Adjuvant chemotherapy is not associated with a survival benefit for patients with early stage mucinous ovarian carcinoma

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H I G H L I G H T S

- Approximately one in three patients with stage I mucinous ovarian cancer received adjuvant chemotherapy.
- Larger tumor size, higher grade, stage IC and performance of LND were associated with its administration.
- Adjuvant chemotherapy was not associated with a survival benefit.

A R T I C L E   I N F O

A B S T R A C T

Objective. Primary mucinous ovarian carcinoma (MOC) is a rare histologic subtype of ovarian cancer. The benefit of adjuvant chemotherapy for patients with MOC is unclear.

Patients and methods. Patients diagnosed with stage I mucinous ovarian cancer (MOC) between 2004 and 2015 were identified from the U.S National Cancer Database. Those with a history of another primary tumor were excluded. Factors independently associated with the receipt of chemotherapy were identified using logistic regression. Impact of chemotherapy on overall survival (OS) for patients diagnosed between 2004 and 2014 was assessed using was Kaplan-Meier curves, and compared with the log-rank test. A multivariate Cox analysis was performed to control for confounders.

Results. We identified 4811 patients with a median age at diagnosis of 51 years (IQR: 21). Chemotherapy was administered to 1488 (30.9%) patients; 20.2% and 60.2% for those with stage IA/IB and IC respectively, $p < 0.001$. Stage IC, larger tumor size, and high tumor grade, were associated with the receipt of chemotherapy. There was no difference in OS between patients who did (n = 1322) and did not (n = 2920) receive chemotherapy, $p = 0.17$; 5-year OS rate was 86.8% vs 89.7%, respectively. No difference was noted following stratification by substage ($p = 0.46$ for IA/IB and $p = 0.11$ for IC). After controlling for substage, patient age, type of insurance, tumor grade, performance of lymphadenectomy and the presence of co-morbidities, the administration of chemotherapy was not associated with better survival (HR:1.18, 95% CI: 0.85, 1.64).

Conclusions. In a large cohort of patients with stage I MOC, receiving chemotherapy was not associated with a survival benefit.

1. Introduction

Primary mucinous ovarian carcinoma (MOC) is a rare histologic sub-type of epithelial ovarian cancer characterized by frequent KRAS muta-tions and accounting for approximately 1–3% of all ovarian tumors [1]. MOC typically arises in premenopausal women who present with large unilateral tumors confined to the ovary [1,2]. Based on a recent meta-analysis, for patients with early stage disease, mucinous histology is associated with better oncologic outcomes compared to the more prevalent serous histology [3]. The surgical management of apparent early stage disease for patients who have completed their reproductive potential includes bilateral salpingo-oophorectomy with hysterectomy and performance of a staging procedure that includes omentectomy, washings and peritoneal biopsies [1]. Given the low incidence of re-gional lymph node metastases, systematic lymphadenectomy can be omitted in the absence of suspiciously enlarged lymph nodes, especially for patients with low grade tumors [4,5].

For patients with stage I high grade serous ovarian carcinoma (SOC), the administration of 6 cycles of carboplatin and paclitaxel following

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surgery is associated with a decreased risk of tumor recurrence [6]. However, the role of adjuvant treatment for patients with early stage MOC is not clearly defined [1,7]. The ACTION and ICON-1 randomized trials included only 180 patients with MOC and did not reveal a statistically significant difference in recurrence rates between the observation and chemotherapy arms [7–9]. Currently, the National Comprehensive Cancer Network (NCCN) guidelines recommend observation for patients with stage IA/IB MOC, while both observation and adjuvant chemotherapy are acceptable for those with stage IC [10]. On the other hand, the European Society for Medical Oncology (ESMO) guidelines do not offer specific guidance for mucinous histology and recommend the administration of adjuvant chemotherapy for patients with epithelial ovarian cancer (including mucinous carcinoma) and high risk characteristics such as substage IB/IC and grade 2/3 tumors, or grade 3 tumors of any substage [11].

Given the paucity of evidence in this area, the aim of the present study was to investigate the prevalence of adjuvant chemotherapy use among patients with MOC and the impact on overall survival using a large hospital-based database. Our primary hypothesis was that adjuvant chemotherapy is not associated with a survival benefit.

2. Materials and methods

The National Cancer Data Base (NCDB) was accessed and a cohort of patients diagnosed between 2004 and 2015 with a pathologically confirmed primary ovarian carcinoma (WHO site code C.569/ovary) was drawn. The NCDB, has been established jointly by the American Cancer Society and Commission on Cancer of the American College of Surgeons, as a hospital-based database capturing data of patients with newly diagnosed cancer in the United States. Patient data are prospectively collected from participating commission-accredited cancer programs and are regularly audited. All data are de-identified and available for research purposes [12]. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytical or statistical methodology employed, or the conclusions drawn from these data. The present study was deemed exempt from the Penn Institutional Review Board (IRB).

Patients with MOC were identified based on ICD-O-3 histology codes (8310/3–8313/3, 9110/3) as grouped by the International Agency for Research on Cancer [13]. Those with stage I disease who underwent primary surgery (as assessed from site-specific surgery codes) and did not have a personal history of another tumor were selected for further analysis. Interval between surgery and chemotherapy administration was calculated, and similar to previous studies [14,15], we excluded patients who received chemotherapy >6 months following primary surgery given the possibility of chemotherapy use in the recurrent setting. In addition, cases without available information on the administration of chemotherapy, those who received neoadjuvant treatment, and those with unknown surgery-chemotherapy interval were excluded from the present study. Based on the information available at the extent of disease of the collaborative staging schema, cases were assigned to sub-stage IA/IB or IC. We opted to exclude cases assigned to stage INOS (not otherwise specified). Supplemental Fig. 1 depicts the patient selection flowchart.

Demographic and clinico-pathological data were extracted from the de-identified NCDB dataset. Performance of lymph node sampling/dissection was assessed from the "regional lymph node surgery" variable while number of removed lymph nodes (LNs) was obtained from pathology report. The presence of medical co-morbidities was evaluated using the Charlson-Deyo Comorbidity index score and was categorized into absent (score 0) and present (score ≥ 1). Each facility reporting cases to the NCDB is assigned a category classification (community, comprehensive community, integrated network and academic/research cancer program) by the Commission on Cancer Accreditation program. For the purpose of this analysis, reporting facility type was divided into academic and non-academic (that includes community,

comprehensive community cancer, integrated network cancer center). In the NCDB database, to protect patient identity, the type of treatment facility is suppressed for patients younger than 40 years (1150 patients in the present cohort). Patient race was recoded as White and non-White/Unknown while patient age was dichotomized into ≤50 and >50 yrs.

The presence of temporal trend in the rate of adjuvant chemotherapy administration was evaluated using the Joint Point Regression Program 4.5.0 [16]. Categorical and continuous variables were compared between patients who did and did not receive adjuvant chemotherapy with the chi-square and Mann-Whitney U tests respectively. A binary logistic regression was performed to identify clinical variables independently associated with the administration of adjuvant chemotherapy.

In the NCDB, overall survival is defined as the number of months elapsed from tumor diagnosis to the date of death or last-follow up. Follow-up data were available for cases diagnosed between 2004 and 2014 and suppressed for patients diagnosed in 2015. Kaplan-Meier curves were generated to determine 5-year OS rates while univariate analysis was performed with the log-rank test. Stratified analyses by tumor grade, and substage were performed. A Cox multivariate model was constructed to evaluate the impact of adjuvant chemotherapy on overall survival after controlling for variables associated with OS in the univariate analysis. For survival analysis, a minimum of 1 month of follow-up was required. Statistical analysis was performed with the SPSS v.24 statistical package (IBM Corp. Armonk, NY), and the alpha level of statistical significance was set at 0.05.

3. Results

A total of 4811 patients met the inclusion criteria. Median patient age was 51 years (IQR: 21). The majority were of White race (86.3%), did not have any comorbidities (84.2%), presented with unilateral tumors (97.4%), and had stage IA/IB disease (73.1%). Median tumor size was 16 cm (n = 3959) and grade 3 tumors were infrequent (8.7%) while the rate of LND was 70%.

In the present cohort, the rate of adjuvant chemotherapy administration (CT) was 30.9% (1488 patients); more specifically 1370 (92.1%) patients received a multi-agent regimen, 50 patients had a single agent regimen, while for 68 patients there was no information available on the number of agents administered. Median interval from surgery to chemotherapy administration was 41 days (IQR: 29 days). The percentage of patients receiving chemotherapy did not change over time (AAPC: 0.85, p > 0.05). On univariate analysis, patients who received chemotherapy were older, had larger tumors, had higher grade histology, and more likely to have stage IC disease (Table 1). No difference was noted based on the type of reporting facility, patient race, median income or the presence of comorbidities. Multivariable analysis showed that tumor size ≥10 cm (OR: 1.30, 95% CI: 1.09, 1.54), stage IC disease (OR: 6.68, 95% CI: 5.74, 7.76), higher histologic grade and performance of LND (OR: 1.41, 95% CI: 1.20, 1.66) were factors associated with the administration of adjuvant chemotherapy (Table 2).

A total of 4242 patients diagnosed between 2004 and 2014, who had at least one month of follow-up were included in the survival analysis. According to the reverse Kaplan-Meier method, the median follow-up in the chemotherapy (n = 1322) and observation (n = 2920) groups was comparable, 63.11 (95% CI: 58.03, 61.55) and 57.82 (95% CI: 55.76, 59.88) months respectively. There was no difference in OS between patients who did and did not receive chemotherapy, p = 0.17 (Fig. 1); 5-yr OS rates were 86.8% and 89.7% respectively. For patients with stage IA/IB disease, there was no difference in OS between the observation (n = 2465) and the chemotherapy groups (n = 618), p = 0.46 (Fig. 2); 5-year OS rates were 90.5% and 88.1% respectively. Similarly, for patients with stage IC disease, there was no difference in OS between the observation (n = 455) and chemotherapy (n = 704) groups, p = 0.11 (Fig. 3); 5-year OS rates were 85.1% and 85.6% respectively.
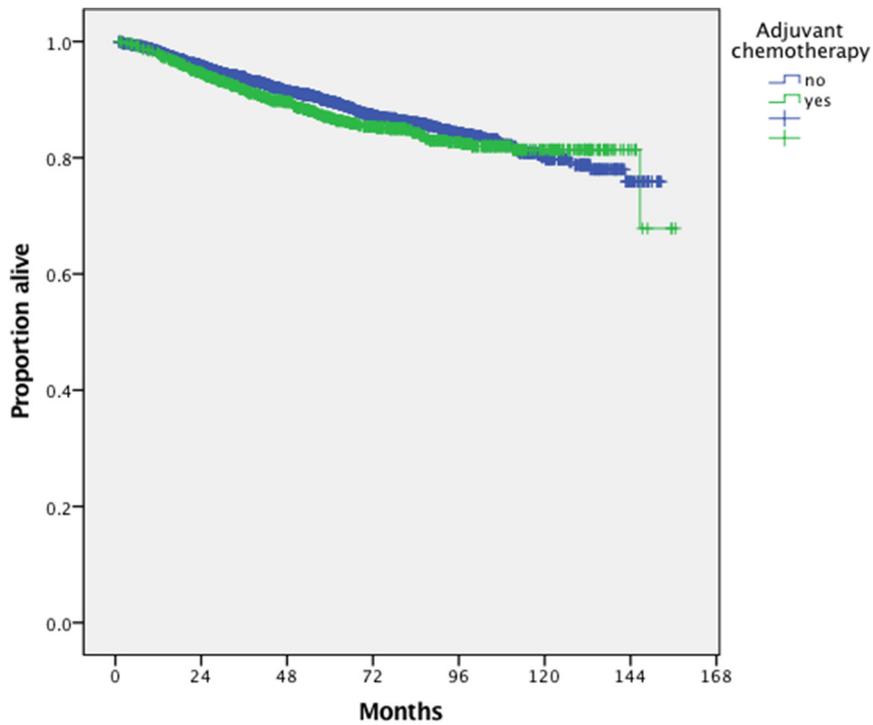
Fig. 1. Overall survival of patients with stage I mucinous ovarian carcinoma who did (n = 1322) and did not (n = 2920) receive adjuvant chemotherapy, p = 0.17 from log-rank.

Following stratification by tumor grade, no difference in OS between patients who did and did not receive chemotherapy was noted for grade 1 (p = 0.51), grade 2 (p = 0.66) or grade 3 (p = 0.99) tumors (Supplemental Figs. 2–4).

When analyzing patients who had at least 10 LNs removed (used as a surrogate for adequate staging), there was no difference in OS between those who received (n = 559) and those who did not (n = 1092) receive chemotherapy, p = 0.95; 5-year OS rates were 90.8% and 90.6% respectively. For patients with stage IA/IB disease, there was no difference in OS between the observation (n = 930) and chemotherapy groups (n = 246), p = 0.24 (Supplemental Fig. 5); 5-year OS rates were 91% and 92.8% respectively. Similarly for patients with stage IC disease there was no difference in OS between the observation (n = 162) and chemotherapy (n = 313) groups, p = 0.94 (Supplemental Fig. 6); 5-year OS rates were 89.4% and 88.8% respectively.
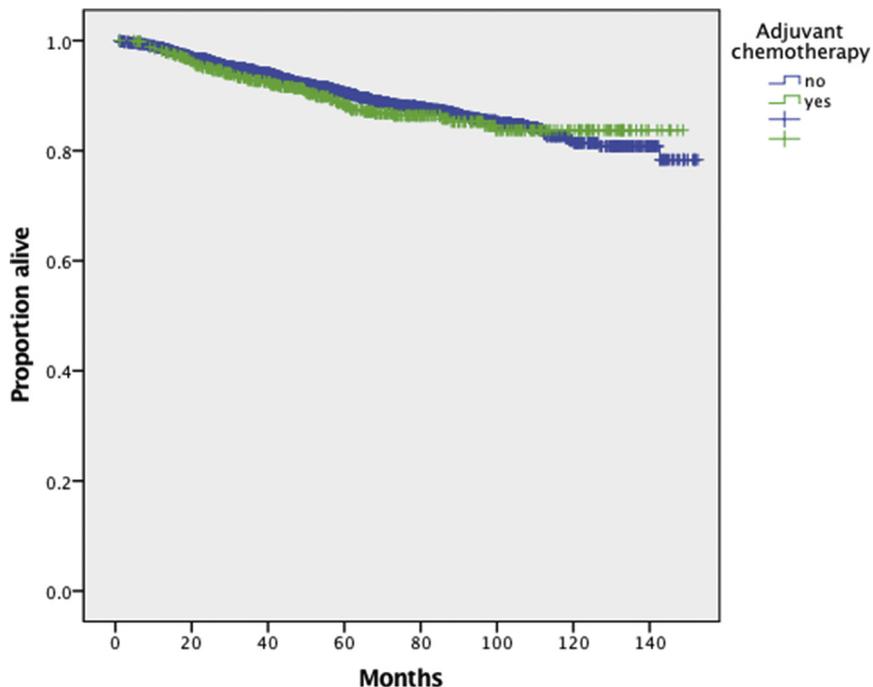

Fig. 2. Overall survival of patients with stage IA/IB mucinous ovarian carcinoma who did (n = 618) and did not (n = 2465) receive adjuvant chemotherapy, p = 0.46 from log-rank.
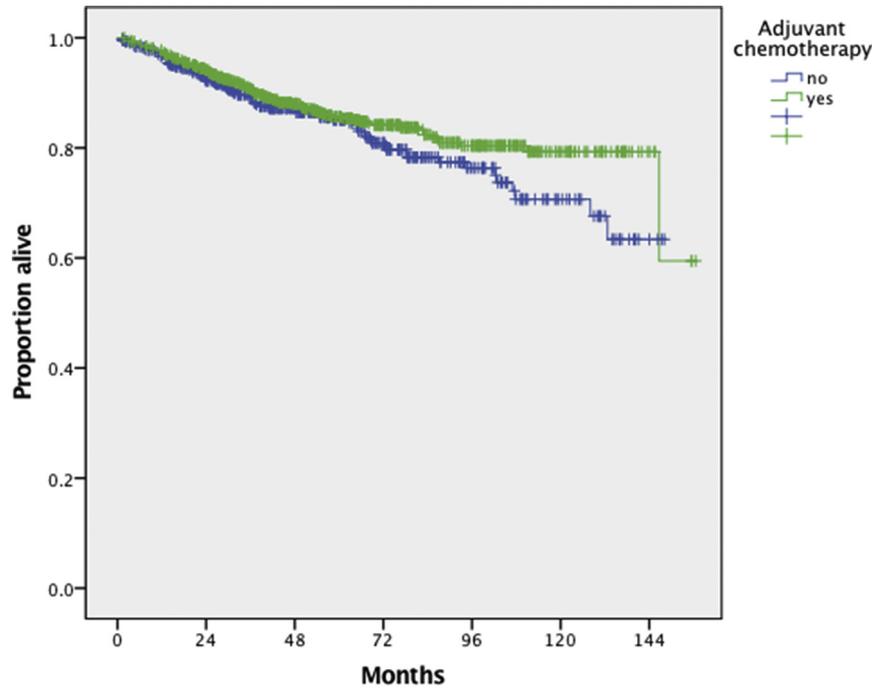
Fig. 3. Overall survival of patients with stage IC mucinous ovarian carcinoma who did (n = 704) and did not (n = 455) receive adjuvant chemotherapy, p = 0.11 from log-rank.

After controlling for patient age, the presence of co-morbidities, the type of insurance, disease sub-stage, tumor grade and size, and the performance of LND, the administration of adjuvant chemotherapy was not associated with a better overall survival (HR: 1.18, 95% CI: 0.85, 1.64) (Table 3).

Table 1
Clinicopathological characteristics of patients with stage I mucinous ovarian carcinoma stratified by the administration of adjuvant chemotherapy.

Variable	Observation	Chemotherapy	p-Value
Age			0.004
≤50 yrs	1638 (49.3%)	667 (44.8%)	
>50 yrs	1685 (50.7%)	821 (55.2%)	
Race			0.80
White	2872 (86.4%)	1282 (86.2%)	
Non-white/unknown	451 (13.6%)	206 (13.8%)	
Comorbidities			0.51
Yes	518 (15.6%)	243 (16.3%)	
No	2805 (84.4%)	1245 (83.7%)	
Insurance status			0.051
Private	1940 (58.4%)	900 (60.5%)	
Government	1017 (30.6%)	458 (30.8%)	
Uninsured/unknown	366 (11%)	130 (8.7%)	
Type of reporting facility			0.69
Academic	1101 (33.1%)	500 (33.6%)	
Non-academic	1416 (42.6%)	644 (43.3%)	
Unknown	806 (24.3%)	344 (23.1%)	
Size			<0.001
<10 cm	891 (26.8%)	324 (21.8%)	
≥10 cm	1925 (57.9%)	958 (64.4%)	
Unknown	507 (15.3%)	206 (13.8%)	
Grade			<0.001
Grade 1	1475 (44.4%)	376 (25.3%)	
Grade 2	914 (27.5%)	651 (43.8%)	
Grade 3	141 (4.2%)	276 (18.5%)	
Unknown	793 (23.9%)	185 (12.4%)	
Substage			<0.001
IA/IB	2808 (84.5%)	710 (47.7%)	
IC	515 (15.5%)	778 (52.3%)	
Lymphadenectomy			<0.001
Yes	2249 (67.7%)	1118 (75.1%)	
No/unknown	1074 (32.3%)	370 (24.9%)	

4. Discussion

In this large cohort of patients with early stage MOC, approximately one in three patients received chemotherapy. We did not observe any clear benefit from adjuvant chemotherapy on overall survival; even after stratification by disease substage or tumor grade. For patients with stage IC disease based on visualization of Kaplan-Meier curves those who received adjuvant chemotherapy had a trend towards a better survival though this difference did not reach statistical significance. However, given that information on the quality of the staging procedures performed is not available in the NCDB, a sensitivity analysis was performed by including only patients who had adequate LND (with at least 10 LNs removed); adequate LND was used as a surrogate marker for adequate staging. In that subgroup, the administration of

Table 2
Independent predictors of adjuvant chemotherapy use for patients with stage I mucinous ovarian carcinoma.

Variable	Odds ratio (95% CI)	
Age		0.34
≤50 yrs	Referent	
>50 yrs.	1.08 (0.93, 1.25)	
Size		0.011
<10 cm	Referent	
≥10 cm	1.30 (1.09, 1.54)	
Unknown	1.24 (0.98, 1.57)	
Insurance status		0.075
Private	Referent	
Government	0.86 (0.73, 1.02)	
Uninsured/unknown	0.77 (0.60, 0.98)	
Grade		<0.001
Grade 1	Referent	
Grade 2	2.90 (2.46, 3.43)	
Grade 3	9.28 (7.21, 11.95)	
Unknown	0.90 (0.73, 1.12)	
Substage		<0.001
IA/IB	Referent	
IC	6.68 (5.74, 7.76)	
Lymphadenectomy		<0.001
No/unknown	Referent	
Yes	1.41 (1.20, 1.66)	

Table 3
Multivariate survival analysis of patients with stage I mucinous ovarian carcinoma.

Variable	Hazard ratio (95% CI)
Age	
≤50 yrs	Referent
>50 yrs	1.94 (1.57, 2.39)
Comorbidities	
No	Referent
Yes	1.25 (0.99, 1.55)
Insurance	
Private	Referent
Government	2.13 (1.75, 2.60)
Uninsured/unknown	1.53 (1.11, 2.11)
Adjuvant chemotherapy[a]	
No	Referent
Yes	1.18 (0.85, 1.64)
Grade	
Grade 1	Referent
Grade 2	1.27 (1.02, 1.58)
Grade 3	1.56 (1.14, 2.12)
Unknown	0.90 (0.69, 1.17)
Substage	
IA/IB	Referent
IC	1.54 (1.25, 1.88)
Lymphadenectomy	
No/unknown	Referent
Yes	0.75 (0.62, 0.91)

[a] Entered as time-dependent variable.

adjuvant chemotherapy was also not associated with improved overall survival.

Two large randomized trials (ICON1 and ACTION) have investigated the role of adjuvant chemotherapy for patients with early stage EOC; concluding that those with high risk characteristics such as clear cell histology, grade 3 tumors and stage IC disease benefit from chemotherapy. However, in both trials only 180 (20%) of 925 patients had MOC. For those 180 patients, there was no statistically significant difference in the relapse rate between the chemotherapy arm (10 recurrences) and the observation arm (22 recurrences) arms [7–9]. While our study here was retrospective in nature, drawing upon over 4000 patients with MOC from a national cancer database, we also did not find a survival advantage for those receiving chemotherapy, in both unadjusted and adjusted analyses.

Ovarian cancer is a heterogeneous disease at the histological and molecular level; the evidence derived from SOC cannot be always extrapolated to other histological subtypes. To date there is no evidence supporting the administration of adjuvant chemotherapy for patients with early stage MOC. It is well demonstrated that MOC is more chemoresistant compared to serous ovarian carcinoma [17,18]. Interestingly, in a post-hoc analysis of the GOG 157 trial that compared the efficacy of three versus six cycles of adjuvant chemotherapy for patients with early stage EOC, those with MOC (n = 31) did not draw any benefit from the 6 cycles course (hazard ratio for relapse was 1.68, 95% CI: 0.30–9.29) [6].

The management of patients with MOC is further complicated by the lack of consensus on the optimal chemotherapy regimen. Based on the current guidelines, both gynecologic (such as carboplatin and paclitaxel) and gastrointestinal chemotherapy regimens (FOLFOX and XELOX) are acceptable options [10]. However, the former seems to be preferred. In a multicenter study, among patients with stage I/II disease, 79% (30/38) received a gynecologic regimen [19]. Data comparing the efficacy of gynecologic versus gastrointestinal regimens are lacking. Unfortunately, the phase II international multicenter study (GOG 241) designed to address this question was prematurely terminated due to poor accrual, with only 50 patients being recruited. The carboplatin-paclitaxel and oxaliplatin-capecitabine (with or without bevacizumab) groups included 24 and 26 patients respectively; the progression free survival (PFS) was not statistically different between the two groups (15.4 vs 10.1 months; HR: 1.08, 95% CI 0.53–2.19, p = 0.83) [20]. In

another small retrospective study, no PFS or OS difference was found between patients who received a gastrointestinal (n = 7) or a gynecologic chemotherapy regimen (n = 14) [21].

Recent molecular studies have revealed that MOC is a heterogeneous tumor at the mutational level [22]. The question arises whether a specific subgroup of patients with a distinct mutational profile could potentially benefit from adjuvant chemotherapy administration. In addition, patients with an infiltrative subtype exhibit worse oncologic outcomes compared to those with expansile histologic subtype [23,24]. However, the administration of adjuvant treatment does not seem to influence recurrence rates among patients with infiltrative MOC [23]. Guy et al. compared the clinico-pathological characteristics and outcomes of patients with stage I expansile (n = 29) and infiltrative (n = 35) MOC. The rate of adjuvant chemotherapy was comparable between the two groups (34% vs 31% respectively). Overall, the rate of relapse was comparable between patients who did and did not receive adjuvant chemotherapy. Interestingly, among the 4 patients with stage IC infiltrative MOC who experienced a relapse, 3 had received adjuvant chemotherapy [23].

Certain limitations of the present study should be noted. Given the absence of central pathology review and data on preoperative investigation (imaging, gastroscopy and colonoscopy rates) possible tumor and staging misclassifications cannot be excluded. The discrimination of a primary mucinous ovarian carcinoma from metastases to the ovary from another primary tumor (usually from a GI source) can be challenging [25]. However, we opted to exclude patients who had a personal history of another tumor to minimize potential misclassifications. Molecular data (such as presence of KRAS mutations) are not collected by the NCDB precluding us from investigating the effect of adjuvant chemotherapy in patients with specific gene mutations. In addition while all patients underwent surgery, the extend and thoroughness of the staging procedures performed was not documented thus a portion of patients would had presumed stage I disease. Moreover, due to the lack of information on cause of death and tumor relapse, analysis of cancer-specific and progression-free survival was not feasible. Also, information on the chemotherapy regimens (specific agents, dosage, and number of cycles) used in the management of each patient was not available. Lastly, unmeasured factors influencing clinician's decision to administer adjuvant chemotherapy such as patient's functional status or primary physician's subspecialty were not available in NCDB.

In this large contemporary cohort of patients with stage I MOC, approximately one in three patients received adjuvant chemotherapy with no clear benefit on overall survival. Given the lack of clear evidence, the decision to administer adjuvant chemotherapy should be individualized following appropriate counseling. Randomized trials are extremely difficult to perform even with international participation. Creation of an international database may further aid in the clarification of the optimal management of these patients and identify any subgroups that can benefit from adjuvant treatment.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2019.05.009.

Conflicts of interest

No conflicts of interest to report.

Contributions

DN: conception, statistical analysis, critical analysis, drafting/final editing.
AH: critical analysis, drafting/final editing.
RG: critical analysis, drafting/final editing.
RB: critical analysis, drafting/final editing.
MM: critical analysis, drafting, final editing.
EK: critical analysis, drafting/final editing.
NA: supervision, critical analysis, drafting/final editing.

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