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Use and Duration of Chemotherapy and its Impact on Survival in Early-Stage Ovarian Cancer

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Abstract

Objective—Although 5-year survival for early-stage ovarian cancer is favorable, prognosis at recurrence is poor, necessitating appropriate initial management. We examined the patterns of care and the impact of the duration of chemotherapy on survival for women with early-stage ovarian cancer.

Methods—We used the SEER-Medicare database to identify women ≥65 years of age with stage I ovarian cancer diagnosed from 1992-2009. Patients were categorized as low-risk (non-clear cell histology, stage IA or IB, grade 1 or 2) or high-risk (clear cell histology, grade 3, or stage IC). We used multivariable logistic regression models to determine predictors of chemotherapy use and duration and Cox proportional hazards models to evaluate the effect of chemotherapy use and duration on survival.

Results—We identified 1394 patients. Among low-risk patients, 32.9% received adjuvant chemotherapy and the use of chemotherapy increased with time. Among high-risk patients, 71.9% received adjuvant chemotherapy; 44.2% had ≤ 3 months of treatment, and 55.8% had >3 months of treatment. Older patients were less likely to receive chemotherapy, while those with higher

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stage and grade were more likely to receive chemotherapy (P<0.05 for all). Among high-risk patients, the duration of chemotherapy did not impact overall (HR=0.93, 95% CI, 0.67-1.27) or cancer specific (HR=0.93; 95% CI, 0.61-1.42) survival.

Conclusions—Among early-stage ovarian cancer patients, practice patterns are widely divergent. Extended duration chemotherapy does not appear to impact survival for women with high-risk disease.

Introduction

Women with early-stage ovarian cancer have a favorable prognosis with five-year survival rates greater than 90% in some subgroups.[1] Standard therapy for early-stage ovarian cancer consists of oophorectomy with surgical staging; prior reports have suggested that approximately 30% of patients with apparent ovary-confined disease have occult nodal, pelvic or abdominal metastases.[2-4] Low socioeconomic status, advanced age, and minority race/ethnicity are associated with failure to receive recommended comprehensive surgical staging.[5]

Recommended adjuvant therapy for early-stage ovarian cancer depends on tumor sub-stage and grade. Two randomized controlled trials by the Gynecologic Oncology Group (GOG) demonstrated that adjuvant chemotherapy did not provide a survival benefit in patients with low-risk tumors (stage IA-IB, grade 1-2).[6] In contrast, patients with high-risk (stage IA-IB grade 3, stage IC, stage II), early-stage ovarian cancer appear to benefit from adjuvant chemotherapy.[1,7-10] The benefit of chemotherapy for subsets of patients with early-stage ovarian cancer has subsequently been confirmed in several trials.[3,10,11]

Although there is general consensus about the use of adjuvant chemotherapy in high-risk early-stage patients, there is debate about the optimal duration of chemotherapy. A randomized GOG trial comparing three versus six cycles of platinum and taxane-based chemotherapy showed no survival benefit for extended chemotherapy although this strategy was accompanied by increased toxicity.[7] While the trial concluded that the optimal treatment for these patients is three cycles of chemotherapy, methodologic concerns have led to continued debate about the optimal duration of chemotherapy.[1,9] While the risk of recurrence for stage I patients is lower, when patients do recur, treatment is palliative.[1] Given these findings, appropriate initial management of early-stage ovarian cancer is paramount.

Given the controversy surrounding the management of early-stage ovarian cancer, we performed a population-based analysis to examine the quality of care and outcomes for women with early-stage ovarian cancer. Specifically, we explored the adherence to guideline-based recommendations for administration of adjuvant chemotherapy and analyzed the influence of duration of chemotherapy on survival for early-stage, high-risk patients.

Methods

Data Source

The Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database was used for analysis.[12-14] SEER is a population-based cancer registry maintained by the National Cancer Institute that provides data on tumor histology, location, stage, treatment, and survival, as well as demographic and selected census tract-level information. The Medicare database includes information on patients with Medicare part A (inpatient) and part B (outpatient) including billed claims, and diagnoses. These two files are linked and provide data on initial services and all follow-up care. Exemption from the Columbia University Institutional Review Board was obtained.

Patient Selection

Women aged ≥ 65 years with stage I epithelial ovarian cancer diagnosed as their first or only cancer between January 1, 1992 and December 31, 2009 were analyzed. Only women who underwent primary cancer-directed surgery including oophorectomy were included.[13] Women who did not have full coverage of both Medicare Parts A and B or were enrolled in a non-Medicare health maintenance organization from 12 months prior through 6 months after cancer diagnosis were excluded because the billing claims for these patients were not submitted to Medicare for reimbursement completely.[15] Similarly, women who received chemotherapy prior to surgery were excluded and only those patients who survived for more than 6 months after cancer-directed surgery were included in the analysis. Patients were risk stratified based on previously published data: low-risk (stage IA or IB, grade 1 or 2, non-clear cell histology), high-risk (stage IA or IB grade 3, any stage clear cell histology, stage IC any grade) and unknown risk (insufficient data on grade available to further classify).[6]

Patient Characteristics

Age at diagnosis was categorized into 5-year intervals and race recorded as white, black, and other. Year of diagnosis was stratified into four time periods: 1992-1996, 1997-2001, 2002-2005, and 2006-2009. The SEER marital status variable was recorded as married, not married, and unknown. An aggregate socioeconomic status (SES) score was calculated from education, poverty level, and income data from the 2000 census tract data, as previously reported by Du and colleagues.[16] Patients' scores were ranked on a scale of 1-5 by use of the formula that incorporated education, poverty, and income weighted equally, with 1 being the lowest value. To assess the prevalence of comorbid medical diseases, we used the Klabunde adaptation of the Charlson comorbidity index (i.e., the Klabunde–Charlson index).[17,18] Medicare inpatient and outpatient claims were searched for diagnostic codes of the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM).[19] Area of residence was categorized as metropolitan or nonmetropolitan and tumor grade grouped as well, moderately, or poorly differentiated or unknown. Tumor histology was classified as serous, mucinous, endometrioid, clear cell or other. Stage was captured using the American Joint Cancer Commission staging criteria.

Treatments

Data on chemotherapy use was extracted from the Medicare files by searching the Level II Healthcare Common Procedure Coding System, Current Procedural Terminology (CPT) codes, ICD-9-CM diagnostic and procedure codes, and revenue center codes from physician claims files, the hospital outpatient claims files, or the Medicare provider review files. If a patient had at least one claim for chemotherapy within 6 months of surgery, she was coded as having received chemotherapy. A second analysis was performed to determine the influence of the duration of chemotherapy on outcomes for high-risk patients.[12,20] To exclude patients with recurrent and progressive disease, only high-risk patients who received <8 months of continuous chemotherapy were included. Patients were stratified based on the duration of chemotherapy as ≤3 months and 4-8 months.

To assess adequacy of surgical staging, we evaluated lymphadenectomy. A patient with any pathologic nodal assessment as defined by SEER was considered to have undergone lymphadenectomy.

Statistical Analysis

Frequency distributions between categorical variables were compared using χ^2 tests. The Cochran-Armitage test was used to examine changes in the use of chemotherapy over time. Multivariable logistic regression models were developed to determine predictors for chemotherapy use and duration. Separate models were developed for low and high-risk patient groups. Survival was calculated from the date of diagnosis to the date of death. The effect of chemotherapy on survival was examined using the Kaplan-Meier method and the results compared with the log-rank test. To examine the association between chemotherapy use and survival while controlling for other clinical and demographic variables, Cox proportional hazards models were developed. Separate analyses were performed for overall and cancer-specific survival. All analyses were conducted with SAS, version 9.4 (SAS Institute, Cary, NC). All statistical tests were two-sided. A P-value of <0.05 was considered statistically significant.

Results

We identified a total of 1394 women with stage I epithelial ovarian cancer. The median follow-up time for the cohort was 73 months. The cohort included 477 patients with low-risk tumors, 754 patients with high-risk early-stage tumors and 163 patients classified as unknown risk. The clinical and demographic characteristics of the low-risk patients are displayed (Table 1). Overall, 32.9% of women with low-risk tumors received chemotherapy. Chemotherapy use increased over time for low-risk patients from 29.4% (95% CI, 7.8-51.1%) in 1992 to 36.0% (95% CI, 17.2-54.8%) in 2009 (P=0.0001) (Figure 1). Lymph node sampling was performed in 223 (46.8%) low-risk patients. Chemotherapy was administered to 88 (56.1%) of patients who underwent lymphadenectomy compared to 69 (44.0%) of those who did not have nodal sampling (P=0.004).

In a multivariable model of factors associated with receipt of chemotherapy for women with low-risk tumors, year of diagnosis was the strongest predictor of use of chemotherapy.

Compared to patients treated in 1992-1996, those diagnosed in 1997-2001 (OR=2.36; 95% CI, 1.19-4.66), in 2002-2005 (OR=3.14; 95% CI, 1.58-6.25) and those treated in 2006-2009 (OR=3.31; 95% CI, 1.63-6.70) were more likely to receive chemotherapy. Patients with grade 2 tumors (vs. grade 1) (OR=2.28; 95% CI, 1.43-3.63) and patients with stage IB (vs. IA) (OR=2.69; 95% CI, 1.26-5.74) neoplasms were also more likely to receive chemotherapy. Use of chemotherapy decreased with advancing age (OR=0.31; 95% CI 0.16-0.60 for ≥80 compared to 65-69 years of age). While race was not associated with receipt of chemotherapy, patients with a comorbidity score of 1 were less likely to receive chemotherapy than those without comorbidities.

Among women with high-risk tumors, chemotherapy was administered to 71.9% of patients (Table 2). Among women who received chemotherapy, 54.6% underwent lymphadenectomy, while 36.3% of those who did not receive chemotherapy had a node dissection. Chemotherapy use increased from 62.5% (95% CI, 43.1-81.9%) in 1992 to 77.1% (95% CI 66.5-87.6%) in 2009 (P=0.17) (Figure 1). For patients with high-risk tumors, advancing stage and higher grade were associated with receipt of chemotherapy (Table 3). In contrast, older women were less likely to receive chemotherapy (P<0.05 for all).

Use of chemotherapy was not associated with survival for women with low-risk tumors. In a multivariable Cox proportional hazards model, chemotherapy use was not associated with improved cancer-specific (HR=1.62; 95% CI, 0.74-3.56) or overall (HR=0.93; 95% CI, 0.65-1.33) survival (Table 4). Among high-risk patients, administration of chemotherapy was associated with improved overall survival (HR=0.70; 95% CI, 0.53-0.91) but not cancer-specific survival (HR=0.89; 95% CI, 0.59-1.35). Figure 2A displays a Kaplan-Meier analysis of overall survival for high-risk patients stratified by receipt of chemotherapy (log-rank P<0.001).

When duration of chemotherapy was analyzed among high-risk patients, we noted that 215 (44.2%) women received ≤3 months of treatment while 271 (55.8%) received 4-8 months of chemotherapy. Advanced stage was the strongest predictor of extended duration chemotherapy. Women with stage IC tumors were more likely to receive chemotherapy for 4-8 months than women with stage IA tumors (OR=2.22; 95% CI, 1.37-3.59). In contrast, those who underwent lymphadenectomy (OR=0.51; 95% CI, 0.34-0.79) were less likely to receive longer duration chemotherapy. Among high-risk women who received chemotherapy and after adjustment for clinical and oncologic characteristics, the duration of chemotherapy had no effect on either cancer-specific (HR=0.93; 95% CI, 0.61-1.42) or overall (HR=0.93; 95% CI, 0.67-1.27) survival. Likewise, in a Kaplan-Meier analysis, duration of chemotherapy had no effect on survival (P=0.76).

Discussion

Our findings demonstrate wide spread variation in practice patterns for elderly women with early-stage ovarian cancer. Fewer than half of the women analyzed underwent lymphadenectomy as part of comprehensive surgically staging. More concerning, 28% of women for whom chemotherapy was indicated did not receive treatment, while nearly a

third of patients with low-risk tumors who are unlikely to derive benefit from chemotherapy were treated with chemotherapy.

These data add to a growing body of literature that suggests that women with early-stage ovarian cancer often receive treatment that is discordant with evidence-based recommendations.[21,22] Prior studies have shown that comprehensive surgical staging is commonly omitted for women with ovarian cancer.[5,22-26] In a study of 4057 early-stage ovarian cancer patients from the Health Care Cost and Utilization Project, only 53% underwent lymph node sampling.[22] Similar to population-based studies in the United States and Europe, our findings demonstrate a lack of adherence to comprehensive surgical staging guidelines in early-stage ovarian cancer, with omission of lymphadenectomy occurring in the majority of patients.[22,27,28] Our study adds to prior analyses by focusing on presumed early-stage disease, a population in whom surgical staging significantly impacts adjuvant treatment planning and survival. In our cohort, only 46.3% of women underwent lymphadenectomy. While performance of lymphadenectomy had no impact on receipt of chemotherapy for both low and high-risk patients, high-risk women who underwent lymphadenectomy were less likely to receive chemotherapy for >3 months. Further, one would expect that approximately 30% of the patients in our series would have been upstaged had they undergone lymphadenectomy.[24]

Women with low-risk tumors are unlikely to derive benefit from chemotherapy.[6] Current recommendations by the National Comprehensive Cancer Center (NCCN) recommend observation for patients with stage IA/IB grade 1 tumors and observation or chemotherapy for grade 2 neoplasms [29]. Consistent with these data, we found no improvement in survival for low-risk patients treated with chemotherapy. We did however note that use of chemotherapy was not only common for women with low-risk tumors, but appeared to be increasing over time.

For women with high-risk early-stage ovarian cancer, clinical trials have demonstrated the benefits of adjuvant chemotherapy.[3,10,11] We noted similar results among our cohort of elderly women with ovarian cancer. Among patients with high-risk, early-stage ovarian cancer, chemotherapy was associated with improved overall survival. In this population the survival benefit was modest and limited to overall survival. Despite the benefits of chemotherapy in this population of women, we noted that 28% of high-risk patients did not receive adjuvant chemotherapy.

Although there is consensus about the benefit of adjuvant chemotherapy for high-risk patients, the optimal duration of chemotherapy remains controversial. While a clinical trial comparing three versus six cycles of chemotherapy demonstrated no survival benefit with six cycles of therapy, these data were only powered to detect a >30% difference in survival.[7] Post-hoc analysis of the GOG data suggested that some groups of women, particularly those with serous histology, derive benefit from longer duration chemotherapy.[30] Our findings are in line with the GOG's data in that there was no improvement in survival for high-risk, early-stage patients treated with longer duration chemotherapy.

While our report benefits from the inclusion of a large sample size, we recognize a number of important limitations. As with any study using administrative data, we cannot control for unmeasured confounding factors that undoubtedly influenced not only the decision to utilize chemotherapy, but also the duration of chemothearpy. Using Medicare billing data, it is difficult to precisely determine the number of cycles of chemotherapy administered. To overcome this limitation, we used duration of chemotherapy as a surrogate for cycles of treatment as has been previously described.[31] Similarly, over the timespan of the study, the therapeutic agents for ovarian cancer and the way these drugs are delivered have evolved. We used a permissive definition of chemotherapy to include treatment with any cytotoxic agent. A priori we also recognize that a large number of patients did not undergo comprehensive staging and may have had occult disease. While this is a limitation in that the reported stage is based on incomplete pathologic assessment, these data capture a “real world” scenario of how patients are managed surgically and how available pathologic data is used to make decisions regarding adjuvant treatment. For some of the subset analysis, particularly for low-risk patients, our sample size and power were limited to detect small differences in survival. Lastly, our data only includes elderly women and may not be generalizable to younger patients.

Our findings demonstrate that the management of early-stage ovarian cancer in clinical practice is widely divergent from evidence-based guidelines in elderly women. Many factors likely contributed to these deviations from standard of care and further efforts should be directed toward exploring why recommended care is not delivered.[32,33] Given the poor prognosis of recurrent ovarian cancer, initiatives to optimize the management of women with early stage ovarian cancer are clearly warranted..

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Research Highlights

-Among early-stage ovarian cancer patients, practice patterns are widely divergent

-Extended duration chemotherapy does not appear to impact survival for women with high-risk disease

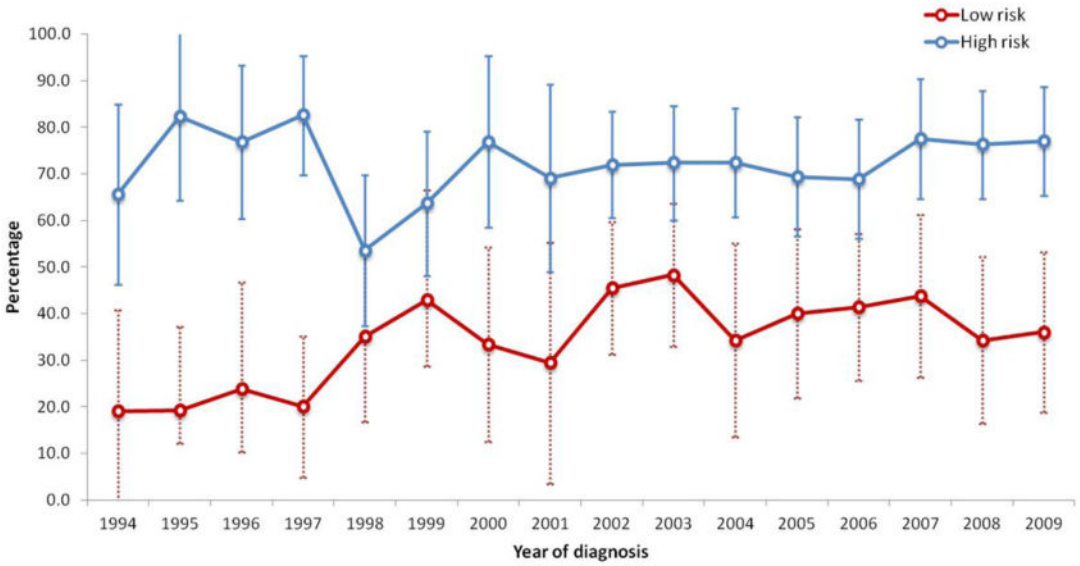

Figure 1. Trends in percentage of early-stage ovarian cancer patients receiving chemotherapy, by risk group and year

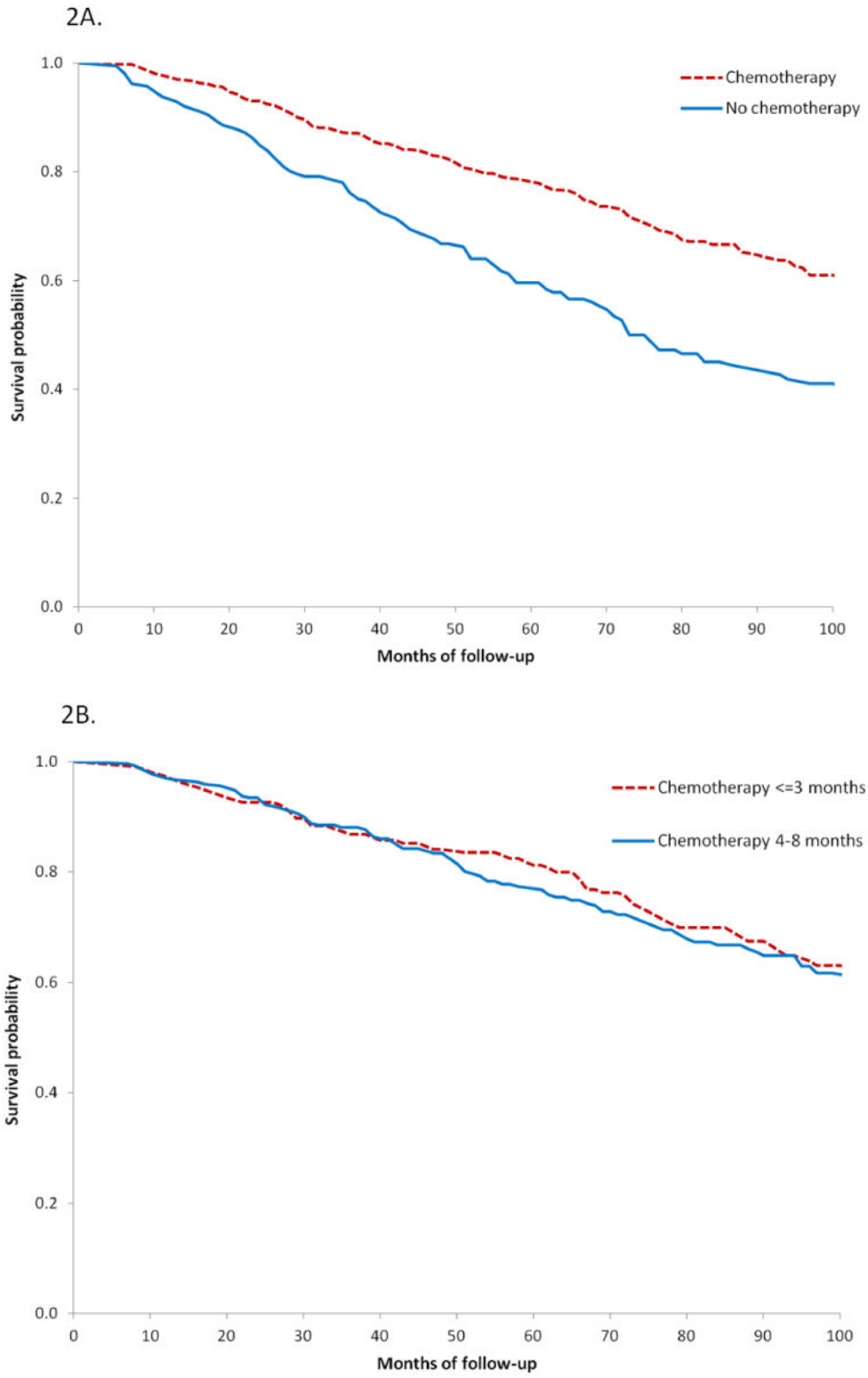

Figure 2.

A. Kaplan-Meier analysis of overall survival for high-risk women based on receipt of chemotherapy (P<0.0001), red line chemotherapy, blue line no chemotherapy.

B. Kaplan-Meier analysis of overall survival based on duration of chemotherapy for high-risk women (P=0.14), red line chemotherapy ≤3 months, blue line chemotherapy 4-8 months.

Table 1

Clinical and demographic characteristics of the cohort stratified by risk and receipt of adjuvant chemotherapy for low risk patients

	Low-risk				
	No chemotherapy		Chemotherapy		
	N	**(%)**	**N**	**(%)**	***P-value***
	320	(67.1)	157	(32.9)	
Age (years)					0.002
65-69	69	(21.6)	51	(32.5)	
70-74	83	(25.9)	42	(26.8)	
75-79	76	(23.8)	42	(26.8)	
≥80	92	(28.8)	22	(14.0)	
Race					0.14
White	274	(85.6)	142	(90.5)	
Black/other/unknown	46	(14.4)	15	(9.6)	
Year of diagnosis					0.002
1992-1996	89	(27.8)	21	(13.4)	
1997-2001	89	(27.8)	41	(26.1)	
2002-2005	68	(21.3)	48	(30.6)	
2006-2009	74	(23.1)	47	(29.9)	
Marital status					0.09
Married	125	(39.1)	74	(47.1)	
Unmarried/unknown	195	(60.9)	83	(52.9)	
SEER registry					0.47
Eastern	64	(20.0)	38	(24.2)	
Midwest	146	(45.6)	72	(45.9)	
West	110	(34.4)	47	(29.9)	
Socioeconomic status					0.23
Lowest (first) quintile	41	(12.8)	12	(7.6)	
Second quintile	80	(25.0)	31	(19.8)	
Third quintile	71	(22.2)	40	(25.5)	

	Low-risk				
	No chemotherapy		Chemotherapy		
	N	**(%)**	**N**	**(%)**	***P-value***
Fourth quintile	59	(18.4)	35	(22.3)	
Highest (fifth) quintile/unknown	69	(21.6)	39	(24.8)	
Comorbidity score					0.003
0	184	(57.5)	113	(72.0)	
1	96	(30.0)	25	(15.9)	
≥2	40	(12.5)	19	(12.1)	
Lymphadenectomy					0.004
No/unknown	185	(57.8)	69	(44.0)	
Yes	135	(42.2)	88	(56.1)	
Histology					0.001
Serous	71	(22.2)	38	(24.2)	
Mucinous	116	(36.3)	31	(19.8)	
Endometrioid/other	133	(41.6)	88	(56.1)	
Clear cell	-	-	-	-	
Grade					<0.001
1	162	(50.6)	46	(29.3)	
2	158	(49.4)	111	(70.7)	
3	-	-	-	-	
Unknown	-	-	-	-	
Stage					0.01
IA	301	(94.1)	137	(87.3)	
IB	19	(5.9)	20	(12.7)	
IC	-	-	-	-	
INOS	-	-	-	-	

Table 2

Univariate analysis of use and duration of use of chemotherapy for high-risk patients

	High-risk					Duration of chemotherapy for high-risk patients				
	No chemotherapy		Chemotherapy			≤3 months		4-8 months		
	N	(%)	N	(%)	*P-value*	N	(%)	N	(%)	*P-value*
	212	(28.1)	542	(71.9)		215	(44.2)	271	(55.8)	
Age (years)					<0.001					0.45
65-69	32	(15.1)	172	(31.7)		64	(29.8)	94	(34.7)	
70-74	39	(18.4)	187	(34.5)		79	(36.7)	84	(31.0)	
75-79	45	(21.2)	105	(19.4)		40	(18.6)	57	(21.0)	
≥80	96	(45.3)	78	(14.4)		32	(14.9)	36	(13.3)	
Race					0.10					0.24
White	184	(86.8)	498	(91.9)		200	(93.0)	246	(90.8)	
Black	11	(5.2)	19	(3.5)		*	*	*	*	
Other/unknown	17	(8.0)	25	(4.6)		*	*	*	*	
Year of diagnosis					0.68					0.20
1992-1996	43	(20.3)	101	(18.6)		32	(14.9)	60	(22.1)	
1997-2001	54	(25.5)	126	(23.3)		54	(25.1)	59	(21.8)	
2002-2005	57	(26.9)	143	(26.4)		62	(28.8)	67	(24.7)	
2006-2009	58	(27.4)	172	(31.7)		67	(31.2)	85	(31.4)	
Marital status					<0.001					0.17
Married	78	(36.8)	277	(51.1)		119	(55.4)	133	(49.1)	
Unmarried/unknown	134	(63.2)	265	(48.9)		96	(44.7)	138	(50.9)	
Area of residence					0.15					0.98
Metropolitan	184	(86.8)	490	(90.4)		195	(90.7)	246	(90.8)	
Non-metropolitan	28	(13.2)	52	(9.6)		20	(9.3)	25	(9.2)	
SEER registry					0.41					0.35
Eastern	43	(20.3)	130	(24.0)		45	(20.9)	72	(26.6)	
Midwest	90	(42.5)	234	(43.2)		97	(45.1)	114	(42.1)	
West	79	(37.3)	178	(32.8)		73	(34.0)	85	(31.4)	

	High-risk					Duration of chemotherapy for high-risk patients				
	No chemotherapy		Chemotherapy			≤3 months		4-8 months		
	N	(%)	N	(%)	*P-value*	N	(%)	N	(%)	*P-value*
Socioeconomic status					0.002					0.02
Lowest (first) quintile	34	(16.0)	55	(10.2)		15	(7.0)	31	(11.4)	
Second quintile	47	(22.2)	89	(16.4)		35	(16.3)	44	(16.2)	
Third quintile	51	(24.1)	126	(23.3)		62	(28.8)	49	(18.1)	
Fourth quintile	45	(21.2)	115	(21.2)		38	(17.7)	68	(25.1)	
Highest (fifth) quintile/unknown	35	(16.5)	157	(29.0)		65	(30.2)	79	(29.2)	
Comorbidity score					0.001					0.14
0	127	(59.9)	377	(69.6)		142	(66.1)	193	(71.2)	
1	46	(21.7)	119	(22.0)		57	(26.5)	52	(19.2)	
≥2	39	(18.4)	46	(8.5)		16	(7.4)	26	(9.6)	
Lymphadenectomy					<0.001					0.001
No/unknown	135	(63.7)	246	(45.4)		79	(36.7)	139	(51.3)	
Yes	77	(36.3)	296	(54.6)		136	(63.3)	132	(48.7)	
Omentectomy					<0.001					0.60
No	90	(42.5)	150	(27.7)		55	(25.6)	75	(27.7)	
Yes	122	(57.6)	392	(72.3)		160	(74.4)	196	(72.3)	
Histology					0.20					0.75
Serous	61	(28.8)	196	(36.2)		78	(36.3)	101	(37.3)	
Mucinous	24	(11.3)	60	(11.1)		21	(9.8)	32	(11.8)	
Endometrioid	45	(21.2)	119	(22.0)		44	(20.5)	61	(22.5)	
Clear cell	54	(25.5)	118	(21.8)		49	(22.8)	55	(20.3)	
Other	28	(13.2)	49	(9.0)		23	(10.7)	22	(8.1)	
Grade					0.13					0.83
1	22	(10.4)	39	(7.2)		14	(6.5)	21	(7.8)	
2	29	(13.7)	102	(18.8)		37	(17.2)	52	(19.2)	
3	116	(54.7)	308	(56.8)		129	(60.0)	152	(56.1)	
Unknown	45	(21.2)	93	(17.2)		35	(16.3)	46	(17.0)	

	High-risk					Duration of chemotherapy for high-risk patients				
	No chemotherapy		Chemotherapy			≤3 months		4-8 months		
	N	(%)	N	(%)	*P-value*	N	(%)	N	(%)	*P-value*
Stage					<0.001					0.003
IA	100	(47.2)	164	(30.3)		84	(39.1)	65	(24.0)	
IB	*	*	29	(5.4)		*	*	*	*	
IC	98	(46.2)	336	(62.0)		119	(55.4)	181	(66.8)	
INOS	*	*	13	(2.4)		*	*	*	*	

* Cell ≤10.

Table 3
Multivariable logistic regression model of predictors of receipt of chemotherapy

	Low risk patients	High risk patients	High risk patients who received chemotherapy, duration >3 months
Age (years)			
65-69	Referent	Referent	Referent
70-74	0.73 (0.41-1.31)	0.90 (0.52-1.55)	0.76 (0.47-1.23)
75-79	0.70 (0.38-1.27)	0.44 (0.25-0.76)*	1.14 (0.64-2.01)
≥80	0.31 (0.16-0.60)*	0.14 (0.08-0.24)*	0.74 (0.38-1.45)
Race			
White	Referent	Referent	Referent
Black	0.78 (0.29-2.08)	0.92 (0.36-2.33)	0.53 (0.17-1.64)
Other/unknown	0.89 (0.33-2.40)	0.74 (0.34-1.60)	2.30 (0.79-6.71)
Year of diagnosis			
1992-1996	Referent	Referent	Referent
1997-2001	2.36 (1.19-4.66)*	0.93 (0.53-1.63)	0.47 (0.25-0.88)*
2002-2005	3.14 (1.58-6.25)*	1.27 (0.72-2.25)	0.50 (0.27-0.93)*
2006-2009	3.31 (1.63-6.70)*	1.10 (0.63-1.91)	0.67 (0.37-1.23)
Marital status			
Married	Referent	Referent	Referent
Unmarried	0.88 (0.56-1.38)	0.82 (0.56-1.20)	1.34 (0.89-2.03)
Unknown	0.49 (0.11-2.23)	1.66 (0.55-5.06)	1.38 (0.50-3.77)
Area of residence			
Metropolitan	Referent	Referent	Referent
Non-metropolitan	0.31 (0.12-0.82)*	1.16 (0.61-2.21)	1.03 (0.48-2.21)
SEER registry			
Eastern	Referent	Referent	Referent
Midwest	0.95 (0.53-1.71)	0.83 (0.50-1.40)	0.68 (0.40-1.16)
West	0.69 (0.37-1.28)	0.73 (0.44-1.22)	0.62 (0.36-1.07)
Socioeconomic status			
Lowest (first) quintile	Referent	Referent	Referent
Second quintile	1.10 (0.46-2.62)	0.73 (0.37-1.43)	0.53 (0.22-1.27)
Third quintile	1.35 (0.56-3.25)	1.01 (0.52-1.95)	0.28 (0.12-0.68)*
Fourth quintile	1.38 (0.56-3.43)	0.83 (0.42-1.66)	0.69 (0.28-1.68)
Highest (fifth) quintile/unknown	1.10 (0.44-2.72)	1.65 (0.82-3.32)	0.48 (0.21-1.13)
Comorbidity score			
0	Referent	Referent	Referent
1	0.42 (0.24-0.74)*	1.19 (0.76-1.87)	0.70 (0.43-1.13)
≥2	0.89 (0.46-1.76)	0.39 (0.22-0.67)*	1.23 (0.59-2.55)
Lymphadenectomy			
No	Referent	Referent	Referent

	Low risk patients	High risk patients	High risk patients who received chemotherapy, duration >3 months
Yes	1.19 (0.75-1.89)	1.47 (0.99-2.17)	0.51 (0.34-0.79)*
Unknown	0.65 (0.19-2.16)	0.58 (0.26-1.27)	0.97 (0.36-2.64)
Histology			
Serous	Referent	Referent	Referent
Mucinous	0.71 (0.37-1.35)	0.91 (0.47-1.77)	0.96 (0.48-1.91)
Endometrioid	1.19 (0.67-2.11)	0.75 (0.45-1.27)	1.17 (0.68-2.01)
Clear cell	-	0.75 (0.42-1.36)	1.06 (0.56-2.01)
Other	1.43 (0.52-3.92)	0.58 (0.31-1.09)	0.45 (0.21-0.93)*
Grade			
1	Referent	Referent	Referent
2	2.28 (1.43-3.63)*	2.13 (1.00-4.54)*	1.05 (0.44-2.47)
3	-	2.31 (1.14-4.68)*	1.21 (0.54-2.73)
Unknown	-	1.51 (0.69-3.29)	1.20 (0.47-3.06)
Stage			
IA	Referent	Referent	Referent
IB	2.69 (1.26-5.74)*	1.46 (0.64-3.36)	2.07 (0.77-5.52)
IC	-	2.52 (1.59-3.97)*	2.22 (1.37-3.59)*
INOS	-	4.14 (1.04-16.58)*	4.86 (1.19-19.87)*

*P<0.05

Table 4

Impact of use of chemotherapy in low-risk and high-risk patients and duration of chemotherapy in high-risk patients on survival

	Overall survival	Cancer-specific survival
Use of chemotherapy in low-risk patients	0.93 (0.65-1.33)	1.62 (0.74-3.56)
Use of chemotherapy in high-risk patients	0.70 (0.53-0.91)*	0.89 (0.59-1.35)
Long versus short duration chemotherapy in high-risk patients	0.93 (0.67-1.27)	0.93 (0.61-1.42)

Hazard ratio (95% confidence interval).

*P<0.05

Adjusted for age, race, year of diagnosis, marital status, area of residence, SEER registry, SES, comorbidity, lymphadenectomy, histology, grade, and stage.