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Adherence to Treatment Recommendations and Outcomes for Women with Ovarian Cancer at First Recurrence

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Abstract

Objective—Treatment selection for recurrent ovarian cancer is typically based on the duration of time between the completion of adjuvant, platinum-based therapy and the time of recurrence, the platinum free interval (PFI). We examined the use of, and outcomes associated with platinum-based chemotherapy based on the PFI in women with recurrent ovarian cancer.

Methods—The Surveillance, Epidemiology, and End Results-Medicare database was used to identify women aged >65 years with epithelial ovarian cancer who underwent surgery and platinum-based chemotherapy and who developed a recurrence >3 months after the completion of adjuvant therapy. Patients were stratified by PFI into 3 groups: PFI <6 months, PFI 7–12 months, and PFI >12 months. Multivariable models were used to examine predictors of use of platinum-based therapy and survival for each group.

Results—A total of 2,369 patients were identified. In women with a PFI of ≤6 months, treatment consisted of platinum-based combination therapy in 28.2%, single agent platinum in 5.2% and non-platinum therapy in 66.6%. Corresponding rates of these treatments among women with a PFI of 7–12 months were 39.7%, 12.4% and 47.9%, respectively; the rates were 57.6%, 13.2% and 29.3% in those with a PFI of >12 months, respectively. Median survival was 13, 18, and 27 months for patients with a PFI of ≤6 months, 7–12 months, and >12 months, respectively (P<0.0001). For all three groups, platinum combination therapy was associated with decreased risk of death compared to non-platinum based therapy.

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Conclusion—Platinum free interval is a strong predictor of survival in elderly women with recurrent ovarian cancer. There is widespread variation in treatment selection for women with recurrent ovarian cancer with many women receiving non-guideline based regimens.

Introduction

Despite a high initial response rate to surgery and chemotherapy, women with ovarian cancer are at significant risk for recurrence following primary treatment. Among patients with early-stage ovarian cancer, 25% will have a recurrence, and 80% of patients with advanced disease will recur.¹ A wide variety of cytotoxic and biologic agents are now available for the treatment of women with recurrent ovarian cancer.^{2–4}

Treatment selection for recurrent ovarian cancer is typically based on the duration of time between the completion of adjuvant platinum-based therapy and the time of recurrence, the so-called platinum free interval (PFI).^{5,6} Those women who have a short PFI are less likely to respond to retreatment with platinum-based therapy, while patients with a longer PFI are more likely to respond.⁷ The PFI is also an important prognostic factor; a longer PFI is associated with improved survival.⁸

Women with recurrent ovarian cancer and a PFI of ≤ 6 months are typically classified as platinum resistant and recommendations are for treatment with non-platinum based chemotherapy. Those women with a PFI of >6 months are considered to have platinum sensitive disease and treatment recommendations generally encourage retreatment with platinum-based therapy, usually platinum-based combination therapy. Patients with a long PFI (>12 months) have the highest response rate to platinum retreatment and thus the strongest rationale for receiving such therapy.^{5,9}

Despite the availability of treatment recommendations for women with recurrent ovarian cancer based on PFI, little is known about the actual patterns of care for women with ovarian cancer in the general population. We performed a population-based analysis in elderly women with recurrent ovarian cancer to determine the use and outcomes of platinum-based chemotherapy based on clinical characteristics and the length of the platinum free interval.

Methods

Data Source

We used the Surveillance, Epidemiology, and End Results (SEER)-Medicare database for the analysis.^{10–16} The SEER program is a population-based tumor registry maintained by the National Cancer Institute that currently covers approximately 28% of the US population.¹⁷ SEER captures data on date of cancer diagnosis, tumor histology, location, stage, treatment, and survival, as well as demographic and selected census tract-level information. Using a matching algorithm, 93–94% of SEER patients diagnosed at age 65 or older are linked to Medicare health care claims.^{18,19} The Medicare claims database captures information on patients with Medicare part A (inpatient) and part B (outpatient), including billed claims, services, and diagnoses. These two files are linked and provide data on initial services and

all follow-up care longitudinally. Exemption from the Columbia University Institutional Review Board was obtained.

Cohort Selection

Women aged 65 years or older with epithelial ovarian cancer were selected. Patients who were diagnosed between January 1, 1992 and December 31, 2009, and received cancer directed surgery from one month before to within 6 months of diagnosis were included. The cohort was limited to women who underwent surgery for ovarian cancer and received combination platinum- and taxane-based chemotherapy after surgery. Patients may have received preoperative (neoadjuvant) chemotherapy in addition to postoperative chemotherapy. Patients who received adjuvant chemotherapy for more than 8 months were excluded. The study specifically focused on treatment of women with recurrent ovarian cancer. We therefore selected patients who initiated second line chemotherapy 3 months after completion of adjuvant treatment. Patients with incomplete claims, such as those who enrolled in a non-Medicare health maintenance organization, those receiving Medicare for a reason other than age, and patients with other primary cancers were excluded (Figure 1).

Patient Characteristics

Age at diagnosis was stratified into 5-year intervals and race was recorded as white, black, and other. Marital status was recorded as married, not married, and unknown. An aggregate socioeconomic status (SES) score was calculated from education, poverty level, and income information from the 2000 census tract data, as previously reported by Du and co-workers.²⁰ The SES 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. The prevalence of comorbid medical diseases was assessed using the Klabunde adaptation of the Charlson comorbidity index (ie, the Klabunde–Charlson index).^{21,22} Medicare claims were examined for diagnostic codes of the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM). Each condition was weighted, and patients were assigned a score that was based on the Klabunde–Charlson index.²² Area of residence was categorized as metropolitan or nonmetropolitan. The SEER registries were grouped as: Eastern, Western and Midwest. Stage was captured using the American Joint Cancer Commission staging criteria. Tumor histology was classified as serous, mucinous, endometrioid, clear cell or other. Tumor grade was grouped as well (1), moderately (2) or poorly differentiated, (3) or unknown.

Treatment and Outcomes

To identify ovarian cancer directed surgery and chemotherapy use, we extracted claims from the Medicare files by searching the Level II Healthcare Common Procedure Coding System codes, Current Procedural Terminology (CPT) codes, and ICD-9-CM diagnostic and procedure codes from Medicare provider and analysis review files, physician claims files, and the hospital outpatient claims files. In addition, revenue center codes were also added when querying chemotherapy data. Cancer directed surgery included any procedure claims for oophorectomy, hysterectomy, oophorectomy and debulking, exenteration, or debulking from 1 month before to 6 months after cancer diagnosis.

If a patient had any chemotherapy claims prior to cancer directed surgery, she was coded as having received neoadjuvant chemotherapy. If a patient had at least one claim for chemotherapy within 90 days of surgery, she was coded as having received postoperative chemotherapy. The duration of initial chemotherapy was calculated from the date of first chemotherapy claim after surgery through the date of last claim without a break of more than 3 months between any two claims. The duration of adjuvant chemotherapy was classified as 1–4, 5–6, and 7–8 months. If a patient had any chemotherapy claims at 3 or more months after the completion of first treatment, she was coded as having received second course of chemotherapy post-surgery. The interval from first to second chemotherapy course (platinum free interval, PFI) was categorized as 6, 7–12, and >12 months. The second course of chemotherapy was classified as single agent platinum if cisplatin, carboplatin or oxaliplatin were used alone. If a second agent was given concurrently, the patient was classified as having received platinum combination therapy. Receipt of any non-platinum containing single or multiagent regimen was considered as non-platinum chemotherapy. The primary outcome was survival. Survival was measured as the time from initiation of the second chemotherapy to death from any cause.

Statistical Analysis

Frequency distributions between categorical variables were compared using χ^2 tests or Fisher's exact test. Multivariable log-linear regression models were developed to determine predictors for the single agent and combination platinum-based second line chemotherapy. Separate models were developed for each platinum free interval group. The effect of the PFI on mortality and the effect of the chemotherapy regimens on mortality at each interval were examined using the method of Kaplan-Meier. Log-rank tests were used to compare the difference of survival curves. Cox proportional hazards models were developed to explore the association between second line chemotherapy and mortality while controlling for patients' demographics and clinical covariates at each time interval. The proportional hazards assumption was tested by examining the scaled Schoenfeld model residuals, as well as by a visual inspection of the mortality curves among groups. 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

A total of 2,369 patients were identified. The cohort included 560 (23.6%) patients who restarted chemotherapy within 3–6 months, 723 (30.5%) who initiated therapy within 7–12 months, and 1086 (45.8%) who restarted treatment >12 months after their initial chemotherapy (Table 1). The median time from completion of adjuvant chemotherapy until initiation of second line chemotherapy was 12 months (IQR 7–20 months) (Figure 2). The majority of patients had advanced stage tumors (60.9% stage III and 25.6% stage IV) at the time of diagnosis.

Early recurrences (PFI <6 months) were more frequent in women treated more recently, in women with higher stage tumors at diagnosis, in those treated with neoadjuvant chemotherapy, and in patients with a longer duration of adjuvant chemotherapy (P<0.05 for

all). In women with a PFI of ≤ 6 months, treatment consisted of platinum-based combination therapy in 28.2%, single agent platinum in 5.2% and non-platinum therapy in 66.6%. Corresponding rates of these treatments among women with a PFI of 7–12 months were 39.7%, 12.4% and 47.9% and 57.6%, 13.2% and 29.3% in those with a PFI of >12 months.

There were few consistent clinical and demographic characteristics associated with treatment received across the groups (Table 2). For women with a PFI of 7–12 or >12 months, none of the clinical, demographic or tumor characteristics were associated with platinum-based therapy. Among women with a PFI of ≤ 6 months, women treated more recently, those who received neoadjuvant chemotherapy, and patients whose adjuvant treatment lasted 5–6 months were less likely to receive platinum-based therapy ($P<0.05$ for all).

The median survival time for the cohort after initiation of second line chemotherapy was 21 months. Earlier recurrence was associated with decreased survival time. Median survival was 13, 18, and 27 months for patients with a PFI of ≤ 6 months, 7–12 months, and >12 months, respectively ($P<0.0001$) (Figure 3). For all three groups, platinum combination therapy was associated with decreased risk of death compared to non-platinum based therapy: HR=0.59 (95% CI, 0.48–0.74) for PFI ≤ 6 months, HR=0.75 (95% CI, 0.62–0.89) for PFI 7–12 months and HR=0.54 (95% CI, 0.47–0.63) for PFI >12 months (Table 3). For women with a PFI of >12 months, single agent platinum therapy was associated with a reduced risk of death compared to non-platinum based therapy (HR=0.75; 95% CI, 0.60–0.94). There was no statistically significant difference in survival between non-platinum and single agent platinum therapy for those with a PFI of ≤ 6 months and 7–12 months.

Discussion

Among elderly women with ovarian cancer, the median survival time after initiation of second line chemotherapy is 21 months. Platinum free interval is a strong predictor of survival in this population. There is widespread variation in treatment selection for women with recurrent ovarian cancer with many women with platinum resistant disease receiving platinum-based therapy and likewise, many women with platinum sensitive disease are treated with non-platinum containing regimens.

Combination platinum and taxane therapy is the standard of care for primary therapy of epithelial ovarian, fallopian tube, and primary peritoneal cancer.^{5,23,24} Treatment selection for recurrent cancers is partly dependent on whether the cancer is likely to be platinum-sensitive or platinum-resistant. Cancers that recur within 6 months after an initial treatment that included platinum, are considered platinum resistant.⁹ Recommended chemotherapy for these patients typically relies on non-platinum based therapy including single agent therapy with taxanes,²⁵ topoisomerase inhibitors,²⁶ the antimetabolite gemcitabine,²⁷ or liposomal doxorubicin among other therapies. Conversely, patients with a recurrence after a platinum free interval of 6 months, are considered platinum-sensitive. Appropriate treatment in this circumstance is either a platinum combination regimen, or platinum alone if side effects are a concern.^{3,5,28,29}

Our data supports previous findings of the association between the duration of initial PFI and outcomes after second line chemotherapy.³⁰ In one of the initial studies of PFI, Markman and colleagues reported response rates of <30% in patients with a PFI of 12 months or less compared to a response rate of 59% in those with a PFI of >24 months⁷. While we are unable to assess response rates, among elderly women with ovarian cancer survival increased with the duration of PFI from 13 months in those with a PFI of <6 months to 27 months in women with a PFI of >12 months.

Like prior studies, we noted widespread variation in treatment for relapsed ovarian cancer.^{10,31} Nearly one-third of the patients in our cohort with likely platinum-sensitive cancers did not receive platinum, and one-third of patients with likely platinum-resistant cancers were retreated with platinum. Platinum use for patients with platinum-resistant cancers has the potential to increase adverse effects without improving clinical response to treatment.³² In our analysis, there were few predictors of non-guideline based treatment. Further study to identify factors associated with non-guideline based care is clearly needed. Prior studies for ovarian cancer have found that patients treated by high volume surgeons and at high volume centers are more likely to receive guideline-based care.^{33,34}

We noted that treatment with platinum-based therapy was associated with improved survival for women with recurrent ovarian cancer.³⁰ For women with a PFI of >12 months, platinum retreatment was associated with a 25–46% reduction in mortality compared to non-platinum based therapy. These data confirm that in elderly women, platinum-based combination therapy is superior to single agent platinum therapy.²⁸ Interestingly, we also noted that survival in women with platinum resistant ovarian cancer was superior with platinum-based therapy compared to non-platinum based regimens. While these results are likely influenced by some degree of selection bias, this finding warrants further study. There has been some evidence of the utility of re-treating with platinum in platinum resistant patients.^{35–38}

While our study benefits from the inclusion of a large number of women, we recognize a number of important limitations. First, chemotherapy use may have been under captured or the platinum free interval miscalculated in a small number of patients. Our data relies on billing claims and is thus subject to some variability in capture. We relied on the date of initiation of second line chemotherapy as opposed to the date of diagnosis of recurrence to calculate the platinum free interval. This is an intrinsic limitation of the dataset. Second, our analysis is limited to elderly women and as such, these findings may be different in younger women. Third, we only included women with recurrent disease who were treated with salvage chemotherapy thus our sample represents a somewhat selected population. While the goal of our analysis was to examine outcomes in women treated with chemotherapy, we acknowledge that there are likely many women who recurred and did not receive treatment. Fourth, while we adjusted for a number of clinical, demographic, and pathologic characteristics, there are likely a number of unmeasured confounders such as performance status, residual tumor burden, and residual toxicity that we could not account for that likely influenced treatment decision making and outcomes. Finally, our study spanned several years in which available treatment options for ovarian cancer evolved. During this time the use of neoadjuvant chemotherapy became more widespread and a number of new

therapeutic options were introduced for recurrent ovarian cancer. All of these factors could have influenced our findings.

In conclusion, we noted widespread variation in the patterns of care of women with recurrent ovarian cancer. Our results support an association between platinum free interval and overall survival. We found that non-guideline based treatment was common, but there were few identifiable significant predictors for this. These findings have a number of implications for the care of women with ovarian cancer. First, further study is warranted to identify factors affecting chemotherapy selection choice outside of standard guidelines for recurrent ovarian cancer. More importantly, initiatives are needed to promote adherence to evidence-based recommendations for women with recurrent ovarian cancer.

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Research Highlights

- Platinum free interval is a strong predictor of survival in elderly women with recurrent ovarian cancer.
- There is widespread variation in treatment selection for women with recurrent ovarian cancer.
- Many women receiving non-guideline based regimens.

Figure 1.
Flowchart for cohort selection.

Figure 2. Duration of platinum free interval between completion of adjuvant therapy and initiation of salvage therapy.

Figure 3.
Kaplan-Meier curves of survival based on platinum free interval.

Table 1

Clinical characteristics of the cohort stratified by platinum free interval.

Total (n=2369)									3–6 months (n=560)		7–12 months (n=723)		>12 months (n=1086)		P-value	
									n	(%)	n	(%)	n	(%)		
Demographics and clinical factors																
Age																
65–69	662 (27.9)									164	(29.3)	199	(27.5)	299	(27.5)	0.492
70–74	830 (35)									197	(35.2)	236	(32.6)	397	(36.6)	
75–79	589 (24.9)									137	(24.5)	188	(26)	264	(24.3)	
>80	288 (12.2)									62	(11.1)	100	(13.8)	126	(11.6)	
Race/ethnicity																
White	2,172 (91.7)									507	(90.5)	654	(90.5)	1,011	(93.1)	0.2573
Black	101 (4.3)									28	(5)	35	(4.8)	38	(3.5)	
Other/Unknown	96 (4.1)									25	(4.5)	34	(4.7)	37	(3.4)	
Marital status																
Married	1,298 (54.8)									313	(55.9)	397	(54.9)	588	(54.1)	0.0867
Unmarried	1,015 (42.8)									235	(42)	300	(41.5)	480	(44.2)	
Other	56 (2.4)									12	(2.1)	26	(3.6)	18	(1.7)	
Residence																
Non-metropolitan	227 (9.6)									56	(10)	71	(9.8)	100	(9.2)	0.8456
Metropolitan	2,142 (90.4)									504	(90)	652	(90.2)	986	(90.8)	
Socioeconomic status																
Lowest (first) quintile	447 (18.9)									121	(21.6)	139	(19.2)	187	(17.2)	0.3784
Second quintile	491 (20.7)									106	(18.9)	141	(19.5)	244	(22.5)	
Third quintile	377 (15.8)									81	(14.5)	125	(17.3)	171	(15.8)	
Fourth quintile	565 (23.8)									133	(23.8)	179	(24.8)	253	(23.3)	
Highest (fifth) quintile	489 (20.6)									119	(21.3)	139	(19.2)	231	(21.3)	
Registry area																
Eastern	518 (21.9)									111	(19.8)	174	(24.1)	233	(21.5)	0.2041
Midwest	923 (39)									217	(38.8)	289	(40)	417	(38.4)	
West	928 (39.2)									232	(41.4)	260	(36)	436	(40.1)	

	Total (n=2369)		3–6 months (n=560)		7–12 months (n=723)		>12 months (n=1086)		P-value
	n	(%)	n	(%)	n	(%)	n	(%)	
Diagnosis year									<.0001
1993–1998	281	(11.9)	56	(10)	66	(9.1)	159	(14.6)	
1999–2004	1222	(51.6)	277	(49.5)	357	(49.4)	588	(54.1)	
2005–2009	866	(36.6)	227	(40.5)	300	(41.5)	339	(31.2)	
Comorbidity Score									0.5083
0	1,650	(69.6)	383	(68.4)	497	(68.7)	770	(70.9)	
1	492	(20.8)	123	(22)	147	(20.3)	222	(20.4)	
>=2	227	(9.6)	54	(9.6)	79	(10.9)	94	(8.7)	
Histology									0.2778
Serous	1,793	(75.7)	439	(78.4)	550	(76.1)	804	(74)	
Endometrioid	161	(6.8)	25	(4.5)	49	(6.8)	87	(8)	
Clear Cell or Mucinous	86	(3.6)	20	(3.6)	21	(2.9)	45	(4.1)	
Other	329	(13.9)	76	(13.6)	103	(14.2)	150	(13.8)	
Stage									<.0001
I or II	243	(10.2)	29	(5.2)	47	(6.5)	167	(15.3)	
III	1,443	(60.9)	331	(59.1)	456	(63.1)	656	(60.4)	
IV	607	(25.6)	185	(33)	196	(27.1)	226	(20.8)	
Unknown	76	(3.2)	15	(2.7)	24	(3.3)	37	(3.4)	
Grade									0.0016
1 or 2	422	(17.8)	85	(15.2)	124	(17.1)	213	(19.6)	
3	1,573	(66.4)	386	(68.9)	454	(62.8)	733	(67.5)	
Unknown	374	(15.8)	89	(15.9)	145	(20.1)	140	(12.9)	
Hospital Control									0.2758
Nonprofit	1,688	(71.3)	407	(72.7)	499	(69)	782	(72)	
Private	180	(7.6)	43	(7.7)	53	(7.3)	84	(7.7)	
Government	317	(13.4)	64	(11.4)	117	(16.2)	136	(12.5)	
Unknown	184	(7.8)	46	(8.2)	54	(7.5)	84	(7.7)	
Hospital Bed Sizes									0.1755
<400	1,194	(50.4)	282	(50.4)	337	(46.6)	575	(52.9)	
400–600	662	(27.9)	157	(28)	226	(31.3)	279	(25.7)	

	Total (n=2369)		3–6 months (n=560)		7–12 months (n=723)		>12 months (n=1086)		P-value
	n	(%)	n	(%)	n	(%)	n	(%)	
>600	329	(13.9)	75	(13.4)	106	(14.7)	148	(13.6)	
Unknown	184	(7.8)	46	(8.2)	54	(7.5)	84	(7.7)	
Teaching Hospital									0.0916
No	558	(23.6)	151	(27)	159	(22)	248	(22.8)	
Yes	1,502	(63.4)	345	(61.6)	476	(65.8)	681	(62.7)	
Unknown	309	(13)	64	(11.4)	88	(12.2)	157	(14.5)	
Initial treatment									<.0001
Neoadjuvant chemotherapy	294	(12.4)	89	(15.9)	116	(16)	89	(8.2)	
Initial chemotherapy duration (months)									<.0001
1 to 4	985	(41.6)	208	(37.1)	325	(45)	452	(41.6)	
5 to 6	1109	(46.8)	262	(46.8)	321	(44.4)	526	(48.4)	
7 to 8	275	(11.6)	90	(16.1)	77	(10.7)	108	(9.9)	
Recurrent chemotherapy regimen									<.0001
Platinum combination	1070	(45.2)	158	(28.2)	287	(39.7)	625	(57.6)	
Platinum alone	262	(11.1)	29	(5.2)	90	(12.4)	143	(13.2)	
Non-platinum	1037	(43.8)	373	(66.6)	346	(47.9)	318	(29.3)	

Table 2

Predictors of use of platinum-based chemotherapy based on platinum free interval.

	3–6 months			7–12 months			>12 months		
	Any Platinum RR (95%CI)	Platinum Combination RR (95%CI)	Referent	Any Platinum RR (95%CI)	Platinum Combination RR (95%CI)	Referent	Any Platinum RR (95%CI)	Platinum Combination RR (95%CI)	Referent
Age									
65–69	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent
70–74	1.25 (0.85, 1.83)	1.13 (0.75, 1.71)		0.99 (0.76, 1.29)	1.17 (0.87, 1.58)		0.98 (0.82, 1.18)	0.90 (0.74, 1.09)	
75–79	1.26 (0.83, 1.91)	1.08 (0.68, 1.70)		0.92 (0.69, 1.22)	0.96 (0.69, 1.34)		0.89 (0.72, 1.09)	0.82 (0.66, 1.03)	
80	1.49 (0.89, 2.50)	1.72 (1.01, 2.92)*		1.01 (0.72, 1.41)	0.95 (0.64, 1.43)		1.02 (0.79, 1.31)	0.80 (0.60, 1.06)	
Race/ethnicity									
White	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent
Black	1.51 (0.80, 2.83)	1.51 (0.76, 3.00)		0.94 (0.57, 1.57)	0.96 (0.55, 1.69)		0.87 (0.57, 1.33)	0.90 (0.57, 1.44)	
Other/Unknown	1.23 (0.65, 2.32)	1.17 (0.57, 2.41)		0.73 (0.42, 1.28)	0.64 (0.33, 1.23)		1.10 (0.75, 1.63)	0.95 (0.60, 1.50)	
Marital status									
Married	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent
Unmarried	0.93 (0.68, 1.26)	0.86 (0.61, 1.20)		1.12 (0.90, 1.39)	1.21 (0.95, 1.55)		1.00 (0.86, 1.16)	1.00 (0.85, 1.18)	
Other	0.74 (0.23, 2.39)	0.91 (0.28, 2.97)		1.41 (0.84, 2.37)	1.46 (0.79, 2.70)		1.19 (0.71, 1.99)	1.03 (0.56, 1.90)	
Residence									
Non-metropolitan	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent
Metropolitan	1.06 (0.61, 1.84)	1.05 (0.58, 1.88)		0.88 (0.62, 1.24)	0.93 (0.63, 1.37)		0.95 (0.73, 1.24)	0.85 (0.64, 1.13)	
Socioeconomic status									
Lowest (first) quintile	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent
Second quintile	0.96 (0.61, 1.53)	0.94 (0.57, 1.55)		1.29 (0.93, 1.78)	1.34 (0.94, 1.92)		0.97 (0.76, 1.23)	0.98 (0.75, 1.27)	
Third quintile	0.75 (0.43, 1.31)	0.72 (0.39, 1.32)		1.03 (0.72, 1.48)	0.99 (0.66, 1.48)		1.00 (0.77, 1.31)	0.98 (0.73, 1.31)	
Fourth quintile	0.79 (0.49, 1.27)	0.80 (0.48, 1.32)		0.98 (0.69, 1.38)	0.84 (0.57, 1.26)		1.00 (0.78, 1.29)	1.01 (0.76, 1.33)	
Highest (fifth) quintile	1.02 (0.63, 1.64)	0.91 (0.53, 1.54)		1.04 (0.73, 1.50)	0.90 (0.59, 1.36)		1.04 (0.80, 1.35)	0.98 (0.74, 1.31)	
Registry area									
Eastern	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent
Midwest	1.37 (0.85, 2.21)	1.49 (0.87, 2.54)		1.21 (0.90, 1.63)	1.21 (0.85, 1.72)		1.13 (0.91, 1.40)	1.05 (0.83, 1.33)	
West	1.65 (1.05, 2.59)*	1.84 (1.11, 3.04)*		1.30 (0.97, 1.75)	1.38 (0.98, 1.95)		1.05 (0.85, 1.28)	1.05 (0.84, 1.32)	

	3–6 months			7–12 months			>12 months		
	Any Platinum RR (95%CI)	Platinum Combination RR (95%CI)	Referent	Any Platinum RR (95%CI)	Platinum Combination RR (95%CI)	Referent	Any Platinum RR (95%CI)	Platinum Combination RR (95%CI)	Referent
	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent
Diagnosis year									
1993–1998									
1999–2004	0.63 (0.41, 0.97)*	0.83 (0.50, 1.37)		0.79 (0.56, 1.11)	1.03 (0.66, 1.60)		1.04 (0.84, 1.30)	1.08 (0.84, 1.38)	
2005–2009	0.52 (0.33, 0.82)*	0.68 (0.40, 1.14)		0.78 (0.54, 1.11)	1.18 (0.75, 1.86)		1.11 (0.87, 1.40)	1.20 (0.92, 1.56)	
Comorbidity Score									
0	Referent	Referent		Referent	Referent		Referent	Referent	
1	1.07 (0.74, 1.55)	1.22 (0.80, 1.85)		1.09 (0.83, 1.43)	1.13 (0.83, 1.55)		1.05 (0.87, 1.26)	1.05 (0.86, 1.29)	
2	1.24 (0.69, 2.23)	1.27 (0.67, 2.43)		0.99 (0.66, 1.48)	1.09 (0.69, 1.71)		1.04 (0.78, 1.39)	0.96 (0.69, 1.33)	
Histology									
Serous	Referent	Referent		Referent	Referent		Referent	Referent	
Mucinous	1.24 (0.43, 3.60)	1.50 (0.51, 4.36)		1.07 (0.42, 2.70)	1.41 (0.49, 4.00)		0.79 (0.44, 1.42)	0.79 (0.41, 1.51)	
Endometrioid	1.45 (0.78, 2.70)	1.38 (0.69, 2.75)		0.85 (0.54, 1.32)	0.77 (0.45, 1.31)		0.92 (0.70, 1.22)	0.97 (0.71, 1.31)	
Clear Cell	1.26 (0.49, 3.23)	1.63 (0.63, 4.25)		0.95 (0.42, 2.15)	1.06 (0.46, 2.45)		1.18 (0.74, 1.87)	1.26 (0.76, 2.08)	
Other	0.83 (0.53, 1.30)	0.95 (0.59, 1.53)		1.09 (0.82, 1.46)	0.96 (0.68, 1.37)		0.98 (0.79, 1.22)	1.08 (0.85, 1.36)	
Stage									
I	Referent	Referent		Referent	Referent		Referent	Referent	
II	2.10 (0.41, 10.80)	1.97 (0.37, 10.53)		0.92 (0.43, 1.93)	0.88 (0.38, 2.01)		1.01 (0.70, 1.47)	0.89 (0.59, 1.35)	
III	1.51 (0.32, 7.02)	1.34 (0.28, 6.46)		0.70 (0.37, 1.31)	0.67 (0.33, 1.34)		0.95 (0.70, 1.29)	0.92 (0.66, 1.29)	
IV	1.69 (0.36, 7.98)	1.68 (0.34, 8.17)		0.72 (0.37, 1.38)	0.69 (0.34, 1.43)		0.93 (0.66, 1.30)	0.95 (0.66, 1.36)	
Unknown	1.62 (0.27, 9.76)	0.95 (0.13, 6.76)		0.60 (0.25, 1.43)	0.36 (0.12, 1.12)		1.07 (0.67, 1.73)	1.00 (0.59, 1.71)	
Grade									
1	Referent	Referent		Referent	Referent		Referent	Referent	
2	0.89 (0.29, 2.69)	0.77 (0.25, 2.35)		1.01 (0.47, 2.17)	1.18 (0.45, 3.10)		1.10 (0.66, 1.83)	0.88 (0.53, 1.49)	
3	0.79 (0.27, 2.33)	0.65 (0.22, 1.96)		1.06 (0.51, 2.20)	1.23 (0.49, 3.10)		1.20 (0.74, 1.96)	0.98 (0.60, 1.60)	
Unknown	0.81 (0.26, 2.50)	0.72 (0.23, 2.26)		1.03 (0.48, 2.19)	1.31 (0.51, 3.39)		1.18 (0.70, 1.99)	0.99 (0.58, 1.69)	
Neoadjuvant chemotherapy									
No	Referent	Referent		Referent	Referent		Referent	Referent	
Yes	0.61 (0.38, 0.99)*	0.62 (0.37, 1.04)		0.98 (0.73, 1.32)	0.95 (0.68, 1.34)		0.97 (0.73, 1.29)	0.82 (0.59, 1.14)	

	3–6 months			7–12 months			>12 months		
	Any Platinum	Platinum Combination		Any Platinum	Platinum Combination		Any Platinum	Platinum Combination	
	RR (95%CI)	RR (95%CI)		RR (95%CI)	RR (95%CI)		RR (95%CI)	RR (95%CI)	
<i>Initial chemotherapy duration (months)</i>									
1 to 4	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent
5 to 6	0.56 (0.40, 0.78)*	0.53 (0.37, 0.75)*	0.86 (0.68, 1.07)	0.89 (0.69, 1.15)	0.97 (0.83, 1.14)	0.99 (0.83, 1.18)			
7 to 8	0.66 (0.42, 1.03)	0.63 (0.39, 1.02)	0.69 (0.47, 1.03)	0.74 (0.47, 1.16)	1.02 (0.79, 1.33)	1.01 (0.75, 1.34)			

* P<0.05,
** P<0.0001

Table 3

Cox proportional hazards models of predictors of survival based on platinum free interval.

	3–6 months HR (95%CI)	7–12 months HR (95%CI)	>12 months HR (95%CI)
Age			
65–69	Referent	Referent	Referent
70–74	1.03 (0.83, 1.29)	0.99 (0.80, 1.22)	1.25 (1.05, 1.50) *
75–79	1.29 (1.01, 1.66) *	1.22 (0.97, 1.52)	1.56 (1.28, 1.89) **
80	1.08 (0.78, 1.49)	1.14 (0.87, 1.49)	1.75 (1.37, 2.24) **
Race/ethnicity			
White	Referent	Referent	Referent
Black	0.93 (0.61, 1.43)	0.98 (0.67, 1.43)	0.87 (0.58, 1.32)
Other/Unknown	0.90 (0.57, 1.43)	0.72 (0.49, 1.06)	0.89 (0.61, 1.31)
Marital status			
Married	Referent	Referent	Referent
Unmarried	1.07 (0.88, 1.30)	0.94 (0.80, 1.11)	1.11 (0.96, 1.27)
Other	0.99 (0.51, 1.94)	1.10 (0.72, 1.69)	0.84 (0.47, 1.49)
Residence			
Non-metropolitan	Referent	Referent	Referent
Metropolitan	1.15 (0.81, 1.62)	1.07 (0.80, 1.43)	0.83 (0.64, 1.07)
Socioeconomic status			
Lowest (first) quintile	Referent	Referent	Referent
Second quintile	1.19 (0.88, 1.60)	0.92 (0.71, 1.19)	0.86 (0.69, 1.08)
Third quintile	1.05 (0.76, 1.46)	1.04 (0.79, 1.36)	0.99 (0.77, 1.27)
Fourth quintile	1.11 (0.83, 1.48)	0.91 (0.70, 1.18)	0.93 (0.73, 1.19)
Highest (fifth) quintile	0.91 (0.67, 1.23)	0.90 (0.69, 1.19)	0.88 (0.68, 1.12)
Registry area			
Eastern	Referent	Referent	Referent
Midwest	1.22 (0.94, 1.60)	1.11 (0.90, 1.38)	1.03 (0.84, 1.27)
West	1.08 (0.83, 1.39)	0.99 (0.80, 1.24)	1.03 (0.85, 1.25)
Diagnosis year			
1993–1998	Referent	Referent	Referent
1999–2004	1.35 (0.99, 1.84)	1.20 (0.91, 1.60)	0.92 (0.76, 1.11)
2005–2009	1.24 (0.90, 1.72)	1.19 (0.88, 1.60)	0.83 (0.66, 1.05)
Comorbidity Score			
0	Referent	Referent	Referent
1	1.00 (0.80, 1.25)	0.96 (0.78, 1.17)	1.06 (0.89, 1.25)
2	1.29 (0.94, 1.76)	1.16 (0.89, 1.51)	1.33 (1.04, 1.71) *
Histology			
Serous	Referent	Referent	Referent
Mucinous	5.08 (2.50, 10.32) **	0.94 (0.46, 1.90)	1.41 (0.85, 2.34)

	3–6 months	7–12 months	>12 months
	HR (95%CI)	HR (95%CI)	HR (95%CI)
Endometrioid	0.71 (0.46, 1.11)	1.20 (0.86, 1.68)	0.79 (0.60, 1.04)
Clear Cell	0.78 (0.41, 1.50)	1.62 (0.87, 3.03)	1.31 (0.81, 2.11)
Other	1.09 (0.82, 1.43)	1.08 (0.86, 1.37)	1.07 (0.88, 1.31)
Stage			
I	Referent	Referent	Referent
II	1.86 (0.67, 5.14)	0.51 (0.26, 0.99) *	0.82 (0.56, 1.20)
III	1.89 (0.75, 4.73)	0.89 (0.52, 1.53)	0.99 (0.73, 1.34)
IV	2.17 (0.86, 5.46)	1.11 (0.64, 1.92)	1.07 (0.77, 1.49)
Unknown	3.31 (1.14, 9.56) *	1.00 (0.50, 1.97)	1.09 (0.67, 1.75)
Grade			
1	Referent	Referent	Referent
2	1.03 (0.45, 2.33)	0.86 (0.48, 1.54)	0.85 (0.54, 1.34)
3	0.95 (0.43, 2.09)	0.86 (0.50, 1.50)	0.95 (0.62, 1.45)
Unknown	0.93 (0.41, 2.10)	0.84 (0.47, 1.49)	0.90 (0.57, 1.44)
Neoadjuvant chemotherapy			
No	Referent	Referent	Referent
Yes	1.62 (1.26, 2.08) *	1.20 (0.95, 1.51)	0.87 (0.66, 1.14)
Initial chemotherapy duration (months)			
1 to 4	Referent	Referent	Referent
5 to 6	1.01 (0.82, 1.24)	0.99 (0.82, 1.18)	0.98 (0.84, 1.14)
7 to 8	1.34 (1.02, 1.77) *	1.07 (0.81, 1.40)	0.93 (0.72, 1.19)
Recurrent chemotherapy regimen			
Non-platinum	Referent	Referent	Referent
Platinum alone	0.70 (0.47, 1.06)	0.81 (0.63, 1.04)	0.75 (0.60, 0.94) *
Platinum combination	0.59 (0.48, 0.74) **	0.75 (0.62, 0.89) *	0.54 (0.47, 0.63) **

* P<0.05,

** P<0.0001