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Effectiveness of postoperative chemotherapy for stage IC mucinous ovarian cancer

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HIGHLIGHTS

- Two large-scale U.S. tumor registries were queried to examine outcomes in stage IC mucinous ovarian cancer (MOC).
- Stage IC disease is encountered in one in eight women with MOCs (12.6%).
- Fewer than 60% of women with stage IC MOC receive postoperative chemotherapy.
- Poor tumor differentiation, large tumor size, and lymphadenectomy are factors associated with postoperative chemotherapy use.
- Postoperative chemotherapy use is not associated with improved survival in stage IC MOC.

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ABSTRACT

Objective. To examine the association between postoperative chemotherapy and survival of women with stage IC mucinous ovarian cancer (MOC).

Methods. Comprehensive nationwide tumor registry data from the Commission on Cancer-accredited facilities in the United States from 2004 to 2014 were retrospectively examined. Women with stage IC MOC who underwent primary surgery followed by postoperative chemotherapy were compared to those who did not receive. Clinico-pathological factors associated with chemotherapy use, and overall survival associated with chemotherapy use were examined with multivariable models and propensity score inverse probability of treatment weighting (IPTW). External validation was performed by examining the Surveillance, Epidemiology, and End Results Program from 1988 to 2014.

Results. There were 532 (58.5%) women who received postoperative chemotherapy and 377 (41.5%) women who did not. On multivariable analysis, those with moderately-/poorly-differentiated tumors, large tumor size, and who underwent lymphadenectomy were more likely to receive postoperative chemotherapy whereas young women and those with capsule rupture alone were less likely to receive postoperative chemotherapy (all, $P < 0.05$). After IPTW, there was no difference in overall survival among women who received postoperative chemotherapy *versus* those who did not on multivariable analysis (adjusted 4-year rates: 85.8% *versus* 86.3%, adjusted-hazard ratio [HR] 0.88, 95% confidence interval [CI] 0.60–1.31). Similarly, there was no benefit with chemotherapy regardless of patient age, tumor differentiation, performance of nodal dissection, and substage groups. Among 912 cases in the validation cohort (postoperative chemotherapy use, $n = 520$ [57.0%]), postoperative chemotherapy use was not associated with cause-specific survival (adjusted-HR 1.296, 95% CI 0.846–1.984,

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$P = 0.233$) or overall survival (adjusted-HR 1.131, 95% CI 0.849–1.508, $P = 0.400$).

Conclusion. Postoperative chemotherapy was received by fewer than 60% of women with stage IC MOC, and postoperative chemotherapy was not associated with improved survival.

1. Introduction

Ovarian cancer remains the most deadly gynecologic malignancy in the United States [1]. Ovarian cancer includes a heterogeneous group of tumors encompassing various histologic types, tumor biologies, and cellular origins [2]. Whereas the serous type represents the most common histology, mucinous ovarian cancer (MOC) is less frequent and accounts for only 2–11% of epithelial ovarian cancers [3–7]. There has been a decreasing incidence over time, and due to its rarity, a paucity of data exists on MOC [3–7].

The majority of MOC are diagnosed at stage I and have an excellent prognosis compared to serous tumors, with 5-year cause-specific survival exceeding 90% [5,7,8]. The standard treatment approach for stage I MOC is primarily surgical, including oophorectomy, hysterectomy, and comprehensive surgical staging [9]. Based on surgical-pathological factors, stage I ovarian cancer is further classified into stage IA, IB, and IC [10].

Despite the recommendation for postoperative chemotherapy for stage IC ovarian cancer per multiple guidelines [11–13], studies demonstrating the benefit of postoperative chemotherapy specific to stage IC MOC remains lacking [12]. Multiple studies have shown that MOC are platinum-resistant tumors that respond poorly to taxane and platinum chemotherapy, a standard choice for postoperative chemotherapy in epithelial ovarian cancer [3,14–16]. The percentage of women with stage IC MOC who receive postoperative chemotherapy is also unknown.

The objective of this study is to *(i)* examine trends and characteristics of postoperative chemotherapy use and *(ii)* determine whether there was an association between the use of postoperative chemotherapy and overall survival in women with stage IC MOC.

2. Materials and methods

2.1. Data source

This retrospective cohort study extracted data from the comprehensive nationwide tumor registry data from the Commission on Cancer (CoC)-accredited facilities in the United States (National Cancer Database [NCDB]) [17–19]. This tumor registry collects over one million invasive cancer cases per year, representing approximately 70% of all new invasive cancers in the United States [18]. >1500 CoC-affiliated institutions participate in the database through a joint mechanism of the CoC of the American College of Surgeons (ACoS) and the American Cancer Society (ACS) Society [17–19].

Variables extracted included patient socio-demographics, tumor characteristics, the first course of treatment before disease progression or recurrence, follow-up and survival [18,19]. Regular audits are performed to guarantee the integrity and completeness of data reported to the database. The study used publicly available deidentified data and was deemed exempt by the Columbia University College of Physicians and Surgeons institutional review board.

2.2. Eligibility

We identified women with invasive ovarian cancer diagnosed from 2004 to 2014 who had histologically confirmed ovarian cancer as their first cancer diagnosis. The cohort was further restricted to stage IC patients who underwent oophorectomy with mucinous histological type, and had not received neoadjuvant chemotherapy or radiation. These women were also required to have complete information regarding chemotherapy status within the 6 months following surgery, and have available follow-up data on vital status.

Exclusion criteria were as follows: non-surgical management, non-mucinous histology, borderline histology, stage other than IC or unknown, neoadjuvant therapy, or postoperative chemotherapy >6 months after initial surgery.

2.3. Clinical and demographic characteristics

Variables for age at diagnosis (<40, 40–49, 50–59, 60–69, 70–79, ≥80 years), race/ethnicity (white, black, Hispanic, other, unknown), year of diagnosis (continues), and insurance status (private, Medicaid, Medicare, uninsured, other governmental/unknown) were collected for patient's demographics. Patient's socio-economic status was measured by median household income (<$30,000, $30,000–$34,999, $35,000–$45,999, ≥$46,000, or unknown) and percentage of adults who did not graduate from high school in a patient's zip code area from census tract survey data (≥29%, 20–28.9%, 14–19.9%, <14%, or unknown). Patient's residential location was estimated by matching state and county code to rural-urban continuum codes from the United States Department of Agriculture Economic Research Service (metropolitan, urban, rural, and unknown). Comorbidity was measured using the Deyo classification of the Charlson comorbidity score (0, 1, or ≥2) [20].

Tumor characteristics included tumor differentiation (well, moderate, poorly, unknown) and tumor size (≤2.0, 2.1–4.0, 4.1–6.0, 6.1–8.0, 8.1–10.0, >10.0, or unknown). Hysterectomy (no, yes, and unknown), lymphadenectomy (no, yes, and unknown), and postoperative chemotherapy status (no, yes, and unknown) were also noted for each patient. Hospital characteristics included facility region (eastern, Midwest, south, west, unknown) and facility type (academic centers, community centers or comprehensive community cancer centers, and integrated network cancer program) as defined by the ACS's CoC Accreditation program criteria [17]. Overall survival (OS), defined as the time interval between diagnosis of MOC and death from all-causes, was examined for survival analysis. Cases without survival event at last follow-up visit were censored.

2.4. Statistical analysis

The trend of postoperative chemotherapy was evaluated using Cochran-Armitage trend test. A multivariable Poisson regression model based on a generalized estimating equation (GEE) was developed to estimate the association between each covariate and the use of postoperative chemotherapy after accounting for hospital clustering and other variables, reported as adjusted-risk ratios (aRR) with 95% confidence intervals (CI).

The inverse probability of treatment weighting (IPTW) approach based on propensity score was used to balance the observed confounders between treatments (postoperative chemotherapy yes *versus* no). The propensity score was estimated as the predicted probability that a patient received the treatment of interest [21]. To calculate the propensity score for postoperative chemotherapy, we fit a logistic regression model that included all covariates prior to the use of chemotherapy.

Table 1
Study cohort description and factors associated with postoperative chemotherapy.

Variables	Overall Cohort	Postoperative chemotherapy	Postoperative chemotherapy
	N (%)	*N* (%)	aRR (95% CI)
Age			
<40	183 (20.1)	102 (55.7)	0.80 (0.65, 0.99)*
40–49	179 (19.7)	98 (54.7)	0.82 (0.71, 0.95)*
50–59	254 (27.9)	166 (65.4)	Referent
60–69	170 (18.7)	107 (62.9)	0.97 (0.82, 1.14)
70–79	77 (8.5)	40 (51.9)	0.90 (0.69, 1.17)
≥80	46 (5.1)	19 (41.3)	0.70 (0.48, 1.02)
Race or ethnic			
Non-Hispanic: White	715 (78.7)	416 (58.2)	Referent
Non-Hispanic: Black	47 (5.2)	28 (59.6)	1.00 (0.77, 1.30)
Hispanic	62 (6.8)	39 (62.9)	1.12 (0.87, 1.43)
Non-Hispanic: Other	49 (5.4)	32 (65.3)	1.11 (0.89, 1.39)
Unknown	36 (4.0)	17 (47.2)	0.81 (0.55, 1.19)
Insurance status			
Private Insurance	533 (58.6)	315 (59.1)	Referent
Medicaid	79 (8.7)	55 (69.6)	1.12 (0.94, 1.34)
Medicare	203 (22.3)	107 (52.7)	0.92 (0.77, 1.09)
Not Insured	64 (7.0)	38 (59.4)	1.01 (0.81, 1.26)
Other Government/Unknown	30 (3.4)	–	1.73 (1.31, 2.29)*
Median household income			
<$30,000	115 (12.7)	64 (55.7)	Referent
$30,000–$35,999	151 (16.6)	103 (68.2)	1.15 (0.94, 1.41)
$36,000–$45,999	242 (26.6)	146 (60.3)	1.05 (0.85, 1.29)
≥$46,000	385 (42.4)	213 (55.3)	0.99 (0.79, 1.24)
Not Available	16 (1.8)	–	0.71 (0.37, 1.36)
Percentage of adults not graduating from high school			
≥29%	142 (15.6)	82 (57.7)	Referent
20–28.9%	216 (23.8)	134 (62.0)	1.04 (0.87, 1.24)
14–19.9%	194 (21.3)	122 (62.9)	1.03 (0.86, 1.24)
<14%	341 (37.5)	188 (55.1)	0.95 (0.76, 1.18)
Not Available	16 (1.8)	–	Non-estimable
Urban/Rural			
Metropolitan	742 (81.6)	429 (57.8)	Referent
Urban	121 (13.3)	75 (62.0)	0.98 (0.84, 1.14)
Rural	20 (2.2)	12 (60.0)	1.02 (0.73, 1.42)
Unknown	26 (2.9)	16 (61.5)	1.09 (0.83, 1.43)
Comorbidity score			
0	758 (83.4)	444 (58.6)	Referent
1	129 (14.2)	78 (60.5)	1.05 (0.91, 1.21)
≥2	22 (2.4)	–	0.86 (0.58, 1.29)
Year of diagnosis			
2004	58 (6.4)	33 (56.9)	Referent
2005	68 (7.5)	39 (57.4)	1.04 (0.77, 1.40)
2006	62 (6.8)	38 (61.3)	1.02 (0.77, 1.34)
2007	67 (7.4)	40 (59.7)	1.12 (0.82, 1.52)
2008	68 (7.5)	40 (58.8)	0.95 (0.73, 1.25)
2009	62 (6.8)	35 (56.5)	1.00 (0.73, 1.37)
2010	83 (9.1)	55 (66.3)	1.11 (0.86, 1.44)
2011	92 (10.1)	50 (54.3)	0.93 (0.70, 1.23)
2012	118 (13.0)	67 (56.8)	0.94 (0.71, 1.24)
2013	115 (12.7)	69 (60.0)	1.04 (0.81, 1.35)
2014	116 (12.8)	66 (56.9)	1.01 (0.78, 1.32)
Tumor differentiation			
Well	308 (33.9)	172 (55.8)	Referent
Moderate	336 (37.0)	223 (66.4)	1.14 (1.02, 1.28)*
Poorly	86 (9.5)	68 (79.1)	1.39 (1.20, 1.61)**
Unknown	179 (19.7)	69 (38.5)	0.69 (0.56, 0.85)*
Tumor size (cm)			
≤2.0	84 (9.2)	31 (36.9)	Referent
2.1–4.0	42 (4.6)	24 (57.1)	1.62 (1.14, 2.30)*
4.1–6.0	26 (2.9)	13 (50.0)	1.25 (0.77, 2.03)
6.1–8.0	39 (4.3)	19 (48.7)	1.27 (0.82, 1.97)
8.1–10.0	55 (6.1)	28 (50.9)	1.39 (0.95, 2.03)
>10.0	531 (58.4)	340 (64.0)	1.67 (1.24, 2.24)*
Unknown	132 (14.5)	77 (58.3)	1.57 (1.14, 2.15)*

(continued on next page)

Table 1 (*continued*)

Variables	Overall Cohort	Postoperative chemotherapy	Postoperative chemotherapy
	N (%)	*N* (%)	aRR (95% CI)
Hysterectomy			
No	211 (23.2)	106 (50.2)	Referent
Yes	569 (62.6)	342 (60.1)	1.06 (0.90, 1.24)
Unknown	129 (14.2)	84 (65.1)	1.11 (0.92, 1.35)
Lymphadenectomy			
No	246 (27.1)	108 (43.9)	Referent
Yes	658 (72.4)	421 (64.0)	1.26 (1.09, 1.46)*
Unknown	–	–	0.86 (0.42, 1.75)
Facility location			
Eastern	164 (18.0)	101 (61.6)	Referent
South	190 (20.9)	101 (53.2)	0.84 (0.69, 1.03)
Midwest	258 (28.4)	162 (62.8)	1.05 (0.88, 1.24)
West	114 (12.5)	66 (57.9)	0.89 (0.70, 1.12)
Unknown	183 (20.1)	102 (55.7)	Non-estimable
Facility type			Referent
Community Cancer Program	30 (3.3)	16 (53.3)	0.96 (0.68, 1.36)
Comprehensive Community Cancer Program	273 (30.0)	151 (55.3)	0.88 (0.76, 1.01)
Academic/Research Program	353 (38.8)	219 (62.0)	Referent
Integrated Network Cancer Program	70 (7.7)	44 (62.9)	0.91 (0.73, 1.14)
Unknown	183 (20.1)	102 (55.7)	Non-estimable

Number and percent per column is shown.
– Indicated number of ≤10, required to suppress per the Healthcare Cost and Utilization Project.
* $P < 0.05$.

The IPTW approach assigned patients who received postoperative chemotherapy a weight of 1/propensity score and those who did not receive chemotherapy a weight of 1/(1-propensity score) [22]. To standardize the variability of IPTW and reduce the influence of extreme weights, we applied a stabilization method, and employed a trimming technique with a threshold of 10 [23].

After IPTW, the balance of measured confounders was assessed *via* a weighted logistic-regression approach, in which each covariate was regressed on the treatment variable [24]. The distributions of categorical variables by treatment groups in the original unweighted cohort were compared using χ^2 tests.

In the propensity score-weighted cohort, we compared survival between the chemotherapy and non-chemotherapy groups. The primary outcome for this analysis was all-cause mortality that was compared using the IPTW adjusted log-rank test and plotted weighted survival functions [25]. We estimated the hazard ratio (HR) for death from any cause after chemotherapy, as compared with non-chemotherapy, with weighted Cox proportional-hazards models expressed with adjusted-HR and 95% CI.

2.5. Sensitivity analysis

A series of sensitivity analyses were conducted to examine the robustness of the findings. In the first sensitivity analysis, we fit a marginal multivariable Cox proportional model accounting for hospital clustering and measured confounders. In addition, a parsimonious adjustment with *a priori* survival factor was fitted (age, race/ethnicity, tumor differentiation, comorbidity, and lymphadenectomy). This is based on the rationale that stage IC MOC is relatively rare and survival events may be limited to fit all covariates.

The second analysis was limited to several sub-groups based on age, tumor differentiation, and lymphadenectomy. Unstaged cases were examined because microscopic metastasis is relatively common in apparent stage I ovarian cancer [9], and the absence of surgical staging results in decreased survival in stage I MOC as shown in a recent population study [26]. Finally, subgroups of stage IC were examined by using extent of disease codes as capsule rupture only (code 350), ovarian surface involvement only (360), and malignant cells in ascites or peritoneal cytology (410 and 430).

2.6. External validation

The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program served as the validation cohort in our study. Details of the methodology are shown in Supplemental Method S1. Briefly, women with stage IC (T1c/N0-x/M0-x) MOC who underwent primary surgical treatment between 1988 and 2014 were eligible for analysis. Trends, characteristics, and survival related to postoperative chemotherapy use were assessed. This study population was chosen as the SEER program is the largest tumor registry in the United States covering ~35% of the U.S. population and the geographic areas and population characteristics of the database are different from the NCDB population. Analysis of the SEER dataset was conducted by an independent team who was blinded for the NCDB results.

All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina), "IPWsurvival" package in R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria), and Statistical Package for Social Sciences (version 24.0, Armonk, NY, USA). All hypothesis testing was two-sided and a *p*-value of <0.05 was considered statistically significant.

3. Results

The patient selection schema is shown in Supplemental Fig. S1. Among 177,707 women with ovarian cancer between 2004 and 2014, 909 had stage IC MOC, had primary surgical treatment, and had complete postoperative chemotherapy information. Of those, 532 (58.5%, 95% CI 55.3–61.7) women received postoperative chemotherapy and the remaining 377 (41.5%) did not. The number of women who received postoperative chemotherapy were similar over time ($P = 0.846$; Supplemental Fig. S2).

The majority of the study population was non-Hispanic white, metropolitan residents, had private insurance, and had no comorbidities (Table 1). The majority of the tumors were well−/moderately-differentiated. On univariable analysis, age, insurance status, zip-code median household income, tumor differentiation, tumor size, hysterectomy, and lymphadenectomy were significantly different between the two groups (all, $P < 0.05$).

Table 2
Multivariable model for all-cause mortality (unweighted overall cohort).

Characteristic	Adjusted-HR (95% CI)
Postoperative chemotherapy	
No	Referent
Yes	0.89 (0.61, 1.30)
Age at diagnosis	
<40	Referent
40–49	1.02 (0.42, 2.47)
50–59	0.95 (0.40, 2.24)
60–69	1.21 (0.52, 2.80)
70–79	1.25 (0.49, 3.20)
≥80	1.55 (0.56, 4.26)
Race/ethnicity	
Hon-Hispanic: White	Referent
Non-Hispanic: Black	1.56 (0.70, 3.45)
Hispanic	1.15 (0.53, 2.49)
Other	1.17 (0.47, 2.94)
Unknown	0.77 (0.30, 1.96)
Health insurance	
Private	Referent
Medicaid	0.66 (0.28, 1.55)
Medicare	1.78 (1.04, 3.06)*
Not Insured	1.23 (0.57, 2.66)
Other Government	Non-estimable
Unknown	2.68 (1.12, 6.43)*
Zip code median household income	
<$30,000	Referent
$30,000–$35,999	1.06 (0.56, 2.00)
$36,000–$45,999	1.29 (0.70, 2.36)
≥$46,000	1.00 (0.50, 2.01)
Not available	1.70 (0.39, 7.49)
Zip code education level	
≥29%	Referent
20–28.9%	1.25 (0.67, 2.32)
14–19.9%	1.15 (0.57, 2.34)
<14%	0.88 (0.42, 1.84)
Not available	Non-estimable
Rural/Urban	
Metropolitan	Referent
Urban	1.03 (0.62, 1.72)
Rural	1.17 (0.36, 3.83)
Unknown	0.20 (0.04, 1.10)
Comorbidity Score	
0	Referent
1	1.20 (0.75, 1.92)
2	1.37 (0.66, 2.84)
Year of diagnosis	
2004	Referent
2005	1.39 (0.61, 3.20)
2006	1.99 (0.90, 4.40)
2007	1.55 (0.70, 3.42)
2008	1.27 (0.55, 2.92)
2009	0.77 (0.31, 1.93)
2010	0.68 (0.24, 1.97)
2011	0.91 (0.38, 2.15)
2012	0.77 (0.32, 1.86)
2013	1.31 (0.52, 3.26)
2014	0.59 (0.18, 1.91)
Tumor differentiation	
Well	Referent
Moderate	1.17 (0.79, 1.76)
Poorly	2.43 (1.35, 4.38)*
Unknown	0.93 (0.56, 1.54)
Tumor size (cm)	
0–2.0	Referent
2.1–4.0	1.37 (0.51, 3.69)
4.1–6.0	1.67 (0.50, 5.53)
6.1–8.0	0.65 (0.15, 2.70)
8.1–10	1.52 (0.57, 4.00)
>10	1.19 (0.55, 2.57)
Unknown	1.28 (0.58, 2.84)
Facility location	
Eastern	Referent
West	1.32 (0.65, 2.66)
Midwest	1.18 (0.72, 1.91)
South	1.26 (0.75, 2.12)
Unknown	Non-estimable
Facility type	
Academic/Research Program	Referent
Community Cancer Program	0.65 (0.30, 1.43)
Comprehensive Community Cancer Program	1.14 (0.77, 1.68)
Integrated Network Cancer Program	1.35 (0.76, 2.42)
Unknown	Non-estimable
Hysterectomy	
Yes	Referent
No	0.71 (0.44, 1.13)
Unknown	0.73 (0.41, 1.30)
Lymphadenectomy	
Yes	Referent
No	2.18 (1.45, 3.29)*
Unknown	4.04 (1.47, 11.11)*

Cox proportional hazard regression model. *$P < 0.05$. Abbreviations: HR, hazard ratio; and CI, confidence interval.

On multivariable analysis (Table 1), women with moderately-differentiated tumors (aRR 1.14, 95% CI 1.02–1.28), poorly-differentiated tumors (aRR 1.39, 95% CI 1.20–1.61), large tumor size, and those who underwent lymphadenectomy (aRR 1.26, 95% CI 1.09–1.46) were more likely to receive postoperative chemotherapy; whereas young women (age < 40, aRR 0.80, 95% CI 0.65–0.99; and age 40–49, aRR 0.82, 95% CI 0.71–0.95) were less likely to undergo postoperative chemotherapy (all, $P < 0.05$). Older women aged ≥80 were also less likely to receive chemotherapy but this did not reach statistical significance (aRR 0.70, 95% CI 0.48–1.02).

The median follow-up time was 4.2 (IQR 2.5–6.3) years for the chemotherapy group and 3.6 (IQR 2.2–5.8) years for the non-chemotherapy group ($P = 0.001$). There were 89 (16.7%) deaths in the chemotherapy group and 67 (17.8%) deaths in the non-chemotherapy group. Unadjusted Kaplan-Meier curves indicated that women who received chemotherapy had OS similar to those who did not receive chemotherapy (crude 4-year survival: 85.4% *versus* 85.8%, Log-rank test for OS function $P = 0.241$; Supplemental Fig. S3).

On multivariable Cox Proportional hazard model (Table 2), postoperative chemotherapy use was not associated with OS (aHR 0.89, 95% CI 0.61–1.30) after adjusting for hospital clustering and other covariates. Poorly-differentiated tumors (aHR 2.43, 95% CI 1.35–4.38), lack of lymphadenectomy (aHR 2.18, 95% CI 1.45–3.29), and Medicare insurance (aHR 1.78, 95% CI 1.04–3.06) were independently associated with decreased OS. In a parsimonious Cox model with *a priori* selected factors, the results were robust (aHR 0.95, 95% CI 0.66–1.37).

Results of the IPTW analysis after propensity score showed well-balanced baseline clinico-pathological factors between the two groups (all, $P > 0.90$; Table 3). IPTW-adjusted 4-year OS rates were similar between the two groups (chemotherapy *versus* non-chemotherapy, 85.8% *versus* 86.3%; Fig. 1A). On IPTW Cox proportional model (Fig. 2), women who received postoperative chemotherapy had OS similar to those who did not receive postoperative chemotherapy (aHR 0.88, 95% CI 0.60–1.31).

The IPTW-adjusted OS were similar between the chemotherapy and non-chemotherapy groups among the women aged <50 years ($n = 362$, adjusted 4-year rates: 87.1% *versus* 86.2%, aHR 0.75, 95% CI 0.90–1.42), those who had lymphadenectomy ($n = 658$, 87.6% *versus* 86.6%, aHR 0.81, 95% CI 0.52–1.27), those who did not undergo pelvic lymphadenectomy ($n = 246$, 78.9% *versus* 82.1%, aHR 0.93, 95% CI 0.52–1.67; Fig. 1B), those with well-differentiated tumors ($n = 308$, 86.4% *versus* 85.7%, aHR 0.79, 95% CI 0.41–1.53; Fig. 1C), and those with tumors that were moderately-/poorly-differentiated ($n = 422$, 81.5% *versus* 89.6%, aHR 1.14, 95% CI 0.66–1.96; Fig. 1D) (Fig. 2).

When stratified by stage IC subgroups, the 448 women with capsule rupture alone were significantly less likely to receive postoperative

Table 3
Distribution of patient's demographics, clinical factors and hospital characteristics by postoperative chemotherapy, before and after propensity score inverse probability of treatment weighting.

	Original unweighted cohort			Inverse probability of treatment weighted cohort*		
	Postoperative chemotherapy Yes	Postoperative chemotherapy No	*P* value†	Postoperative chemotherapy Yes	Postoperative chemotherapy No	*P* value‡
Age of diagnosis			0.0113			0.991
<40	102 (19.2)	81 (21.5)		120 (20.3)	94 (20.4)	
40–49	98 (18.4)	81 (21.5)		111 (18.9)	93 (20.3)	
50–59	166 (31.1)	88 (23.3)		166 (28.1)	125 (27.1)	
60–69	107 (20.1)	63 (16.7)		110 (18.6)	86 (18.7)	
70–79	40 (7.5)	37 (9.8)		49 (8.2)	39 (8.5)	
≥80	19 (3.6)	27 (7.2)		35 (6.0)	23 (5.0)	
Race or ethnic			0.500			0.996
Non-Hispanic: White	416 (78.2)	299 (79.3)		465 (78.6)	358 (77.8)	
Non-Hispanic: Black	28 (5.3)	19 (5.0)		29 (4.9)	23 (5.1)	
Hispanic	39 (7.3)	23 (6.1)		41 (6.9)	33 (7.2)	
Non-Hispanic: Other	32 (6.0)	17 (4.5)		32 (5.4)	28 (6.0)	
Unknown	17 (3.2)	19 (5.0)		24 (4.1)	18 (3.9)	
Insurance status			0.040			0.989
Not Insured	38 (7.1)	26 (6.9)		42 (7.0)	32 (6.9)	
Private	315 (59.2)	218 (57.8)		342 (57.9)	267 (58.0)	
Medicaid	55 (10.3)	24 (6.4)		55 (9.3)	48 (10.4)	
Medicare	107 (20.1)	96 (25.5)		133 (22.5)	100 (21.8)	
Other/Unknown	17 (3.2)	13 (3.4)		19 (3.4)	14 (3.0)	
Median household income			0.027			0.991
<$30,000	64 (12.0)	51 (13.5)		74 (12.6)	58 (12.7)	
$30,000–$35,999	103 (19.4)	48 (12.7)		99 (16.7)	80 (17.4)	
$36,000–$45,999	146 (27.4)	96 (25.5)		162 (27.4)	125 (27.1)	
≥$46,000	213 (40.0)	172 (45.6)		241 (40.9)	189 (41.1)	
Percentage of adults not graduating from high school			0.119			0.986
≥29%	82 (15.4)	60 (15.9)		93 (15.7)	75 (16.4)	
20–28.9%	134 (25.2)	82 (21.8)		138 (23.4)	111 (24.0)	
14–19.9%	122 (22.9)	72 (19.1)		126 (21.3)	98 (21.4)	
<14%	188 (35.3)	153 (40.6)		220 (37.2)	168 (36.4)	
Urban/Rural			0.8400			0.982
Metropolitan	429 (80.6)	313 (83.0)		486 (82.3)	377 (81.9)	
Urban	75 (14.1)	46 (12.2)		78 (13.2)	64 (13.9)	
Rural or unknown	28 (5.3)	18 (4.8)		27 (4.5)	19 (4.2)	
Comorbidity score			0.417			0.961
0	444 (83.5)	314 (83.3)		488 (82.5)	376 (81.7)	
1	78 (14.6)	51 (13.5)		91 (15.4)	74 (16.1)	
≥2	–	12 (3.2)		12 (2.1)	–	
Year of diagnosis			0.971			0.999
2004	33 (6.2)	25 (6.6)		35 (6.0)	28 (6.1)	
2005	39 (7.3)	29 (7.7)		45 (7.7)	35 (7.6)	
2006	38 (7.1)	24 (6.4)		41 (6.9)	35 (7.7)	
2007	40 (7.5)	27 (7.2)		49 (8.2)	40 (8.7)	
2008	40 (7.5)	28 (7.4)		41 (6.9)	32 (7.0)	
2009	35 (6.6)	27 (7.2)		45 (7.6)	33 (7.2)	
2010	55 (10.3)	28 (7.4)		50 (8.5)	36 (7.9)	
2011	50 (9.4)	42 (11.1)		61 (10.3)	49 (10.6)	
2012	67 (12.6)	51 (13.5)		78 (13.2)	67 (14.5)	
2013	69 (13.0)	46 (12.2)		73 (12.3)	50 (10.9)	
2014	66 (12.4)	50 (13.3)		73 (12.4)	55 (11.9)	
Tumor differentiation			<0.001			0.999
Well	172 (32.3)	136 (36.1)		202 (34.2)	156 (33.9)	
Moderate	223 (41.9)	113 (30.0)		217 (36.8)	169 (36.8)	
Poorly	68 (12.8)	18 (4.8)		56 (9.5)	43 (9.5)	
Unknown	69 (13.0)	110 (29.2)		115 (19.5)	92 (19.9)	
Tumor size (cm)			<0.001			0.999
≤2.0	31 (5.8)	53 (14.1)		57 (9.7)	43 (9.3)	
2.1–4.0	24 (4.5)	18 (4.8)		25 (4.3)	18 (4.0)	
4.1–6.0	13 (2.4)	13 (3.4)		16 (2.8)	12 (2.6)	
6.1–8.0	19 (3.6)	20 (5.3)		24 (4.0)	19 (4.2)	
8.1–10.0	28 (5.3)	27 (7.2)		39 (6.7)	32 (6.9)	
>10.0	340 (63.9)	191 (50.7)		344 (58.3)	271 (59.0)	
Unknown	77 (14.5)	55 (14.6)		84 (14.3)	64 (14.0)	
Hysterectomy			0.014			0.917
No	106 (19.9)	105 (27.9)		133 (22.5)	106 (22.9)	
Yes	342 (64.3)	227 (60.2)		366 (62.0)	286 (62.2)	
Unknown	84 (15.8)	45 (11.9)		91 (15.5)	68 (14.8)	
Lymphadenectomy			<0.001			
No	108 (20.3)	138 (36.6)		148 (25.0)	121 (26.3)	
Yes	421 (79.1)	237 (62.9)		440 (74.5)	337 (73.2)	

Table 3 (*continued*)

	Original unweighted cohort			Inverse probability of treatment weighted cohort*		
	Postoperative chemotherapy Yes	Postoperative chemotherapy No	*P* value†	Postoperative chemotherapy Yes	Postoperative chemotherapy No	*P* value‡
Facility location			0.255			0.999
Eastern	101 (18.9)	63 (16.7)		110 (18.6)	85 (18.4)	
South	101 (18.9)	89 (23.6)		122 (20.6)	98 (21.3)	
Midwest	162 (30.4)	96 (25.5)		167 (28.3)	126 (27.5)	
West	66 (12.4)	48 (12.7)		72 (12.3)	57 (12.4)	
Unknown	102 (19.2)	81 (21.5)		120 (20.3)	94 (20.4)	
Facility type			0.364			0.999
Community Cancer Program	16 (3.0)	14 (3.7)		21 (3.5)	17 (3.8)	
Comprehensive Community Cancer Program	151 (28.3)	122 (32.4)		183 (31.0)	144 (31.3)	
Academic/Research Program	219 (41.1)	134 (35.5)		221 (37.3)	169 (36.6)	
Integrated Network Cancer Program	44 (8.3)	26 (6.9)		46 (7.8)	36 (7.8)	
Unknown	102 (19.2)	81 (21.5)		120 (20.3)	94 (20.4)	

– Indicated number of ≤10, required to suppress per the Healthcare Cost and Utilization Project.

* Count in the weighted cohort may not sum up to the totals due to rounding. Percentage may not sum up to 100 because of rounding, and the inconsistence between numbers and percentages in the weighted cohort are resulted from the rounding of non-integer number values.

† *P*-values were calculated by chi-square test.

‡ *P*-values were calculated by inverse probability of treatment-weighted logistic-regression model.

chemotherapy as compared to other subgroups of stage IC disease (56.3% *versus* 66.7–67.3%, $P < 0.05$; Supplemental Table S1). On PS-IPTW (Fig. 2), the OS was similar between the two groups in the setting of capsule rupture alone (adjusted 4-year rates: 85.5% *versus* 85.1%, aHR 0.68, 95% CI 0.42–1.11; Fig. 1E) as well as ovarian surface involvement/malignant cells in ascites or cytology testing (adjusted 4-year survival rates 86.2% *versus* 89.7%; aHR 1.07, 95% CI 0.53–2.15; Fig. 1F).

3.1. External validation cohort

Detailed results of the SEER cohort are shown in Supplemental Result S1 and Table S2–6. In this cohort, there were 7217 (5.2%, 95% CI 5.1–5.3) women who had a diagnosis of MOC histology among 139,456 cases, including 912 (12.6%, 95% CI 11.9–13.4) women with stage IC MOC who had primary surgical treatment. Among stage IC MOC, 520 (57.0%, 95% CI 53.8–60.2) women received postoperative chemotherapy (Supplemental Fig. S4). There was no change in the rate of chemotherapy use over time (annual percent change 0.0, $P = 0.989$; Supplemental Fig. S5).

Women with poorly-differentiated tumors represented 12.5% of the study population. These women had the highest frequency of postoperative chemotherapy use (75.4%). This was followed by those with moderately differentiated tumors who represented 34.3% of the study population (62.3%) (Supplemental Fig. S6). In a multivariable analysis, women with moderately-/poorly-differentiated tumors were more likely to receive postoperative chemotherapy whereas those of older age and those who did not undergo hysterectomy were less likely to receive postoperative chemotherapy (all, $P < 0.05$; Supplemental Table S2).

After propensity score matching (Supplemental Table S3), postoperative chemotherapy use was not associated with cause-specific survival (7-year rates 84.6% *versus* 88.3%, aHR 1.296, 95% CI 0.846–1.984; Fig. 3A) or OS (77.1% *versus* 77.1%, aHR 1.131, 95% CI 0.849–1.508; Fig. 3B) (Supplemental Table S4). Similarly, postoperative chemotherapy was not associated with cause-specific survival in women aged ≥50 years (aHR 0.879, 95% CI 0.558–1.386), those with moderately-/poorly-differentiated tumors (aHR 1.099, 95% CI 0.646–1.867), and those who did not undergo lymphadenectomy (adjusted-HR 1.245, 95% CI 0.712–2.176) (all, $P > 0.05$; Supplemental Table S5).

4. Discussion

This study found that fewer women than expected with stage IC MOC receive postoperative chemotherapy (57.0–58.5%), and this did not change over time during the study period. This number seems significantly lower as compared to stage IC ovarian clear cell carcinoma (75.2%) [27], another tumor type known to have limited benefit from postoperative chemotherapy due to poor response to the taxane/platinum regimen [28]. The exact causality for the low utilization of postoperative chemotherapy for stage IC MOC is unknown, but, it is speculated that care providers may be reluctant to prescribe chemotherapy for stage IC MOC due to a lack of solid evidence demonstrating its survival benefit and the poor response of women with advanced mucinous ovarian tumors to chemotherapy.

Our analysis of two-large cohorts including total 1821 cases of stage IC MOC showed that postoperative chemotherapy was not associated with overall survival (4-year rates for chemotherapy *versus* non-chemotherapy, 85.8% *versus* 86.3% in the NCDB analysis; and 7-year rates 77.1% *versus* 77.1% in the SEER analysis). No sub-stage of IC disease appeared to have survival benefit from postoperative chemotherapy. As stage IC disease is fairly common in MOC, representing approximately one in eight MOCs (12.6%), addressing the effectiveness of postoperative chemotherapy in stage IC disease is a crucial clinical question in the management of MOC.

Sub-group analysis from prior trials, as well as a recent multicenter retrospective study showed no survival difference between observation and postoperative chemotherapy in stage I MOC; however their analyses were not specific for stage IC and the sample sizes were limited [29–31]. Furthermore, prior studies have confirmed that MOC is chemoresistant, particularly to a taxane/platinum doublet [3,14–16]. Collectively, it remains controversial whether stage IC MOC benefits from postoperative chemotherapy.

Epithelial ovarian cancer is not a single disease entity, and response to therapy differs by histology. For this reason, the National Comprehensive Cancer Network (NCCN) included histology type-specific treatment recommendations in 2016. Under these new guidelines, observation without chemotherapy is an alternative option to treatment with a taxane/platinum regimen for stage IC MOC [11]. With the exception of MOC and low-grade serous carcinoma, postoperative chemotherapy is recommended for stage IC disease for all other histologic types.

This study further supports the new NCCN guidelines for stage IC MOC, in demonstrating a lack of survival benefit with the addition of postoperative chemotherapy, a finding which remained even in the setting of high risk histological features. This association was even observed in staged cases and in moderately−/poorly-differentiated tumors which were identified as factors for increased utilization of postoperative chemotherapy. Yet, the NCCN guidelines do not provide evidence supporting postoperative observation of stage IC MOC, and

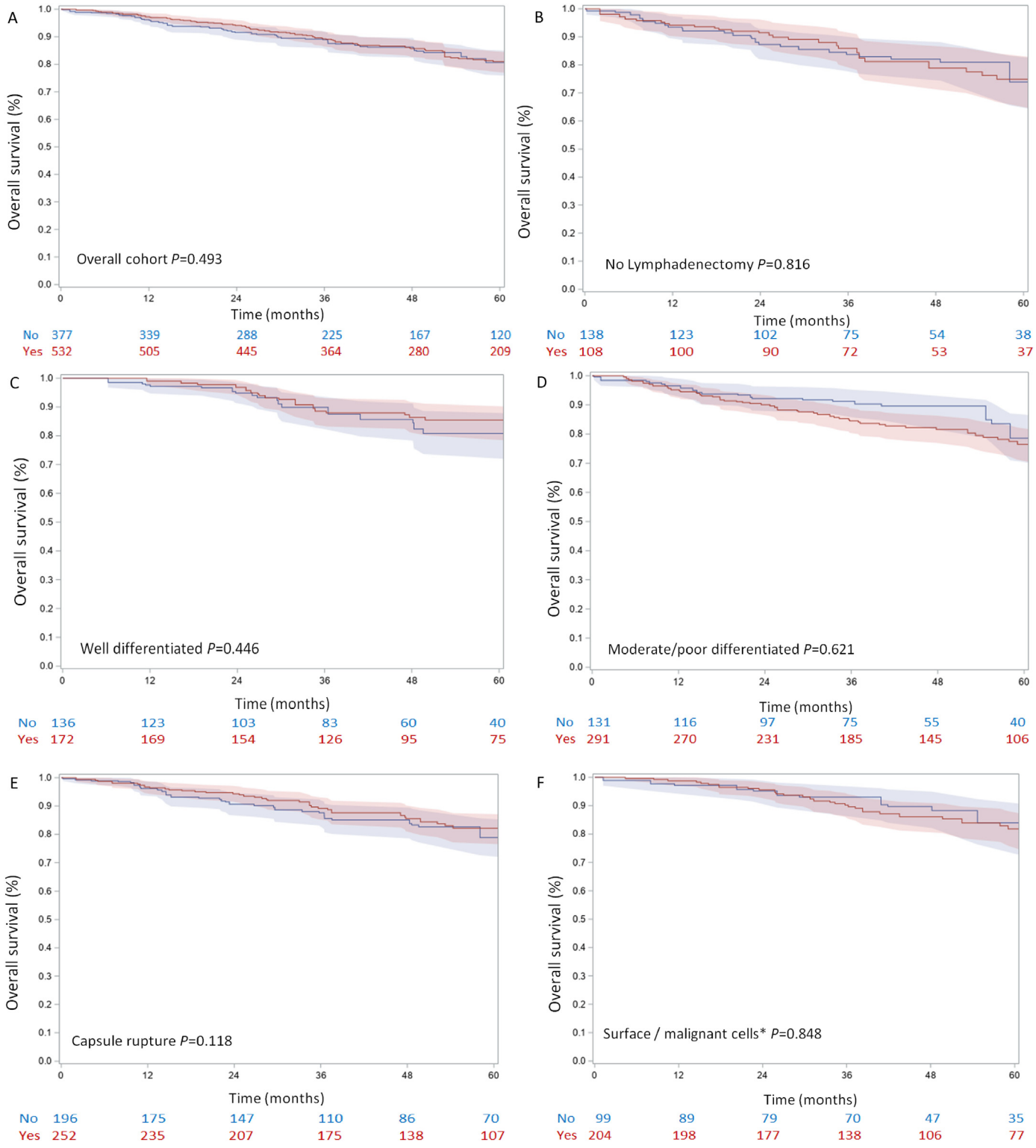

Fig. 1. IPTW-adjusted survival curves by postoperative chemotherapy use (NCDB cohort). The IPTW-adjusted overall survival based on postoperative chemotherapy is shown for **A)** Overall cohort, **B)** Unstaged case, **C)** Well-differentiated tumors, **D)** Moderately-/poorly-differentiated tumors, **E)** Capsule rupture only, and **F)** Surface involvement/malignant cells in cytology testing. Red lines indicate postoperative chemotherapy and blue lines indicates no chemotherapy. *P*-values were derived from IPTW-adjusted log-rank test. *Ovarian surface involvement/malignant cells in ascites or cytology testing. The solid lines are adjusted-survival function, and the color bands indicate 95% confidence interval. "Yes" indicates chemotherapy use, and "No" indicates no chemotherapy. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

many authorities continue to favor postoperative chemotherapy in this scenario [4,11]. Thus, identifying any predictor for response to chemotherapy in this disease would be useful.

For example, histologic architecture pattern may provide a compelling argument favoring postoperative chemotherapy, serving as a strong predictor for tumor aggressiveness and poor prognosis [32]. Specifically, the expansile (confluent) subtype of MOC, exhibiting back-to-back glands with an absence of stromal tumor invasion, displays more indolent tumor behavior, whereas the infiltrative subtype, exhibiting destructive stromal tumor invasion, acts more aggressively [32]. Even in

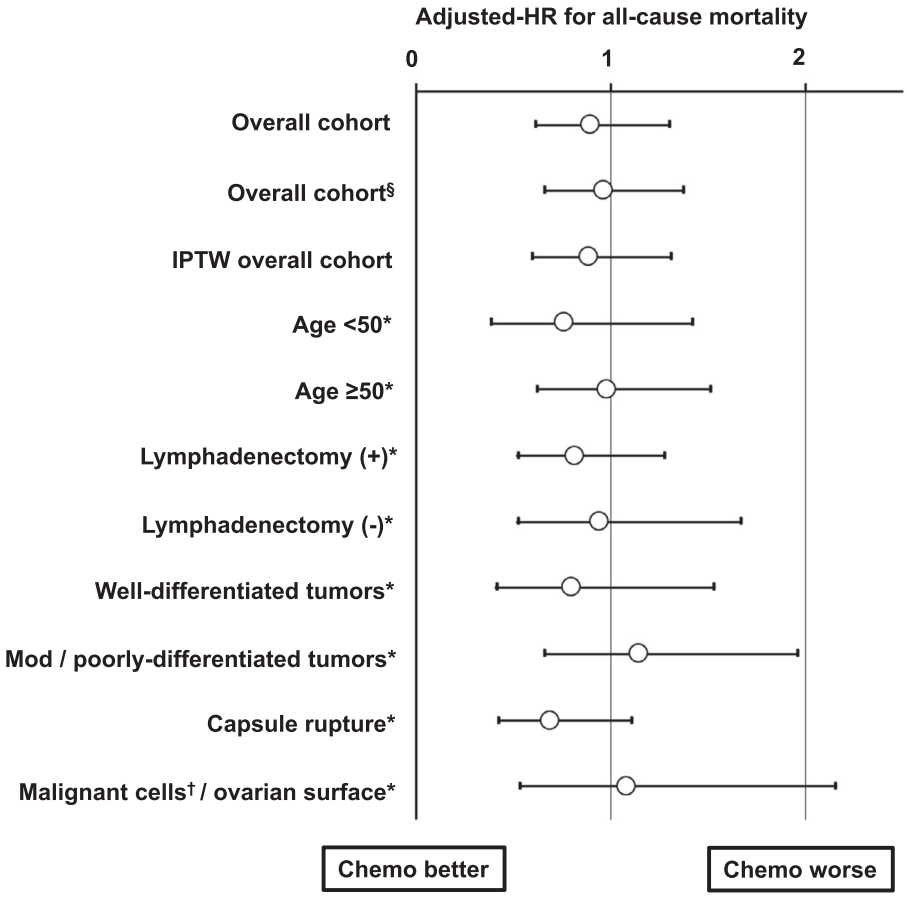

Fig. 2. Forest plots for adjusted-HR for all-cause mortality in the whole cohort and sub-groups (NCDB cohort). Cox proportional hazard regression models for multivariable analysis. Overall cohort: association of chemotherapy use and OS was adjusted for patient demographics, tumor characteristics, and treatment type. §Parsimonious Cox proportional hazard regression model, adjusted for age, race/ethnicity, tumor differentiation, comorbidity, and lymphadenectomy. *IPTW models. †Malignant cells in ascites or peritoneal cytology testing. Circles represent adjusted-HR. Bars represent 95% confidence interval. Abbreviations: HR, hazard ratio; OS, overall survival; chemo, postoperative chemotherapy; and IPTW, inverse probability of treatment weighting.

apparent stage I MOC, occult nodal metastasis occurs frequently in the infiltrative type, resulting in a poor prognosis [32].

In 2014, the WHO adopted the use of these histological subtypes in MOC, and some experts highly recommend distinguishing between them, particularly in stage I MOC as it can influence treatment approaches including the use of postoperative chemotherapy [32]. It is speculated that chemotherapy might be beneficial when the MOC is infiltrative, while the prognosis for expansile tumors may be favorable

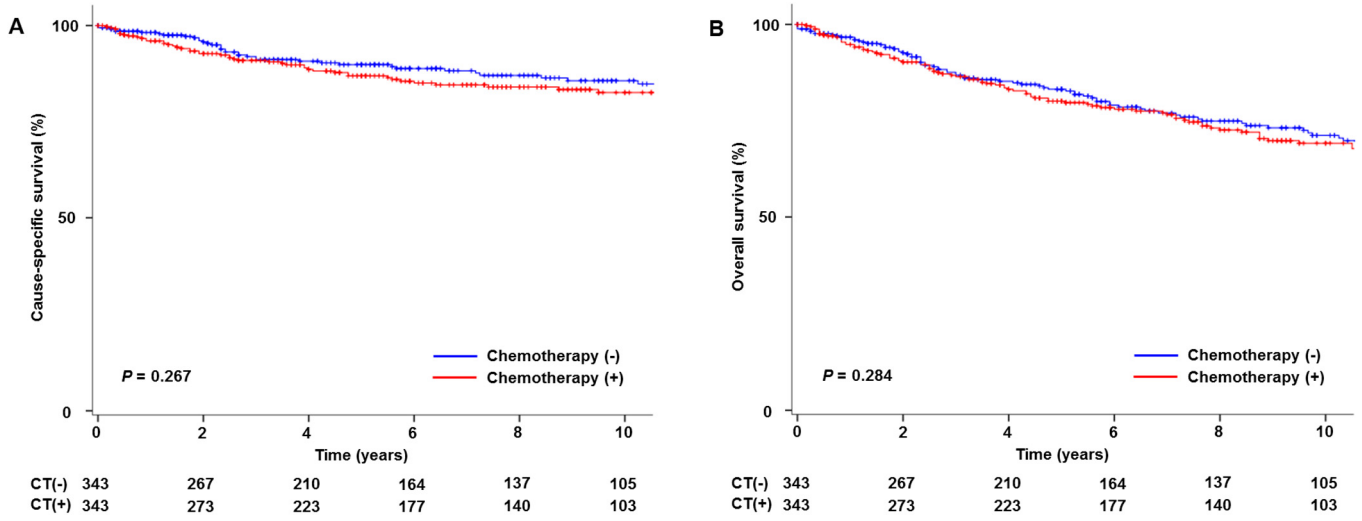

Fig. 3. Survival outcome based on chemotherapy use (SEER validation cohort). Log-rank test for *P*-values. **A)** Cause-specific survival and **B)** Overall survival are shown based on chemotherapy use in the post-matching model. Abbreviation: CT, chemotherapy.

even without chemotherapy. Both SEER and NCDB datasets do not have this histological information and incorporating this into the data variables should be considered.

Misidentification of metastatic gastro-intestinal (GI) tumors as MOC poses continued challenges, both histologically and clinically. A considerable proportion of MOC are ultimately reclassified as GI tumors following expert pathology review [4,6]. This, combined with the low response of MOC to standard ovarian cancer paclitaxel/carboplatin regimens, prompted the Gynecologic Cancer InterGroup (GCIG) in 2014 to adopt a consensus recommendation for the use of GI regimens such as oxaliplatin/fluoropyrimidine in the treatment of MOC [29]. However, to date there is no level I evidence available to support the benefit of GI-based regimens over paclitaxel/carboplatin regimens. GOG-241 examined these two regimens in MOC but the study was prematurely closed due to slow accrual [33]. No statistical difference for survival was detected between the two regimens but the low number of patients limited interpretation.

Apart from GI regimens, anti-angiogenic therapy with bevacizumab is of interest in the chemotherapeutic treatment of ovarian cancer based on recent trial results [34,35]. However, MOC represented only 1–2% of the study population in these studies, making the adaptation of their result difficult in MOC. Moreover, when it comes specifically to MOC, the results are not encouraging. In a sub-analysis of GOG-241 trial, addition of bevacizumab did not improve overall survival in advanced and recurrent MOC [33].

Our study showed that lack of lymphadectomy is independently associated with a nearly two-fold increased risk of all-cause mortality. The finding validates a prior population-based study demonstrating that lack of lymphadenectomy is associated with 1.5-fold increased risk of ovarian cancer-specific mortality in apparent stage I MOC ($n = 4066$) [26]. Historically, prevalence of lymph node metastasis is known to be low in clinical stage I MOC [36]. As the historical study was limited in sample size ($n = 107$) [36], these recent population-based studies may provide more accurate information for the role of lymphadenectomy in stage I MOC.

Strengths of this study include that this is the largest study examining the effectiveness of postoperative chemotherapy for stage IC MOC. Multiple sensitivity analyses examined in the analysis increase the statistical rigor. Additionally, consistent results within the validation cohort enhance the robustness of the study.

We recognize a number of important limitations in the study. First, this is a retrospective study, and there may be unmeasured confounding factors missing in the analysis. For example, reasons for administering or omitting postoperative chemotherapy were not available. Another weakness of the study is that adverse events and patient quality of life measurements related to chemotherapy were not available. Thus, composite endpoints in addition to survival could not be assessed. It is speculated that the decreasing trend of chemotherapy use in the elderly in this study may be due to a concern for toxicity. Also a concern is the lack of information regarding specific chemotherapy regimens in the database.

Central pathology review was not performed in this study and the diagnostic accuracy for MOC is unknown. Indeed, a major challenge in the treatment of MOC that may interfere with chemotherapy effectiveness is the diagnostic accuracy of mucinous tumors [6]. As discussed earlier, the aforementioned GOG-241 trial demonstrated that nearly half of MOCs were reclassified as non-ovarian tumors after expert pathology review (45.0%, 95% CI 29.6–60.4) [33]. Thus, some of the cases in our study population may have indeed been mucinous tumors of other origins.

Taken together, when an ovarian tumor is of mucinous histology, *(i)* comprehensive review with an experienced gynecologic pathologist and *(ii)* more sectioning (1–2 blocks per 1 cm tumor) are highly recommended in order to rule out gastrointestinal tumor as well as borderline ovarian tumor [6,32]. In addition, a thorough evaluation of the gastrointestinal system *via* systemic imaging is highly recommended to rule out a non-ovarian origin [6,32].

Information on subgrouping of stage IC is not available in our study. The NCDB data has information for capsule rupture but distinguishing intraoperative rupture *versus* spontaneous rupture was not possible. As the prognosis of stage IC ovarian cancer can be distinct across the sub-stages, further study is necessary whether there may be a substage specific benefit of postoperative chemotherapy in stage IC MOC disease. Recurrence and specific cause of death were not available and complete survival analysis was not feasible.

Last, it is noteworthy to remark the limitation of SEER coding for chemotherapy. A recent study comparing the SEER database and SEER-Medicare linked database showed that the accuracy for chemotherapy code as "yes" in the SEER database is fairly high in ovarian cancer patients (positive predictive value, 94.7%) but when chemotherapy is recorded as "no/unknown", there is a small chance of misclassification (negative predictive value, 79.7%) [37]. The SEER program therefore recommends additional external validation when interpreting chemotherapy efficacy, which we have provided with the consistent findings demonstrated in the NCDB dataset.

The main clinical utility of our study may be in the area of postoperative counseling. Based on our observation, women with stage IC MOC have a similar prognosis regardless of chemotherapy use. It appears that tumor characteristics such as differentiation and size may not be the factors that indicate a benefit of chemotherapy. As long-term toxicity rates from postoperative chemotherapy for early-stage ovarian cancer can reach ~60% [38], balanced counseling would need to be emphasized. Further study of chemotherapy use in the infiltrative subtype of stage IC MOC is warranted, and identification of an integral biomarker or biomarkers indicative of a response to chemotherapy might further pinpoint patient who might benefit from this treatment with stringent criteria.

Author contributions

Conceptualization: K.M.; Data curation: Y.H., H.M.; Formal analysis: Y.H., K.M.; Funding acquisition: K.M., J.D.W.; Investigation: all authors; Methodology: K.M., Y.H., J.D.W.; Project administration: J.D.W., K.M.; Resources: J.D.W., K.M.; Software: Y.H., H.M.; Supervision: J.D.W.; Validation: Y.H., K.M.; Visualization: Y.H., K.M.; Writing - original draft: K.M.; Writing - review & editing: all authors.

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Declaration of Competing Interest

Consultant, Tesaro and Clovis Oncology (J.W.); honorarium, Chugai, book editorial, Springer, and meeting attendance expense, VBL therapeutics (K.M.); Consultant, Tempus Lab (L.D.R.); none for others.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2019.06.021.

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