and high utilization hospitals are those with a rate above predicted.

² Log-rank test.

³ Adjusted for age, race, ethnicity, insurance, stage, histology, grade, ethnicity, Charlson comorbidity index, year of diagnosis, and case volume.

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Highlights

Neoadjuvant chemotherapy use varied widely, from 5–55%, among high volume hospitals.

Hospital level patterns of neoadjuvant chemotherapy use are associated with survival.

Hospitals with low neoadjuvant chemotherapy utilization had decreased survival.

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Figure 1.
CONSORT Diagram

Figure 2.
Survival by Hospital Level Utilization of Neoadjuvant Chemotherapy

Table 1

Demographic, Clinical and Facility Characteristics Associated with Receipt of Neoadjuvant Chemotherapy

Characteristics	All Patients (n=11574)	Unadjusted % Receipt of Neoadjuvant Chemotherapy	Adjusted RRs (95% CI) ^{1,2} for Receipt of Neoadjuvant Chemotherapy
Age			
18–30	0.8 (92)	7.6 (7)	1.0
31–40	2.9 (334)	11.7 (39)	1.4 (0.6–3.3)
41–50	14.2 (1643)	15.2 (250)	1.8 (0.9–3.8)
51–60	28.0 (3245)	18.7 (606)	2.2 (1.0–4.6)
61–70	30.6 (3536)	24.4 (861)	2.7 (1.3–5.6)
71–80	19.0 (2195)	26.8 (588)	2.9 (1.4–6.3)
81–90	4.6 (529)	27.0 (143)	2.9 (1.4–6.3)
Race			
White	89.6 (10365)	21.3 (2203)	1.0
Black	6.2 (722)	24.9 (180)	1.1 (0.9–1.3)
Asian	2.6 (302)	22.2 (67)	1.1 (0.9–1.4)
Other	1.6 (185)	23.8 (44)	1.1 (0.8–1.5)
Hispanic			
Non-Hispanic	92.1 (10659)	21.6 (2297)	1.0
Hispanic	3.5 (399)	24.6 (98)	1.1 (0.9–1.4)
Unknown	4.5 (516)	19.2 (99)	1.0 (0.8–1.2)
Insurance			
Uninsured	3.0 (343)	20.7 (71)	1.0
Private insurance	50.2 (5815)	17.6 (1025)	0.9 (0.7–1.1)
Medicaid	5.2 (596)	25.8 (154)	1.2 (0.9–1.6)
Medicare/other gov	39.1 (4521)	25.2 (1138)	0.9 (0.7–1.2)
Unknown	2.6 (299)	35.5 (106)	1.5 (1.1–2.0)
CCI			
0	82.2 (9519)	21.0 (2000)	1.0
1	14.6 (1684)	23.0 (388)	1.0 (0.9–1.2)
2	3.2 (371)	28.6 (106)	1.2 (1.0–1.4)
Stage			
IIIC	73.7 (8534)	16.6 (1420)	1.0
IV	26.3 (3040)	35.3 (1074)	1.9 (1.8–2.1)
Histology			
Serous	77.4 (8961)	21.7 (1944)	1.0
Clear cell	3.2 (371)	10.8 (40)	0.5 (0.4–0.7)
Mixed adenocarcinoma	6.2 (720)	12.5 (90)	0.6 (0.4–0.7)
Endometrioid	4.0 (466)	8.4 (39)	0.5 (0.4–0.7)

Characteristics	All Patients (n=11574)	Unadjusted % Receipt of Neoadjuvant Chemotherapy	Adjusted RRs (95% CI) ^{1,2} for Receipt of Neoadjuvant Chemotherapy
Mucinous	1.6 (179)	8.4 (15)	0.5 (0.3–0.8)
Epithelial, other	7.6 (877)	41.8 (366)	1.6 (1.4–1.8)
Grade			
1	2.9 (334)	8.7 (29)	1.0
2	8.6 (998)	10.8 (108)	1.2 (0.8–1.8)
3	74.3 (8600)	20.6 (1774)	1.7 (1.2–2.5)
Unknown	14.2 (1642)	35.5 (583)	2.7 (1.8–3.9)
Year of Diagnosis			
2006	14.6 (1684)	17.2 (289)	1.0
2007	14.5 (1679)	15.7 (263)	0.9 (0.8–1.1)
2008	14.2 (1642)	17.8 (293)	1.0 (0.8–1.2)
2009	14.2 (1647)	21.1 (347)	1.2 (1.0–1.4)
2010	13.7 (1580)	23.9 (377)	1.3 (1.1–1.5)
2011	14.9 (1729)	25.4 (439)	1.4 (1.2–1.7)
2012	13.9 (1613)	30.1 (486)	1.7 (1.4–1.9)
Case Volume			
Low (20–23 cases/yr)	23.3 (2701)	16.9 (455)	1.0
Medium (23–30 cases/yr)	30.9 (3573)	23.9 (852)	1.4 (1.3–1.6)
High (30–87 cases/yr)	45.8 (5300)	22.4 (1187)	1.3 (1.1–1.4)

CCI – Charlson comorbidity index; RR – relative risk

Data presented as % (n) unless otherwise specified.

¹ Modified Poisson regression.

² Adjusted for age, race, ethnicity, insurance, Charlson comorbidity index score, stage, histology, grade, year of diagnosis, and case volume.

Table 2

Observed and Predicted Neoadjuvant Chemotherapy Rates at Low, Average, and High Utilization Hospitals

	Low utilization ¹	Average utilization ¹	High utilization ¹	p-value²
Total patients (% , n)	23.1 (2671)	60.4 (6993)	16.5 (1910)	–
Hospitals (n)	14	31	10	–
Patients per hospital (median, range)	176 (141–266)	198 (141–608)	189 (143–308)	0.55
Observed Neoadjuvant Chemotherapy Hospital Rate (Median %, range)	10 (5–17)	20 (8–28)	39 (23–55)	<0.001
Predicted Neoadjuvant Chemotherapy Hospital Rate (Median %, range)	22 (15–28)	21 (11–37)	22 (15–28)	0.87

¹Low utilization hospitals are those with an observed neoadjuvant chemotherapy rate below predicted, average utilization are those with a rate within predicted and high utilization hospitals are those with a rate above predicted.

²Kruskal-Wallis Test

Table 3

Demographic, Clinical and Facility Characteristics Associated with Treatment at Low, Average, and High Neoadjuvant Chemotherapy Utilization Hospitals

Characteristics	Low Utilization ^I	Average Utilization ^I	High Utilization ^I	p value
Age				0.31
18–30	0.7 (19)	0.8 (58)	0.8 (15)	
31–40	2.7 (71)	2.9 (201)	3.3 (62)	
41–50	13.4 (357)	14.0 (979)	16.1 (307)	
51–60	28.6 (764)	28.0 (1961)	27.2 (520)	
61–70	30.0 (802)	31.1 (2174)	29.3 (560)	
71–80	19.5 (521)	18.8 (1317)	18.7 (357)	
81–90	5.1 (137)	4.3 (303)	4.7 (89)	
Race				<0.001
White	88.8 (2372)	90.0 (6290)	89.2 (1703)	
Black	7.6 (202)	6.1 (428)	4.8 (92)	
Asian	2.4 (65)	2.7 (185)	2.7 (52)	
Other	1.2 (32)	1.3 (90)	3.3 (63)	
Hispanic				<0.001
Non-Hispanic	92.2 (2462)	92.6 (6478)	90.0 (1719)	
Hispanic	2.3 (61)	3.7 (260)	4.1 (78)	
Unknown	5.5 (148)	3.7 (255)	5.9 (113)	
Insurance				<0.001
Uninsured	3.1 (83)	3.0 (206)	2.8 (54)	
Private insurance	48.8 (1302)	50.0 (3499)	53.1 (1014)	
Medicaid	5.6 (150)	4.8 (337)	5.7 (109)	
Medicare/other gov	41.8 (1116)	38.4 (2682)	37.9 (723)	
Unknown	0.8 (20)	3.9 (269)	0.5 (10)	
CCI				0.80
0	82.6 (2206)	81.9 (5730)	82.9 (1583)	
1	14.2 (378)	14.8 (1034)	14.2 (272)	
2 +	3.3 (87)	3.3 (229)	2.9 (55)	
Stage				0.03
IIIC	75.6 (2020)	72.9 (5101)	74.0 (1413)	
IV	24.4 (651)	27.1 (1892)	26.0 (497)	
Histology				<0.001
Serous	77.1 (2058)	78.2 (5465)	75.3 (1438)	
Clear cell	3.3 (87)	3.2 (223)	3.2 (61)	
Mixed adenocarcinoma	5.2 (138)	7.0 (489)	4.9 (93)	
Endometrioid	4.5 (119)	4.0 (278)	3.6 (69)	

Characteristics	Low Utilization ^I	Average Utilization ^I	High Utilization ^I	p value
Mucinous	2.3 (62)	1.3 (92)	1.3 (25)	
Epithelial, NOS	7.8 (207)	6.4 (446)	11.7 (224)	
Grade				<0.001
1	2.7 (71)	2.9 (202)	3.2 (61)	
2	9.4 (250)	8.4 (586)	8.5 (162)	
3	67.9 (1814)	77.6 (5425)	71.3 (1361)	
Unknown	20.1 (536)	11.2 (780)	17.1 (326)	
Year of Diagnosis				0.09
2006	14.6 (389)	14.5 (1017)	14.6 (278)	
2007	14.2 (378)	14.7 (1028)	14.3 (273)	
2008	13.7 (365)	14.3 (1002)	14.4 (275)	
2009	15.0 (400)	13.7 (955)	15.3 (292)	
2010	14.9 (398)	13.2 (922)	13.6 (260)	
2011	15.5 (414)	15.0 (1049)	13.9 (266)	
2012	12.2 (327)	14.6 (1020)	13.9 (266)	
Hospital Volume				<0.001
Low (20–23 cases/yr)	28.0 (747)	19.4 (1353)	31.5 (601)	
Medium (23–30 cases/yr)	42.5 (1134)	23.7 (1657)	40.9 (782)	
High (30–87 cases/yr)	29.6 (790)	57.0 (3983)	27.6 (527)	

^ILow utilization hospitals are those with an observed neoadjuvant chemotherapy rate below predicted, average utilization are those with a rate within predicted and high utilization hospitals are those with a rate above predicted.

Table 4**Hospital Case-mix Adjusted Neoadjuvant Chemotherapy Utilization and Survival**

Neoadjuvant Chemotherapy Utilization ¹	Unadjusted Median Survival (months)	p-value ²	Unadjusted HR (95% CI)	Adjusted HR (95% CI) ³
Low utilization	42.6	<0.001	1.0	1.0
Average utilization	46.7		0.88 (0.82–0.96)	0.90 (0.83–0.97)
High utilization	48.4		0.84 (0.74–0.94)	0.85 (0.75–0.95)

¹ Low utilization hospitals are those with an observed neoadjuvant chemotherapy rate below predicted, average utilization are those with a rate within predicted and high utilization hospitals are those with a rate above predicted.

² Log-rank test.

³ Adjusted for age, race, ethnicity, insurance, stage, histology, grade, ethnicity, Charlson comorbidity index, year of diagnosis, and case volume.