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Socioeconomic factors may contribute to neoadjuvant chemotherapy use in metastatic epithelial ovarian carcinoma

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ABSTRACT

Objective. To identify patient characteristics which predict receipt of neoadjuvant chemotherapy (NCT) versus standard therapy (ST) in metastatic ovarian cancer.

Methods. A retrospective matched case control study was conducted of 52 women treated with NCT compared to 104 women who received standard treatment from 1996 to 2007. The *t* test was used for comparison of means between the groups, and the χ^2 test was used for categorical data. Multivariable analysis was performed with logistic regression models and only two-tailed analyses with a *P* value <0.05 were considered statistically significant.

Results. Age, employment and marital status, and insurance alone did not affect treatment allocation (*P* = NS). However, non-Hispanic White (NHW) patients were more as likely to receive ST ($P<0.05$). When insurance was stratified by ethnicity, NHW patients were twice as likely to have private insurance (OR = 2.29, CI = 1.16–4.53). Furthermore, medically compromised (MC) patients who were NHW were almost three times more likely to receive ST (OR = 2.72, CI = 1.02–5.00). In multivariate analysis, only MC and publically funded women were more likely to receive NCT (OR 3.83 CI = 1.35–11.11); $P=0.01$). During surgery, patients receiving NCT were found to have smaller tumors and less ascites, and were more likely to be optimally debulked with lower estimated blood loss and shorter hospital stays. The median survival for ST was 55.8 months versus 26 months for NCT ($P<0.001$).

Conclusions. Non-clinical factors such as publically funded status and non-Hispanic White race may influence the allocation of NCT for women with metastatic ovarian cancer.

Introduction

Ovarian cancer is the 5th leading cause of cancer death in women in the United States and there will be approximately 21,650 new cases and 15,520 deaths in 2009 [21]. The challenge of treating ovarian cancer is that 75% of women are diagnosed at an advanced stage [1]. Further, most of these women are postmenopausal and often have numerous associated co-morbidities [2]. Surgery can be complicated for this group and 70% are optimally debulked [3]. While the standard treatment of ovarian cancer is maximum cytoreductive surgery followed by adjuvant platinum-based chemotherapy, neoadjuvant chemotherapy (NCT) is a second option for some patients. However because NCT may negatively impact survival, it is still considered a less optimal treatment option. The rationale behind the use of NCT is that patients will tolerate chemotherapy better if given prior to aggressive surgery and that pre-operative chemotherapy will reduce tumor volume thus facilitating optimal debulking and resulting shorter operative times and hospital stays [4–6]. This may be especially useful in patients with multiple comorbidities that preclude immediate aggressive cytoreductive surgery.

Certain clinical factors have been traditionally associated with the neoadjuvant approach: medical infirmity, extra-abdominal metastasis and the high likelihood of unresectable intra-abdominal disease. One may also hypothesize that additional patient characteristics may be associated with receipt of NCT by looking at the overall rates of advanced ovarian cancer in the population. While the incidence of ovarian cancer in Caucasian women is decreasing in the United States, the incidence in non-Caucasian women has remained stable over the last decade [7]. Because mortality rate has remained unchanged across all ethnicities throughout this time period, the representation of non-White ethnicities in the ovarian cancer population is likely on the rise [7]. Recent studies have also documented a larger proportion of non-White women presenting with advanced stage ovarian cancer in 75% of the total U.S. cancer population [8]. Furthermore, race, income and age have been associated with substandard treatment choices for ovarian cancer [9]. Thus, in the United States, ethnicity may be a proxy for certain patient characteristics that present obstacles in the standard treatment of advanced ovarian cancer [9]. Therefore, the primary objective of this study was to document

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certain pre-treatment characteristics that might predispose a woman to receipt of NCT.

Material and methods

IRB approval was obtained for this retrospective case control study of all ovarian cancer patients seen at UCI Medical Center from 1996 to 2007. Using the UCI Society for Gynecologic Oncology (SGO) database and billing databases, the women treated with NCT during this time period were identified. The SGO database and the UCI tumor registry were then linked to locate all patients with stage III or IV ovarian cancer diagnosed during that time period. Patients were excluded if they had not undergone surgical exploration and/or if they had non-epithelial ovarian cancer.

For each patient the following variables were examined: clinical presentation, comorbidities, socioeconomic status, surgical outcome, number of chemotherapy cycles and survival data. The Charlson Comorbidity Index (CCI) was calculated for each patient. This index has been widely used and validated in the oncology literature and has demonstrated utility for most major cancers [10]. The CCI is a composite score based on the patient's age in decades and associated comorbidities. Table 1 represents the scoring system for the CCI. For example, one point is assigned for myocardial infarction or congestive heart failure, two for diabetes with end-organ damage, four for moderate-severe liver disease and six points for metastatic solid tumor. All of the patients included in this study had a minimum CCI of two based on their cancer diagnosis. For these analyses, a score of greater than or equal to four was considered to be medically compromised.

These data were analyzed using the 2008 Statistical Analysis Software Version 9.2. Only two tailed analyses with a *P*-value less than 0.05 were considered statistically significant. The *t*-test and the chi square test were used for univariate analyses. Kaplan–Meier survival analysis was used to compare outcomes between standard treatment and NCT using the log-rank test. Multivariable analysis was performed using logistic regression models.

Results

From 1996 to 2007, 1127 patients were treated for ovarian cancer within the UCI system. Patients were excluded if treated at facilities other than UCI Medical Center. When excluding stage I and II patients as well as non-epithelial histologies, 63 patients treated with NCT were identified. Eleven patients who had received NCT were excluded because they had not undergone surgery and/or had non-epithelial histologies. Therefore, data were collected on a total of 156 patients. 104 patients who had received standard treatment were matched two to one with 52 patients who received NCT based on date of initial treatment.

Table 1
Calculation of the Charlson Comorbidity Index (CCI) [6].

ASSIGN POINTS BASED ON COMORBIDITIES BELOW			
1 point	2 points	3 points	6 points
Myocardial infarction	Hemiplegia	Liver disease. moderate or severe	Metastatic solid malignancy
Congestive heart failure	Renal disease moderate or severe		AIDS
Peripheral vascular disease	Diabetes with end organ damage		
Cerebrovascular disease	Any malignancy		
Dementia	Leukemia		
Chronic pulmonary disease	Malignant lymphoma		
Connective tissue disease			
Ulcer disease			
Liver disease mild			
Diabetes			

CCI = Sum of points tallied above + 1 point for each decade above 50 years.

The demographic data is presented in Table 2. The mean age of the NCT group was 64 years (SD 12.7) compared to 60 (SD 12.4) in the standard group (P = NS). Employment status, marital status and insurance alone did not affect treatment allocation (P = NS). In univariate analysis, the only significant difference between the two groups was in ethnicity. Of note, initially the analysis was divided by into Non-Hispanic White, Hispanic White and Asian but similar trends were seen in both Non-Hispanic White and Asian groups so they were combined for the analysis. Of note, there were no African-American women in this patient population. In this analysis, Non-Hispanic White women were twice as likely as Hispanic White patients to receive standard treatment. When insurance was stratified by ethnicity, Non-Hispanic White patients were twice as likely to have private insurance, when compared to Hispanic White patients (OR 2.29; CI = 1.16–4.53).

Table 2 also describes the clinical characteristics at time of initial presentation between the two groups. In examining the clinical characteristics at presentation between the two groups the only significant difference that patients who received NCT had larger volumes of ascites assessed by imaging, however all other measured clinical characteristics–Ca-125, size of largest mass on imaging, albumin and BMI–were not statistically significant. However, in patients with a Charlson Comorbidity Index score greater than or equal to four, or medically compromised patients, they were more than three times as likely to receive NCT (OR 3.66 CI = 1.18–11.11; $P = 0.02$). The mean CCI for White and non-Caucasian women was 6.9 and 6.8, respectively (P = NS). Ethnicity did not affect treatment allocation if the CCI was less than 4 (OR 0.41, CI = 0.09–1.93), yet in contrast, in medically compromised patients, non-Whites were almost three times more likely to receive NCT than Whites (OR 2.72, CI = 1.02–5.00).

Multivariable analyses to determine the factors that predicted treatment with NCT are presented in Table 3. Variables that were statistically significant in univariate analysis were included in the logistic regression modeling. The interaction between ethnicity and CCI and ethnicity and insurance was tested as to evaluate for the presence of multi-colinearity and thus this interaction was included in the model. Medically compromised women and those with public insurance were more than three times more likely to receive NCT (OR 3.66, CI = 1.18–11.11; OR 3.83 CI = 1.35–11.11, respectively), however, the volume of ascites and ethnicity were no longer significant predictors of NCT.

Preoperative imaging data was not available and consistent for all of the included patients. Furthermore the imaging studies were frequently from multiple institutions. However, there were only 3 patients in the NCT and 7 in the standard group for who we did not have imaging data. In the remaining patients, we did note that the 2 groups were similar in terms of pleural effusions (OR 2.32 CI = 0.98–5.46; P = NS), lymphadenopathy (OR 2.6 CI = 0.74–8.83; P = NS), and omental caking (OR 1.23 CI = 0.56–2.70; P = NS). However, the NCT group did have more liver metastases on imaging reports (OR 7.00 CI = 1.80–27.17; $P<0.05$).

Clinical and surgical outcomes were then examined (Table 2). During surgery, NCT patients had smaller tumors and less ascites. They were more likely to be optimally debulked and had lower EBL and shorter hospital stays. The mean number of cycles of NCT was 3.69, ranging from 2 to 9, and the total number of cycles of first line treatment was not statistically significant between the two groups. Of note, there were five patients in the NCT group who had received non-platinum-based chemotherapy, such as the one outlier who had received 9 cycles of alkeran prior to surgery. Similar Ca-125 responses to chemotherapy was seen between the two groups, with the mean

Table 2
Patient Characteristics.

	Neoadjuvant ($N=52$)	Standard ($N=104$)	P-value or OR (95% CI)
Mean age (years)	64 (SD 12.7)	60 (SD 12.3)	$P=0.08$
Ethnicity (% Caucasian)	27.3	72.7	2.17(1.10–4.35)
Employment (% employed)	27.9	31.4	1.18 (0.54–2.59)
Marital Status (% married)	29.6	32.4	1.14 (0.56–2.31)
Insurance (% private)***	59.3	53.8	1.25 (0.64–2.43)
CA 125* (U/ml)	3100 (SD 1473)	1109 (SD 162)	$P=0.19$
Size of adnexal mass* (cm)	7.8 (SD 0.82)	8.1 (SD 0.68)	$P=0.75$
Volume of ascites** (ml)	3000 (SD 2000)	1000 (SD 1000)	$P<0.01$
Albumin* (g/dl)	3.46 (SD 0.64)	3.27 (SD 0.65)	$P=0.19$
Body Mass Index*	26.5 (SD 5.9)	27.2 (SD 6.3)	$P=0.54$
Charlson Comorbidity Index—medically compromised (%)	85.2	64.8	OR 3.12 (CI = 1.34–7.39)
Size of largest mass (cm)	7.1 (SD 5.9)	10.7 (SD 6.4)	$P<0.01$
Volume of ascites (ml)	561 (SD 1333)	1786 (SD 2227)	$P<0.01$
Bowel resection (%)	14.6	20.9	OR 0.9 (CI = 0.80–1.7)
EBL (ml)	365 (SD 257)	656 (SD 528)	$P<0.01$
Optimal cytoreduction (%)	86.0	67.3	OR 3.03 (CI = 1.22–7.14)
Length of stay (days)	5 (SD 2)	8 (SD 10)	$P<0.01$

* Mean values listed.
** Volume of ascites is based on imaging report estimations.
*** Private = health maintenance organization or preferred provider organization.

Ca-125 30.8 for NCT after chemotherapy versus 38.9 after adjuvant chemotherapy for standard treatment (P = NS).

Although not the primary objective of this study, outcomes were also examined. Despite improved surgical outcomes, similar chemotherapy agents and response to treatment, the median survival between NCT and standard treatment was 55.8 months for standard treatment to 26 months for NCT (Fig. 1). This survival disadvantage was present for all ethnic groups. For non-Hispanic White patients the median survival was 63.8 months for standard care to 22.1 months for NCT. In the Hispanic group there was a decrease in median survival with the receipt of NCT, from 56.6 months in standard care to 37.6 months in NCT. The survival difference was present even with stratification by insurance status. By multivariable analyses inclusive of insurance, ethnicity, and comorbidities, only the treatment type, NCT, was prognostic for poor survival outcome in these groups of patients.

Discussion

The standard management of advanced stage ovarian cancer is surgical debulking followed by platinum-based chemotherapy. The value of optimal cytoreduction may stem from the better response rates of smaller tumors to chemotherapy and the potential removal of chemoresistant cell populations in large tumors [11]. Unfortunately initial surgery is not feasible in some women who present with comorbidities and/or widely metastatic or bulky disease. In this study, pretreatment patient characteristics, such as public insurance status, CCI greater than 4 and Hispanic ethnicity, directed treatment allocation in preference to NCT.

These data substantially contribute to the growing body of literature on disparities and cancer care. Societal factors may unfortunately influence how advanced ovarian cancer patients present to gynecologic oncologists. These pre-treatment factors then affect treatment allocation. It has been documented that out of 12 cancer sites, ovary has the largest amount of uninsured patients [8]. Several studies have demonstrated that African-Americans and Hispanics are more likely to present in advanced stages in various cancers including ovarian. However, not only does race have an effect on stage at presentation, it can also impact treatment allocation. There is a rapidly growing body of literature on the effect of socioeconomic status and/or ethnicity on treatment allocation. For example, in a recent study on breast cancer, the authors demonstrated that while sentinel lymph node biopsy has been the standard of care for early breast cancer, non-Whites and publically funded patients were less likely to receive this type of treatment [12]. This needs to be explored in the setting of ovarian cancer as it might be related to allocation of NCT.

The unique findings of this study are that non-White ethnicity and public funding are associated with the receipt of neoadjuvant chemotherapy. One may hypothesize that this is due to lack of immediate access to a gynecologic oncologist along with delays in evaluation imposed by language limitations and/or insurance authorizations. Although this has yet to be proven, one doubts that the treatment allocation is based on a bias in physicians against the

Table 3
Multivariable analysis for predictors of treatment allocation.

Variable	OR (95% CI)	P
Charlson Comorbidity Index		
Healthy	1.0	0.02
Medically compromised	3.66 (1.18–11.11)	
Insurance		
Private insurance	1.0	0.01
Public insurance (Medical, Medicare, None)	3.83 (1.35–11.11)	
Ethnicity		
White	1.0	0.11
Non-White	2.29 (0.83–6.27)	
Volume of ascites (Dx)		
≤1000 ml	1.0	0.58
>1000 ml	1.48 (0.41–5.01)	

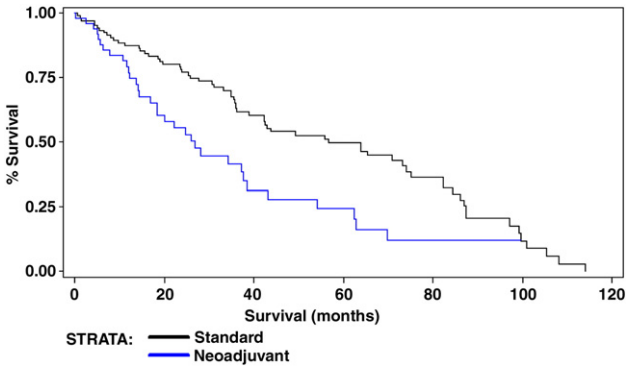

Fig. 1. Overall survival by treatment type (26 months for NCT versus 55.8 months for Standard).

publically funded or non-Whites. In fact, in this study, there did not appear to be physician bias in terms of use of NCT, for example, when all 6 gynecologic oncology attendings at this institution are compared, the frequency of NCT use was not significantly different between providers ($P=0.56$). However, an important non-clinical factor not considered in this retrospective study is geographical location. Based on our experience and knowledge of this practice, it is likely that some patients given NCT were being referred in from outlying areas where there is lack of direct access to a gynecologic oncologist. These cases often present with metastatic disease and are referred to a medical oncologist who may begin chemotherapy while the insurance authorizations are being processed and the referral to gynecologic oncology is being made.

Although not the initial intent of this study, the survival outcomes documented must be discussed. Published literature has shown that, with the use of NCT, a reduction of tumor volume and decreased surgical morbidity can be achieved [13]. Of note, whether or not patients given chemotherapy alone were included in the analysis, the survival disadvantage with NCT persisted. Furthermore, despite improved rates of optimal debulking after NCT, there was a survival disadvantage with NCT. This has also been documented in other studies [14,15]. In a review by Bristow in 2007 [15], the author documented 10 studies which showed worse survival with NCT, 9 with equal survival and 7 with improved survival. The authors concluded that initial maximal cytoreduction is the standard of care, and that criteria for giving NCT need to be better defined. In 2007, a Cochrane analysis was performed and forty-eight articles were reviewed however only one trial met the Cochrane inclusion criteria [1]. This study included embolization of the iliac and reported an unchanged overall survival and better surgical outcomes with NCT [16].

In this study we identified that patients treated with NCT have an inferior survival when compared to those treated by standard therapy, this finding is now complicated by this recently reported prospective trial. In an EORTC (European Organization for Research and Treatment of Cancer) trial, neoadjuvant chemotherapy was compared to primary debulking surgery in a prospective randomized trial [17]. The two arms did not demonstrate differences in either overall survival, 29 months versus 30 months, (HR: 0.98; CI = 0.85–1.14), or progression-free survival, 11 months in both arms (HR: 0.99; CI = 0.87–1.13). However, of note, even in the primary debulking arm, OS is strikingly lower than reported in this review, as in this retrospective cohort patients with primary debulking had an overall survival of 55.8 months versus 30 months in the EORTC trial. These differences are perhaps secondary to the low numbers of optimally debulked patients in the EORTC study where only 46% were reported to be optimally debulked in the primary debulking group.

Recent statistics have also demonstrated inferior cancer survival for non-White ethnicities in multiple cancer sites [18,19]. In this study, while there was a large impact on NCT on overall survival, disparities in ethnicity and insurance on survival were not statistically significant. White and non-White women had similar overall survival. This is likely because the treatment effect of NCT on survival was greater than the impact of any other variable.

One may theorize as to why the NCT patients in this study performed strikingly inferior to the standard treatment. First, the median survival for the standard arm approached 5 years which is superior to current estimates between 2 and 3 years [3,20]. Of note, in optimally debulked patients alone, median survival approaches 4 to 5 years in the most recent randomized trials [3]. If the patients who were given standard treatment did not respond exceedingly well then perhaps their outcomes would match the NCT group more closely. Conversely perhaps there was selection bias in terms of giving NCT to those who would naturally perform worse, i.e. those with higher CCI scores and/or more liver metastases. Therefore one might consider matching cases based on CCI scores as to eliminate this bias. However, in the previous studies that have documented improved or equivalent survival between the two treatment types, it is possible that their NCT group was just healthier in general.

The strengths of this study are that it is the first documentation of the importance of socioeconomic status, insurance and ethnicity in the proscription of NCT. Furthermore, the data contributes to current body of literature on impact of insurance and Charlson Comorbidity Index on NCT. This study is limited by its small sample size, long study period, and retrospective nature which has a potential for selection bias. Future trials should be designed to better identify the criteria that determine treatment with NCT because in certain patient populations it will continue to be an important mainstay in the treatment of advanced ovarian cancer. The impact of provider, institution and societal bias in allocating patients to NCT needs to be documented. The remaining question is whether changes can be made during the initial cancer diagnosis to improve access to the standard of care for certain at-risk populations.

Conflict of interest statement

The authors of this manuscript do not have any financial and personal relationships with other people or organizations that could inappropriately influence (bias) this work.

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