

# Refusal of Recommended Chemotherapy for Ovarian Cancer: Risk Factors and Outcomes; a National Cancer Data Base Study

Sumer K. Wallace, MD<sup>a</sup>; Jeff F. Lin, MD<sup>b</sup>; William A. Cliby, MD<sup>a</sup>; Gary S. Leiserowitz, MD<sup>c</sup>; Ana I. Tergas, MD<sup>d</sup>; and Robert E. Bristow, MD, MBA<sup>e</sup>

## Abstract

**Objective:** To identify risk factors associated with refusal of recommended chemotherapy and its impact on patients with epithelial ovarian cancer (EOC). **Methods:** We identified patients in the National Cancer Data Base diagnosed with EOC from January 1998 to December 2011. Patients who refused chemotherapy were identified and compared with those who received recommended, multiagent chemotherapy. Univariate and multivariable analyses were performed using chi-square test with Bonferroni correction, binary logistic regression, log-rank test, and Cox proportional hazards modeling. The threshold for statistical significance was set at a *P* value of less than 0.05. **Results:** From a cohort of 147,713 eligible patients, 2,707 refused chemotherapy. These patients were compared with 92,212 patients who received recommended multiagent chemotherapy. Older age, more medical comorbidities, not having insurance, and later year of diagnosis were directly and significantly associated with chemotherapy refusal when analyzed using multivariable logistic regression. In addition, lower-than-expected facility adherence to NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Ovarian Cancer, treatment at low-volume center, lower grade, and higher stage were all significantly and independently associated with chemotherapy refusal. Median overall survival of patients who received multiagent chemotherapy was significantly longer than that of those who refused chemotherapy (43 vs 4.8 months; *P* < .0005). After controlling for known patient, facility, and disease prognostic factors, chemotherapy refusal is significantly associated with increased risk of death. **Conclusions:** Refusal of recommended chemotherapy carries significant risk of early death from ovarian cancer. Our data demonstrate that the decision to refuse chemotherapy is multifactorial and, in addition to unalterable factors (eg, stage/grade, age), involves factors that can be changed, including facility type and payor. Efforts at addressing these discrepancies in care can improve compliance with chemotherapy recommendations in the NCCN Guidelines for Ovarian Cancer and outcomes.

*J Natl Compr Canc Netw* 2016;14(5):539–550

## NCCN: Continuing Education

### Accreditation Statement

This activity has been designed to meet the educational needs of physicians and nurses involved in the management of patients with cancer. There is no fee for this article. No commercial support was received for this article. The National Comprehensive Cancer Network (NCCN) is accredited by the ACCME to provide continuing medical education for physicians.

NCCN designates this journal-based CME activity for a maximum of 1.0 AMA PRA Category 1 Credit™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

NCCN is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

NCCN designates the education activity for a maximum of 1.0 contact hour. Accreditation as a provider refers to recognition of

From <sup>a</sup>Mayo Clinic, Rochester, Minnesota; <sup>b</sup>Magee-Womens Hospital of University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; <sup>c</sup>University of California Davis Medical Center, Sacramento, California; <sup>d</sup>New York-Presbyterian Hospital/Columbia University Medical Center, New York, New York; and <sup>e</sup>University of California Irvine Medical Center, Orange, California.

Submitted June 15, 2015; accepted for publication March 1, 2016.

The authors have disclosed that they have no financial interests, arrangements, affiliations, or commercial interests with the manufacturers of any products discussed in this article or their competitors. Dr. Tergas is the recipient of a fellowship (NCI R25 CA094061-11) from the National Cancer Institute.

Correspondence: Sumer K. Wallace, MD, Department of Obstetrics and Gynecology, Gynecologic Oncology, 200 First Street SW, Rochester, MN 55905. E-mail: wallace.sumer@mayo.edu

### EDITOR

**Kerrin M. Green, MA**, Assistant Managing Editor, *JNCCN—Journal of the National Comprehensive Cancer Network*

Ms. Green has disclosed that she has no relevant financial relationships.

### CE AUTHORS

**Deborah J. Moonan, RN, BSN**, Director, Continuing Education, has disclosed that she has no relevant financial relationships.

**Kristina M. Gregory, RN, MSN, OCN**, Vice President, Clinical Information Operations, has disclosed that she has no relevant financial relationships.

**Rashmi Kumar, PhD**, Senior Manager, Clinical Content, has disclosed that she has no relevant financial relationships.

**Miranda Hughes, PhD**, Oncology Scientist/Senior Medical Writer, has disclosed that she has no relevant financial relationships.

Wallace et al

educational activities only; accredited status does not imply endorsement by NCCN or ANCC of any commercial products discussed/displayed in conjunction with the educational activity. Kristina M. Gregory, RN, MSN, OCN, is our nurse planner for this educational activity.

All clinicians completing this activity will be issued a certificate of participation. To participate in this journal CE activity: 1) review the learning objectives and author disclosures; 2) study the education content; 3) take the posttest with a 66% minimum passing score and complete the evaluation at <http://education.nccn.org/node/78550>; and 4) view/print certificate.

Release date: May 12, 2016; Expiration date: May 12, 2017

### Learning Objectives

Upon completion of this activity, participants will be able to:

- Identify risk factors associated with refusal of recommended chemotherapy in patients with ovarian cancer
- Describe the impact on patient outcomes related to refusal of recommended chemotherapy in patients with ovarian cancer

### Background

Ovarian cancer remains the deadliest gynecologic malignancy, with relative 5-year survival rates for patients diagnosed with epithelial ovarian cancer (EOC) ranging from 17% to 90% depending on stage at diagnosis.<sup>1</sup> Treatment of ovarian cancer has evolved over several decades; the standard treatment for advanced-stage disease is either debulking surgery followed by chemotherapy or neoadjuvant chemotherapy with (or without) surgery.<sup>2-4</sup> Multiple studies have defined the role and efficacy of chemotherapy in ovarian cancer, showing increased progression-free survival (PFS) and overall survival (OS) in patients receiving the standard treatment of combination platinum- and taxane-based chemotherapy, as recommended in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Ovarian Cancer.<sup>6-8</sup>

As with any treatment, patient autonomy is the center of decision-making. As such, after discussing and recommending chemotherapy to patients with ovarian cancer, not all patients will elect to proceed with this treatment. The decision to proceed with known, effective cancer therapy is not always clear-cut, and various demographic, socioeconomic, and psychological influences have been implicated in the decision to refuse therapy. Racial disparities, medical comorbidities, and physical access to care have been shown to be barriers in health systems with universal insurance coverage, and other studies have highlighted subjective reasons patients may give for

refusing recommended chemotherapy.<sup>9,10</sup> Patient education of risks/benefits of therapy, goals of care, and quality-of-life (QOL) considerations have also been shown to be of utmost importance in the decision to refuse recommended therapy. A study by Havrilesky et al<sup>11</sup> suggests that women with ovarian cancer would exchange improved PFS for reduced treatment side effects resulting in improved QOL.

Although patient autonomy is a cornerstone of modern medical ethics and the current health care delivery paradigm, it seems that for some patients, refusal of recommended therapy may sometimes be reflective of incompletely informed decisions. We are unaware of prior studies that have examined the possible interactions of such externalities on treatment decisions among patients with ovarian cancer, whose socioeconomic circumstances and concentration of care with gynecologic oncology subspecialists may be different from those of other cancer populations.

Furthermore, a recent article in *Time* magazine highlighted patients' decision to refuse chemotherapy, and explained motives for such decisions, thus bringing national attention to this important and relevant topic. The article reminded physicians that respecting patient decisions and wishes remains integral to a healthy physician-patient relationship.<sup>12</sup> Given the possibility of chemotherapy refusal among patients with ovarian cancer, and the importance of maintaining patient rapport, we sought to understand the parameters of refusal of treatment in the ovarian cancer patient population. As such, the objective of this study was to identify risk factors associated with refusal of recommended chemotherapy and its impact on OS using multivariable models in an attempt to control for confounders in patients with EOC using data from the National Cancer Data Base (NCDB).

### Methods

We identified patients in the used the NCDB diagnosed with EOC from January 1998 to December 2011. The NCDB is an extensive database established jointly by the American Cancer Society and American College of Surgeons Commission on Cancer. The database collects approximately 70% of new cancer diagnoses from more than 1,500 accredited hospitals. The data are used to track new diagnoses and outcomes, in addition to quality improvement

## Chemotherapy Refusal in Ovarian Cancer

measures and surveillance.<sup>13</sup> Initial data selection was as previously described by Cliby et al<sup>14</sup> in their recently published NCDB-based article. Patients who refused chemotherapy were identified and compared with those who received recommended, multiagent chemotherapy; prior surgery was not requisite to be included in this group. We compared specific data points collected regarding chemotherapy administration. These data points were defined in the NCDB as, “Multiagent chemotherapy administered as first course therapy,” which was compared with, “Chemotherapy was not administered. It was recommended by the patient’s physician, but this treatment was refused by the patient, a patient’s family member, or the patient’s guardian. The refusal was noted in patient record.” Our primary end point was to determine what risk factors identifiable in the NCDB are associated with refusal of recommended chemotherapy. Secondary end points include effects on OS and associated risk of death. Univariate analyses were performed using Chi-square tests with Bonferroni correction and log-rank test. Multivariable analyses were performed using Cox proportional hazards modeling and binary logistic regression. OS was determined using the Kaplan-Meier method. Threshold for statistical significance was set at a *P* value of less than 0.05. Odds ratios (OR) and hazard ratios (HR) with 95% CIs were created, and an OR greater than 1.0 implied an increased likelihood of association with chemotherapy refusal and an HR of greater than 1.0 implied increased likelihood of death. Data were analyzed using SPSS statistical software (IBM, Armonk, NY). The University of Pittsburgh Medical Center Institutional Review Board granted this study exempt status. The data used in this study were derived from a de-identified NCDB 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 nor the conclusions drawn from these data by the investigator.

## Results

A total of 147,713 patients were identified, of whom 2,707 (1.8%) refused chemotherapy. The patients who were defined as refusing chemotherapy were identified in the NCDB by the entry, “Chemotherapy was not administered. It was recommended by the

patient’s physician, but this treatment was refused by the patient, a patient’s family member, or the patient’s guardian. The refusal was noted in patient record.” In general, most patients in our cohort were younger than 60 years (44.6%), followed closely by those aged 60 to 75 years (40.3%), and least commonly by those older than 75 years (15.1%). When evaluating stage, 12.8% were diagnosed as stage I, 0.09% as stage II, 50.1% as stage III, and 28.2% as stage IV. Charlson-Deyo comorbidity scores of 0 were recorded in 81.5%, a score of 1 was recorded in 14.9%, and scores of 2 or greater were recorded in 3.6% of cases. Most facilities that administered chemotherapy reported treating 16.5 to 27.7 (26.3%) or more than 27.7 (27.0%) cases per year. The median OS of patients who received multiagent chemotherapy was 43 months, whereas the median survival time was 4.8 months for those who refused chemotherapy (*P*<.0005).

When comparing those who received chemotherapy and those who refused, several factors were found to be associated with chemotherapy refusal. On exploratory univariate analysis, older age, African American race, more medical comorbidities, having Medicare/Medicaid or no insurance, lower income, lower education level, residence near the treating facility, facilities in the Northeast, low-volume facilities, facilities with lower-than-expected adherence rate to the NCCN Guidelines for Ovarian Cancer, later year of diagnosis, lower grade, and higher stage of disease were all significantly associated with chemotherapy refusal (all *P*<.0005), whereas unplanned surgical readmission and residential setting were not (Tables 1 and 2).

On multivariable logistic regression, older age (>70 vs ≤50 years; OR, 4.2), more medical comorbidities (≥2 vs 0; OR, 1.8), not having insurance (OR, 1.4–2.9, depending on type), later year of diagnosis (2009–2011 vs 2002–2004; OR, 1.3), lower-than-expected facility adherence to NCCN Guidelines (OR, 1.2), treatment at a low-volume center (lowest vs highest; OR, 1.6), lower grade (1 vs 3; OR, 2.0), and stage (I vs IV; OR, 2.2) were all significantly and independently associated with chemotherapy refusal, whereas patient race, residential urban status/income/education level, unplanned surgical readmission, and treatment facility academic status/location/distance were not. After controlling for known patient, facility, and disease prognostic factors, chemotherapy re-

Wallace et al

Table 1. Comparison of Variables in Univariate Analyses in Those Who Received and Refused Chemotherapy					
Variables Examined	Chemotherapy Given		Chemotherapy Refused		P Value
		%		%	
Univariate (Chi-Square Tests)					
Patient age					<.0005
≤50 y	19,686	98.8%	248	1.2%	
51–60 y	24,799	98.7%	329	1.3%	
61–70 y	24,651	98.4%	409	1.6%	
≥71 y	23,076	93.1%	1,721	6.9%	
Race					<.0005
Caucasian	78,031	97.2%	2,259	2.8%	
African American	6,107	96.2%	241	3.8%	
Hispanic	4,056	97.6%	99	2.4%	
Native American	255	97.7%	6	2.3%	
Asian/Pacific Islander	2,377	97.3%	67	2.7%	
Charlson/Deyo score					<.0005
0	48,273	97.4%	1,299	2.6%	
1	8,677	96.0%	357	4.0%	
2	2,028	92.5%	165	7.5%	
Insurance type					<.0005
Uninsured	3,725	96.9%	120	3.1%	
Private insurance	46,905	98.7%	631	1.3%	
Medicare/Medicaid	38,573	95.3%	1,894	4.7%	
Governmental insurance	769	98.8%	9	1.2%	
Income (of residential zip code)					<.0005
≤\$30,000	10,443	96.7%	358	3.3%	
\$30,000–\$34,999	15,498	97.0%	478	3.0%	
\$35,000–\$45,999	24,706	96.9%	778	3.1%	
>\$46,000	36,174	97.4%	967	2.6%	
Education					<.0005
≤29%	13,073	96.8%	426	3.2%	
20%–28.9%	19,213	97.0%	590	3.0%	
14%–19.9%	20,919	96.8%	682	3.2%	
<14%	33,606	97.4%	883	2.6%	
Residential setting					.363
Metropolitan	70,901	97.1%	2,129	2.9%	
Urban	13,581	97.3%	381	2.7%	
Rural	1,842	97.4%	49	2.6%	
Distance from facility to patient residence					<.0005
≤5.00 miles	23,210	95.9%	998	4.1%	
5.01–10.00 miles	17,862	96.9%	576	3.1%	
10.01–25.00 miles	21,621	97.6%	534	2.4%	
≥25.01 miles	25,149	98.1%	497	1.9%	

(continued on next page)

fusal was found to be independently associated with a 2.89-fold risk of mortality when analyzed using a multivariable Cox model (95% CI, 2.56–3.26;  $P < .0005$ )

(Tables 3 and 4). This risk is proportionally higher than that conferred by age, African American race, comorbidity, and grade of disease.

## Chemotherapy Refusal in Ovarian Cancer

**Table 1. Comparison of Variables in Univariate Analyses in Those Who Received and Refused Chemotherapy (cont.)**

Variables Examined	Chemotherapy Given		Chemotherapy Refused		P Value
		%		%	
<b>Univariate (Chi-Square Tests)</b>					
Facility type					<.0005
Community cancer program	5,988	95.1%	306	4.9%	
Comprehensive community	46,830	96.9%	1,505	3.1%	
Academic/Research program	37,211	97.9%	804	2.1%	
Facility location					<.0005
Northeast/Atlantic	19,896	96.8%	661	3.2%	
South	25,656	97.6%	642	2.4%	
Midwest	30,418	97.0%	940	3.0%	
West	16,242	97.2%	464	2.8%	
Average annual facility volume					<.0005
≤7.1 cases/year	20,667	95.3%	1,016	4.7%	
7.1–16.5 cases/year	22,431	96.9%	728	3.1%	
16.5–27.7 cases/year	24,259	97.8%	552	2.2%	
>27.7 cases/year	24,855	98.4%	411	1.6%	
Facility adherence to NCCN care observed/expected ratio					<.0005
<1	36,028	96.9%	1,145	3.1%	
≥1	53,803	97.4%	1,457	2.6%	
Year of diagnosis					<.0005
≤2001	26,561	97.5%	679	2.5%	
2002–2004	19,184	97.3%	536	2.7%	
2005–2008	26,370	97.1%	788	2.9%	
≥2009	20,097	96.6%	704	3.4%	
Grade					<.0005
1	4,710	96.6%	164	3.4%	
2	14,550	97.7%	337	2.3%	
3	52,347	98.2%	955	1.8%	
Corrected overall stage					<.0005
I	11,693	96.4%	432	3.6%	
II	8,168	97.1%	241	2.9%	
III	46,670	98.3%	812	1.7%	
IV	25,516	95.5%	1,208	4.5%	
Unplanned surgical readmission (within 30 days)					.877
No	38,806	98.4%	622	1.6%	
Yes	2,423	98.4%	40	1.6%	

## Discussion

Standard treatment for patients with EOC follows the recommendations in the NCCN Guidelines for Ovarian Cancer.<sup>7</sup> Following these treatment guidelines can result in significantly improved outcomes, which translates into increased PFS and OS for these patients.<sup>15</sup> Cliby et al<sup>14</sup> showed that adherence to

NCCN Guidelines ranged from 30.8% in community cancer centers to 49.1% in academic comprehensive cancer centers. This finding was associated with a significantly improved 5-year OS in those treated at academic comprehensive cancer centers with higher adherence to recommendations in the NCCN Guidelines.<sup>14</sup> In addition, patients are more

Wallace et al

Table 2. Comparison of Variables in Multivariable Analyses in Those Who Received and Refused Chemotherapy				
Variables Examined	Multivariable (Logistic Regression)			
	Odds Ratio (Refusing Chemotherapy)	Lower Bound 95% CI	Upper Bound 95% CI	P Value
<b>Patient age</b>				
≤50 y		Reference		
51–60 y	1.28	1.01	1.62	.04
61–70 y	1.23	0.95	1.60	.11
≥71 y	4.15	3.21	5.36	<.0005
<b>Race</b>				
Caucasian		Reference		
African American	1.21	0.93	1.57	.15
Hispanic	0.81	0.57	1.15	.23
Native American	1.26	0.39	4.07	.70
Asian/Pacific Islander	0.89	0.56	1.41	.62
<b>Charlson/Deyo score</b>				
0		Reference		
1	1.10	0.92	1.32	.28
2	1.81	1.38	2.37	<.0005
<b>Insurance type</b>				
Uninsured		Reference		
Private insurance	0.51	0.37	0.70	<.0005
Medicare/Medicaid	0.72	0.51	1.00	.05
Governmental insurance	0.34	0.12	0.96	.04
<b>Income (of residential zip code)</b>				
≤\$30,000		Reference		
\$30,000–\$34,999	0.98	0.76	1.27	.88
\$35,000–\$45,999	0.94	0.73	1.22	.65
>\$46,000	0.88	0.66	1.18	.39
<b>Education</b>				
≤29%		Reference		
20%–28.9%	1.04	0.82	1.32	.75
14%–19.9%	0.99	0.77	1.28	.94
<14%	0.95	0.72	1.24	.69
<b>Residential setting</b>				
Metropolitan				
Urban		Not entered into model		
Rural				
<b>Distance from facility to patient residence</b>				
≤5.00 miles		Reference		
5.01–10.00 miles	1.03	0.85	1.25	.77
10.01–25.00 miles	0.91	0.75	1.10	.34
≥25.01 miles	0.86	0.71	1.05	.13

(continued on next page)

likely to receive chemotherapy and have improved outcomes, including increased OS, when receiving care at a center with a high volume of cases.<sup>1</sup>

Therefore, it may be prudent for low-volume centers to refer patients refusing chemotherapy for a second opinion at a higher-volume facility.

## Chemotherapy Refusal in Ovarian Cancer

Table 2. Comparison of Variables in Multivariable Analyses in Those Who Received and Refused Chemotherapy (cont.)				
Variables Examined	Multivariable (Logistic Regression)			
	Odds Ratio (Refusing Chemotherapy)	Lower Bound 95% CI	Upper Bound 95% CI	P Value
Facility type				
Community cancer program		Reference		
Comprehensive community	0.82	0.63	1.08	.15
Academic/Research program	0.78	0.58	1.06	.11
Facility location				
Northeast/Atlantic		Reference		
South	0.86	0.70	1.06	.15
Midwest	0.90	0.75	1.07	.23
West	0.90	0.71	1.13	.36
Average annual facility volume				
≤7.1 cases/year		Reference		
7.1–16.5 cases/year	0.92	0.75	1.13	.41
16.5–27.7 cases/year	0.72	0.57	0.89	<.005
>27.7 cases/year	0.64	0.51	0.81	<.0005
Facility adherence to NCCN care observed/expected ratio				
<1		Reference		
≥1	0.81	0.70	0.93	.00
Year of diagnosis				
≤2001		Too few cases for modeling		
2002–2004		Reference		
2005–2008	1.22	1.01	1.47	.04
≥2009	1.25	1.03	1.52	.03
Grade				
1		Reference		
2	0.65	0.51	0.83	<.005
3	0.49	0.39	0.62	<.0005
Corrected overall stage				
I		Reference		
II	0.59	0.47	0.75	<.0005
III	0.35	0.30	0.42	<.0005
IV	0.46	0.37	0.56	<.0005
Unplanned surgical readmission (within 30 days)				
No		Not entered into model		
Yes		Not entered into model		

Given lack of good screening measures, it remains difficult to diagnose ovarian cancer at an early stage. Bristow et al<sup>15</sup> reported on racial and socioeconomic disparities in patients diagnosed with ovarian cancer. Their study showed that insurance status and household income less than \$35,000 translated into worse OS, with an approximately 30% increased risk

of death. Investigation of patients with colorectal cancer found that 8.1% refused chemotherapy due to economic difficulty, and 11.9% declined chemotherapy due to cost or lack of family support.<sup>9</sup> Similarly, our study showed that having insurance coverage decreased the rate of chemotherapy refusal. Offering comprehensive care, complete with financial coun-

Wallace et al

Table 3. Comparison of Variables in Univariate Analyses With Respect to Effect on Survival				
Variables Examined	Univariate (Kaplan-Meier Analysis)			P Value
	Median OS (mo)	Lower Bound 95% CI	Upper Bound 95% CI	
Patient age				<.0005
≤50 y	90.48	86.98	93.98	
51–60 y	55.23	53.90	56.56	
61–70 y	38.28	37.49	39.07	
≥71 y	19.15	18.69	19.61	
Charlson/Deyo Score				<.0005
0	45.83	44.97	46.69	
1	30.72	29.23	32.21	
2	14.65	12.91	16.39	
Race				<.0005
Caucasian	40.74	40.23	41.25	
African American	25.33	24.14	26.52	
Hispanic	45.63	42.89	48.37	
Native American/American Indian	57.07	42.19	71.95	
Asian/Pacific Islander	61.08	54.78	67.38	
Insurance type				<.0005
Uninsured	45.47	42.48	48.46	
Private insurance	60.25	59.16	61.34	
Medicare/Medicaid	25.17	24.71	25.63	
Governmental insurance	48.99	41.29	56.69	
Stage				<.0005
I	175.38	N/A	N/A	
II	113.18	108.23	118.13	
III	36.80	36.31	37.29	
IV	17.05	16.65	17.45	
Grade				<.0005
1	173.47	N/A	N/A	
2	64.20	62.19	66.21	
3	38.80	38.27	39.33	
Facility type				<.0005
Community cancer program	29.80	28.47	31.13	
Comprehensive community cancer program	39.36	38.70	40.02	
Academic/Research program	43.99	43.19	44.79	
Average annual facility volume				<.0005
≤7.1 cases/year	30.88	30.10	31.66	
7.1–16.5 cases/year	40.34	39.39	41.29	
16.5–27.7 cases/year	43.33	42.36	44.30	
>27.7 cases/year	46.55	45.54	47.56	
Chemotherapy				<.0005
Chemotherapy given	42.97	42.43	43.51	
Chemotherapy refused	4.83	4.07	5.59	

Abbreviations: N/A, not available; OS, overall survival.



## Chemotherapy Refusal in Ovarian Cancer

**Table 4. Comparison of Variables in Multivariable Analyses With Respect to Effect on Survival**

Variables Examined	Multivariable (Cox Proportional Hazards)			
	Hazard Ratio (Death)	Lower Bound 95% CI	Upper Bound 95% CI	P Value
<b>Patient age</b>				
≤50 y		Reference		
51–60 y	1.13	1.07	1.19	<.0005
61–70 y	1.19	1.13	1.27	<.0005
≥71 y	1.53	1.43	1.63	<.0005
<b>Charlson/Deyo score</b>				
0		Reference		
1	1.15	1.10	1.22	<.0005
2	1.45	1.31	1.60	<.0005
<b>Race</b>				
Caucasian		Reference		
African American	1.19	1.11	1.28	<.0005
Hispanic	0.91	0.82	1.00	.05
Native American/American Indian	0.66	0.44	0.97	.04
Asian/Pacific Islander	0.94	0.82	1.07	.34
<b>Insurance type</b>				
Uninsured		Reference		
Private Insurance	0.87	0.79	0.96	.01
Medicare/Medicaid	1.07	0.97	1.19	.18
Governmental Insurance	0.87	0.69	1.09	.24
<b>Stage</b>				
I		Reference		
II	1.79	1.59	2.01	<.0005
III	5.30	4.84	5.81	<.0005
IV	8.24	7.50	9.07	<.0005
<b>Grade</b>				
1		Reference		
2	1.59	1.42	1.77	<.0005
3	1.76	1.58	1.95	<.0005
<b>Facility type</b>				
Community cancer program		Reference		
Comprehensive community cancer program	0.96	0.88	1.04	.29
Academic/Research program	0.92	0.84	1.01	.09
<b>Average annual facility volume</b>				
≤7.1 cases/year		Reference		
7.1–16.5 cases/year	0.98	0.93	1.05	.61
16.5–27.7 cases/year	0.96	0.91	1.03	.24
>27.7 cases/year	0.95	0.89	1.01	.09
<b>Chemotherapy</b>				
Chemotherapy given		Reference		
Chemotherapy refused	2.89	2.56	3.26	<.0005

selling and discussion of options for insurance coverage, may help attenuate these disparities, thereby increasing access to treatment adherent to the NCCN Guidelines, reducing refusal of chemotherapy, and improving OS.

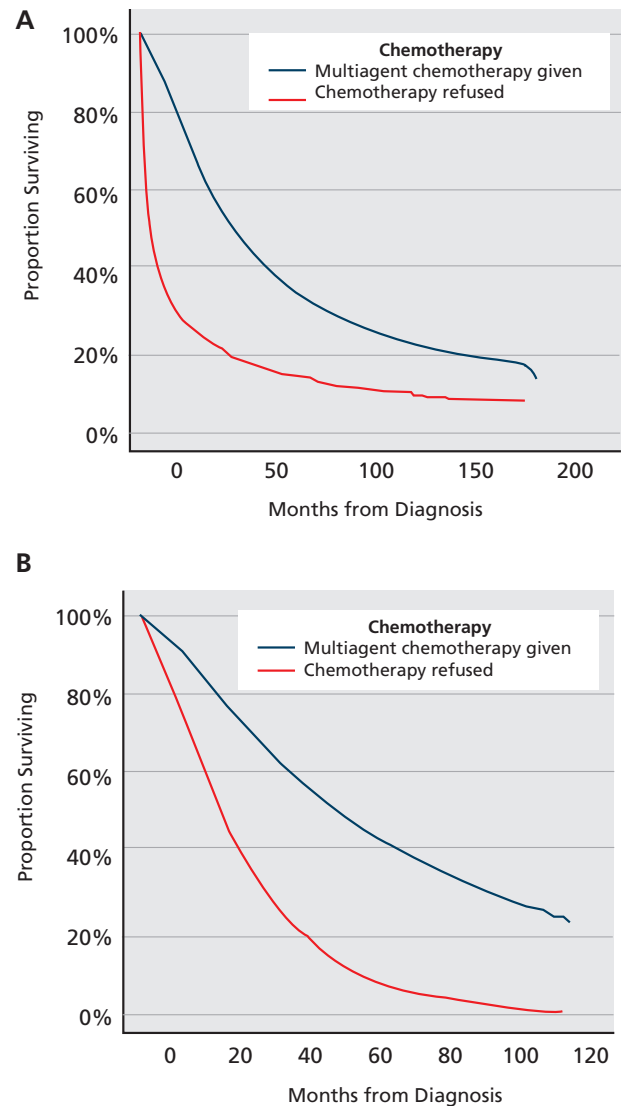
On occasion, regardless of all efforts, patients will continue to decline chemotherapy. Shared decision-making and patient autonomy remain extremely important aspects of care. Collaborating with the patient and her family to discuss chemotherapy and options or

Wallace et al

alternatives is essential to this shared decision-making.<sup>16</sup> Previous studies have evaluated patient QOL and preferences in relation to receiving treatment for EOC. Emotional and psychological aspects of treatment, such as patient outlook toward treatment, body image, and fatigue, can often play a significant role in a patient's treatment experience.<sup>17,18</sup> Havrilesky et al<sup>11</sup> queried patients regarding symptoms, side effects, and PFS preferences when choosing chemotherapy. Their data showed that patients prefer improved QOL with reduced symptoms over PFS. That study showed that participating patients would choose to decrease nausea and vomiting from severe to mild during chemotherapy even if this decision resulted in PFS decreasing by 6.7 months. Similar results were observed when evaluating peripheral neuropathy and abdominal symptoms, with patients preferring fewer symptoms and/or adverse effects despite decreasing PFS.<sup>11</sup> In patients who ultimately refuse chemotherapy, early referral to and institution of palliative care has been shown to improve QOL.<sup>19</sup>

This study demonstrates that, despite standard surgical and chemotherapeutic treatments with known efficacy, approximately 1.8% of patients diagnosed with EOC will refuse recommended chemotherapy, which appears to be in line with, or slightly better than, the percentages for other cancer sites.<sup>9,10</sup> This is limited by the relative proportion of unavailable data in our study, which is a limitation of the ongoing nature of the NCDB data collection process; although demographic data from recent cases may be captured, treatment and survival data do not mature for at least 5 years.

Our study reports multiple factors, both modifiable and not, associated with refusal of recommended chemotherapy in patients with EOC. In addition, our data show a significant reduction in unadjusted OS of 38.2 months, with an adjusted 189% increased risk of death, in patients who refuse chemotherapy (Figure 1). Given this, one might consider improving patient and practitioner education and discussion regarding the risks and benefits of chemotherapy in the treatment of ovarian cancer, and focus on goals of care. This is borne out in the data showing that patients being treated at high-volume centers seem to refuse chemotherapy less frequently, perhaps due to interactions with other cancer survivors or frequent interactions of health care providers and patients. Interestingly, being in an academic setting does not necessarily confer this advantage.



**Figure 1.** Unadjusted (A) and adjusted (B) overall survival according to chemotherapy refusal.

One encouraging finding from this study is the lack of geographic or facility distance factor on the patient refusal, suggesting that physical parameters may be less of a barrier to care for patients with ovarian cancer compared with other cancers.

Overall, our study suggests opportunities to reduce the rate of chemotherapy refusal, including improved education, counseling, and access to high-volume centers.

This study is limited by the retrospective nature, significant proportion of unavailable data points, and the inherent selection bias and dependence on reporting accuracy that comes with such study design. As mentioned previously, our study is limited by the

## Chemotherapy Refusal in Ovarian Cancer

proportion of unavailable data in the NCDB. For example, although we were able to identify patients who decided to refuse chemotherapy, we do not have information regarding why they made such a decision. In addition, 36.2% of patients did not receive chemotherapy due to contraindication or for unknown reasons, or died before treatment initiation; however, we do not have an explanation or further information for these patients. In our cohort, performance status data were not reported, and we used the previously validated Charlson-Deyo comorbidity score<sup>20</sup> for patient frailty, which is not as immediate and proximate as the Gynecologic Oncology Group/ECOG/Karnofsky performance status scores, none of which are available in the NCDB.

Strengths include the use of the NCDB—a large comprehensive database that covers most new cancer diagnoses in the United States, with more variables than previously available in other national databases, such as SEER<sup>21</sup>—to allow for a big data analytical approach to this question regarding which patients with ovarian cancer are refusing therapy and what happens to them. Because of the large cohort size, with many collected data points, we were able to control for confounding factors on multivariable analysis. This study is the first to evaluate risk factors for and associations with chemotherapy refusal in patients with ovarian cancer, and the findings highlight the need for offering a broad approach when recommending chemotherapy.

## Conclusions

The goal of this study was to identify patients who are at increased risk of refusing chemotherapy, a standard treatment with known efficacy in patients with ovarian cancer. Further research could focus on what therapies, if any, are received by patients who refuse chemotherapy, and the efficacy and tolerance of those treatments. Further research is also needed to identify individualized best practices for this high-risk subgroup. Consideration should be given for low-volume centers to refer patients refusing chemotherapy for second opinion at a higher-volume facility. The study results suggest that improved health care access and individualized counseling may im-

prove care delivery, thereby providing patients with all treatment options and improved outcomes.

## References

1. Lin JF, Berger JL, Krivak TC, et al. Impact of facility volume on therapy and survival for locally advanced cervical cancer. *Gynecol Oncol* 2014;132:416–422.
2. Lund B, Hansen HH. Chemotherapy in ovarian carcinoma. *Cancer Surv* 1989;8:681–691.
3. Longo DL, Young RC. The natural history and treatment of ovarian cancer. *Annu Rev Med* 1981;32:475–490.
4. Hainsworth JD, Grosh WW, Burnett LS, et al. Advanced ovarian cancer: long-term results of treatment with intensive cisplatin-based chemotherapy of brief duration.
5. Fleming GF, Seidman J, Lengyel E, et al. Epithelial ovarian cancer. In: Barakat RR, Berchuck A, Markman M, et al., eds. *Principles and Practice of Gynecologic Oncology*, 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2013:757–847. *Ann Intern Med* 1988;108:165–170.
6. Barlin JN, Dao F, Bou Zgheib N, et al. Progression-free and overall survival of a modified outpatient regimen of primary intravenous/intraperitoneal paclitaxel and intraperitoneal cisplatin in ovarian, fallopian tube, and primary peritoneal cancer. *Gynecol Oncol* 2012;125:621–624.
7. Copeland LJ, Bookman M, Trimble E; Gynecologic Oncology Group Protocol GOG 182-ICON5. Clinical trials of newer regimens for treating ovarian cancer: the rationale for Gynecologic Oncology Group Protocol GOG 182-ICON5. *Gynecol Oncol* 2003;90(Suppl 2):S1–7.
8. Morgan RJ Jr, Armstrong DK, Alvarez RD, et al. NCCN Clinical Practice Guidelines in Oncology: Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer. Version 2.2015. Accessed April 13, 2016. To view the most recent version of these guidelines, visit NCCN.org.
9. Li P, Li F, Fang Y, et al. Efficacy, compliance and reasons for refusal of postoperative chemotherapy for elderly patients with colorectal cancer: a retrospective chart review and telephone patient questionnaire. *PLoS One* 2013;8:1–8.
10. Huang HL, Kung PT, Chiu CF, et al. Factors associated with lung cancer patients refusing treatment and their survival: a national cohort study under a universal health insurance in Taiwan. *PLoS One* 2014;9:e101731.
11. Havrilesky LJ, Alvarez Secord A, Ehrisman JA, et al. Patient preferences in advanced or recurrent ovarian cancer. *Cancer* 2014;120:3651–3659.
12. Konigsberg RD. The Refuseniks. Time. June 2, 2011. Available at: [http://content.time.com/time/specials/packages/article/0,28804,2075133\\_2075127\\_2075099,00.html](http://content.time.com/time/specials/packages/article/0,28804,2075133_2075127_2075099,00.html). Accessed April 13, 2016.
13. National Cancer Data Base. American College of Surgeons Web site. Available at: <https://www.facs.org/quality%20programs/cancer/ncdb>. Accessed April 13, 2016.
14. Cliby WA, Powell MA, Al-Hammadi N, et al. Ovarian cancer in the United States: contemporary patterns of care associated with improved survival. *Gynecol Oncol* 2015;136:11–17.
15. Bristow RE, Powell MA, Al-Hammadi N, et al. Disparities in ovarian cancer care quality and survival according to race and socioeconomic status. *J Natl Cancer Inst* 2013;105:823–832.
16. Makoul G, Clayman ML. An integrative model of shared decision making in medical encounters. *Patient Educ Couns* 2006;60:301–312.
17. Stavrou C, Ford A, Ghaem-Maghani S, et al. A study of symptoms described by ovarian cancer survivors. *Gynecol Oncol* 2012;125:59–64.
18. Teng FF, Kallinger SE, Brotto L, McAlpine JN. Determinants of quality of life in ovarian cancer survivors: a pilot study. *J Obst Gynaecol Can* 2014;36:708–715.
19. Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med* 2010;363:733–742.
20. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol* 1992;45:613–619.
21. National Cancer Institute. Surveillance, Epidemiology, and End Results Program. SEER Data, 1973–2012. Available from: <http://seer.cancer.gov/data/>.

Wallace et al

## Instructions for Completion

To participate in this journal CE activity: 1) review the learning objectives and author disclosures; 2) study the education content; 3) take the posttest with a 66% minimum passing score and complete the evaluation at <http://education.nccn.org/node/78550>; and 4) view/print certificate. After reading the article, you should be able to answer the following multiple-

choice questions. Credit cannot be obtained for tests completed on paper. You must be a registered user on NCCN.org. If you are not registered on NCCN.org, click on “New Member? Sign up here” link on the left hand side of the Web site to register. Only one answer is correct for each question. Once you successfully answer all posttest questions you will be able to view and/or print your certificate. Software requirements: Internet

## Posttest Questions

1. All of the following patient risk factor(s) was/were shown to be significantly and independently associated with refusal of chemotherapy in this study of patients with ovarian cancer EXCEPT...
  - a. Older age and more medical comorbidities
  - b. Patient race, residential urban status, income, and education level
  - c. Lack of health insurance
  - d. Lower-than-expected facility adherence to the NCCN Guidelines for Ovarian Cancer
  - e. Treatment at a low-volume cancer center
  - f. Lower grade or higher stage disease
2. True or False: Following chemotherapy recommendations in the NCCN Guidelines for Ovarian Cancer can result in significantly improved outcomes, which translates into increased

PFS and OS for patients with ovarian cancer.

3. Shared decision-making and patient autonomy are important aspects of cancer care. Which of the following strategies could be implemented to increase access to treatment adherent to NCCN Guidelines, reduce refusal of chemotherapy, and improve OS of patients with ovarian cancer?
  - a. Financial counseling and discussion of options for insurance coverage
  - b. Referral to high-volume cancer center
  - c. Practitioner/patient discussion of risks/benefits of chemotherapy with focus on goals of care
  - d. All of the above

