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Original Article

Could fertility-sparing surgery be considered for women with early stage ovarian clear cell carcinoma?

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

ABSTRACT

Objective: The aim of the present retrospective population-based study was to investigate the oncologic impact of uterine and ovarian preservation (OP) in premenopausal women with stage IA or IC ovarian clear cell carcinoma (OCCC).
Methods: The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database was accessed and a cohort of surgically-staged premenopausal women (age <50 years) diagnosed with unilateral stage IA or IC OCCC was drawn. Based on site-specific surgery codes, women who did not undergo hysterectomy and/or bilateral salpingo-oophorectomy (BSO) were identified. Overall survival (OS) and cancer-specific survival (CSS) rates were calculated following generation of Kaplan-Meier curves; comparisons were made with the log-rank test. Multivariate Cox analysis was performed to control for possible confounders.
Results: A total of 741 premenopausal women who met the inclusion criteria were identified. Based on available information, rate of uterine preservation was 14.5% (96/663) while the rate of OP was 28.1% (71/253). Five-year CSS rates were 90.8% for women who did not undergo hysterectomy compared with 87.7% for those who did (p=0.290). Similarly, 5-year CSS rates in the OP and BSO groups were 92.6% and 85%, respectively (p=0.060). After controlling for disease sub-stage (IA vs. IC), uterine or OP was not associated with a worse overall or cancer-specific mortality.
Conclusion: In the present cohort, uterine and OP did not have a negative impact on oncologic outcomes. Selection criteria for fertility-sparing surgery (FSS) could be expanded to include women with stage IA OCCC.

Keywords: Ovarian Neoplasms; Adenocarcinoma, Clear Cell; Fertility; Fertility Preservation

INTRODUCTION

Ovarian cancer is a heterogenous group of tumors, each associated with unique clinicopathological and epidemiological characteristics [1]. Clear cell carcinoma (CCC) is a histologic subtype of epithelial ovarian carcinoma (EOC) accounting for approximately 5%–25% of all cases [2]. Women with CCC most commonly present with disease confined to the ovary, while an increased incidence is observed among those of Asian, especially Japanese, ancestry [2,3]. CCC is also characterized by a relative resistance to first line platinum-based chemotherapy and can frequently arise from endometriotic foci [2,3].

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Standard surgical management of EOC includes bilateral salpingo-oophorectomy (BSO) and hysterectomy. However, ovarian cancer can arise in premenopausal women who may have not completed childbearing; almost 14% of women diagnosed with early stage EOC are under 40 years old [4]. While the safety of fertility-sparing surgery (FSS, preservation of the uterus and contralateral ovary) has been established for women with ovarian germ cell tumors, currently the concept is also applied to those with EOC and low-risk characteristics [5-7]. FSS is more commonly offered to premenopausal patients with grade 1 or grade 2 serous/mucinous/endometrioid tumors and stage IA or IC disease [6,7]. Clear cell histology is regarded as a "high-risk" tumor subtype since it is associated with poorer outcomes [8]. As such, fertility-preserving options are less frequently pursued for women with these tumors [6,7].

Since randomized trials on the safety of FSS for early stage EOC have not been performed, evidence supporting the safety of FSS for premenopausal women with CCC mainly derives from single institutional case-control studies plagued by small sample sizes and inadequate statistical power [9-13]. A recent comprehensive systematic review identified only 115 patients with early stage CCC who underwent FSS [6]. Given the paucity of evidence, the aim of the present retrospective study was to investigate the oncologic impact of uterine and ovarian preservation (OP) in premenopausal women with stage IA or IC ovarian CCC (OCCC) using a multi-institutional, population-based database. Moreover, in a secondary analysis we evaluated the prevalence of regional lymph node (LN) metastasis among premenopausal women with stage I apparent OCCC who are potential candidates for FSS.

MATERIALS AND METHODS

In the present retrospective study, a cohort of premenopausal women (age <50 years) diagnosed between 1988–2013 with a primary ovarian tumor was drawn from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database. In the present study, data deriving from 18 cancer registries were included (Detroit, Iowa, Kentucky, Louisiana, Utah, Connecticut, New Jersey, Atlanta, Rural and Greater Georgia, Alaska, California, Hawaii, Los Angeles, New Mexico, San Francisco, San Jose, and Seattle), which cover approximately 27.8% of the total US population based on the 2010 census [14]. All patient data are de-identified and available to the public for research purposes. An exemption was also granted from obtaining institutional review board approval.

Using the 3rd edition of International Classification of Diseases for Oncology (ICD-O-3)/World Health Organization (WHO) 2008 site code "C.569/ovary" and the ICD-O-3 morphology codes "8310-8313/3, 9110/3" as grouped by the International Agency for Research on Cancer (IARC), cases of OCCC were identified [15]. Women with a history of a previous primary tumor at another site, those with bilateral tumors, without microscopic tumor confirmation or active follow-up as well as women who did not undergo cancer-directed surgery were excluded from the present study. Only those with the International Federation of Gynecology and Obstetrics (FIGO) stage IA or IC disease were selected for further analysis. Based on site-specific surgery codes the nature of cancer-directed surgery was assessed and women who did not undergo hysterectomy and/or BSO were identified. A flowchart with the patient selection process is presented in **Fig. 1**. For analysis purposes, year of diagnosis was dichotomized into 1988–2003 and 2004–2013 based on the year of publication of the Adjuvant ChemoTherapy in Ovarian Neoplasm (ACTION) and International Collaborative Ovarian Neoplasm Trial 1 (ICON1) studies on the value of adjuvant chemotherapy in early stage epithelial ovarian cancer [16].

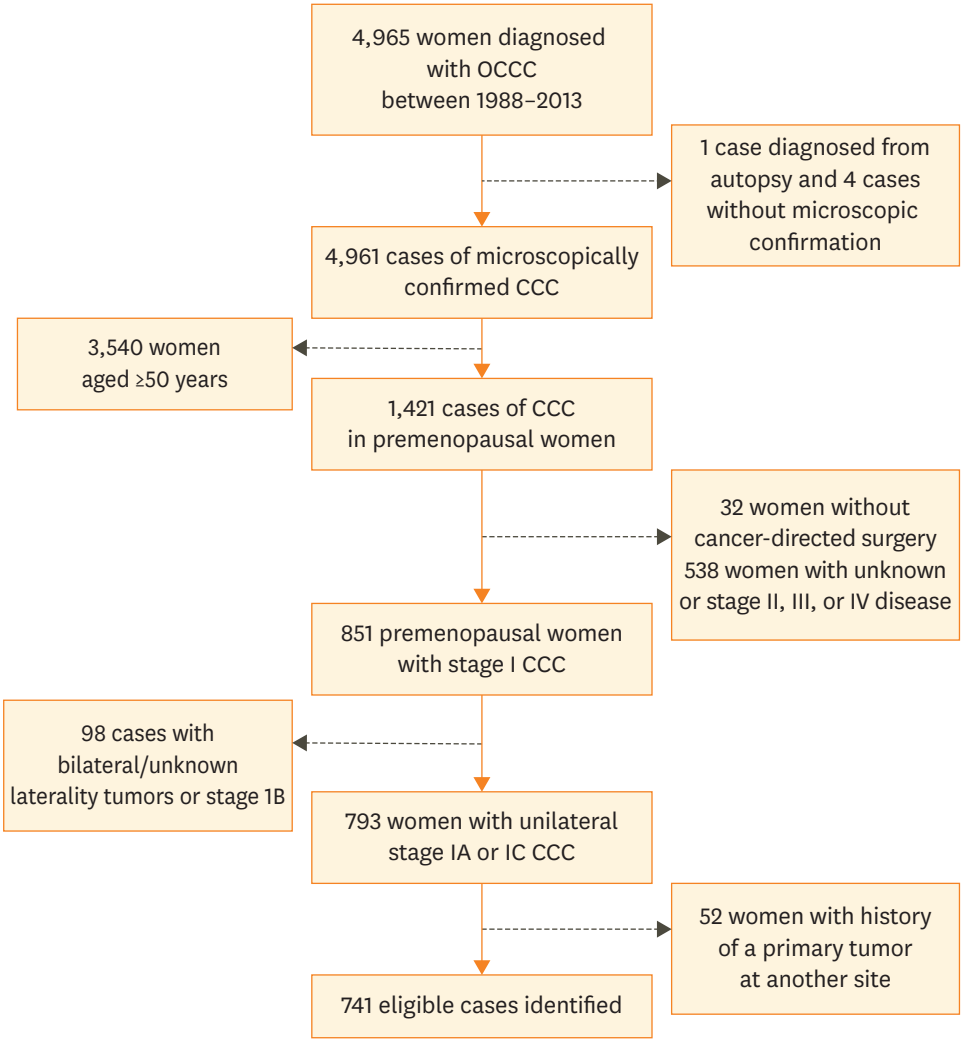

Fig. 1. Patient selection flowchart.
CCC, clear cell carcinoma; OCCC, ovarian clear cell carcinoma.

Primary outcome of interest was death from ovarian cancer (cancer-specific survival, CSS) while secondary outcome was death from any cause (overall survival, OS). The SEER database does not collect information on tumor recurrence precluding us from investigating progression free survival. Five-year OS and CSS rates were estimated following generation of Kaplan-Meier curves. For the estimation of CSS, women who died from causes other than ovarian cancer were censored. Patients who were alive with <1 months of follow-up were excluded from the survival analysis. Univariate comparison of OS and CSS was performed with the log-rank test. Moreover, Cox multivariate models were constructed to evaluate the effect of uterine and OP on mortality after controlling for possible confounders. Variables that were statistically significantly (or approached statistical significance) associated with survival by univariate analysis were selected for entry in the multivariate model. For the estimation of the prevalence of LN metastasis among premenopausal women with stage I apparent disease (T1/Nx/M0) information deriving from the histopathology report was evaluated to identify those who underwent LN dissection (LND) and the status of the examined LNs. Frequency of categorical variables was compared with the chi-square test and that of continuous variables with Mann-Whitney U test. All statistical analysis was performed

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with the SPSS v.24 statistical package (IBM Corp., Armonk, NY, USA) and the alpha level of statistical significance was set at 0.05. The Joinpoint Regression Program 4.4.0 provided by the National Cancer Institute was used to evaluate and visualize temporal trends in use of uterine and ovarian conservation [17]. Rate of uterine and ovarian conservation were modeled as a function of calendar year following log transformation.

RESULTS

A total of 741 premenopausal women with stage IA or IC unilateral OCCC who underwent cancer-directed surgery were identified. The mean patient age was 42.85 years (range, 18–49; standard deviation [SD], 5.2); more specifically 54.7% and 45.3% were <45 and 45–49 years old, respectively. The majority were White (75%) followed by Asian/Pacific Islander (21.2%) and other (3.8%). Most women presented with stage IA disease (468 cases, 63.2%) while 36.8% (272 cases) had stage IC disease. Based on available information median tumor size was 9 cm (range, 0.1–30; n=543). LN sampling/LND was performed in the majority of cases (72.5%) while a median of 13 LNs were removed and histopathologically examined (range, 1–67; n=498). According to the reverse Kaplan-Meier method, median follow-up of the cohort was 114 months. Five-year OS and CSS were 87.2% and 88%. Only stage IA was associated with better OS by univariate analysis (p=0.001) but not age (p=0.510), year of diagnosis (p=0.400), race (p=0.180), or performance of LND (p=0.410). Similarly, stage IA was associated with better CSS (p<0.001), but not age (p=0.350), race (p=0.780), year of diagnosis (p=0.580), or performance of LND (p=0.970).

Based on site-specific surgery codes, the rate of uterine preservation was 14.5% (96 out of 663 patients). A statistically significant decrease in the rate of hysterectomy was noted between 1988 and 2014 (annual percent change, −0.57; 95% confidence interval [CI], −0.96, −0.19; p=0.010) (**Fig. 2**). Rate of uterine preservation was 19.1% for women diagnosed between 2004–2013 compared to 9.9% for those diagnosed between 1988–2003 (p=0.001). The rate of uterine preservation were 16.3% and 11.3% for women diagnosed with stage IA and IC, respectively (p=0.086). Women who did not undergo hysterectomy were younger (median age, 39.5 years vs. 44 years; p<0.001) and they were less likely to receive LND (55.8% compared to 74.4%; p<0.001). According to the reverse Kaplan-Meier method, median follow-up in the uterine preservation group was 82 months. Five-year CSS rates was 90.8% for women who did not undergo hysterectomy compared with 87.7% for those who did (p=0.290 from log-rank test) (**Fig. 3**). Similarly, the 5-year OS rate were 89.3% and 87.2% in the uterine preservation and hysterectomy groups respectively (p=0.420 from log-rank test). No difference in OS (p=0.540) or CSS (p=0.610) was noted when only women who underwent LND were analyzed separately. Following stratification by disease sub-stage, 5-year OS and CSS rates for those with stage IA and preserved uterus (n=67) were 93.1% and 95.0% compared to 91.5% (p=0.420) and 92.1% (p=0.210) respectively for those who underwent hysterectomy (n=352). For women with stage IC disease, 5-year OS and CSS rates in the uterine preservation group (n=27) were 77.5% and 77.5% compared with 79.7% (p=0.930) and 79.4% (p=0.840) respectively for those who underwent hysterectomy (n=212). After controlling for disease sub-stage (IA vs. IC), uterine preservation was not associated with a worse cancer-specific (hazard ratio [HR], 0.75; 95% CI, 0.36, 1.56) or overall (HR, 0.84; 95% CI, 0.44, 1.62) mortality.

The rate of OP was 28.1% (71 out of 253 cases). A statistically significant decrease in the rate of BSO was noted between 1988–2014 (annual percent change, −1.85; 95% CI, −2.78, −0.90)

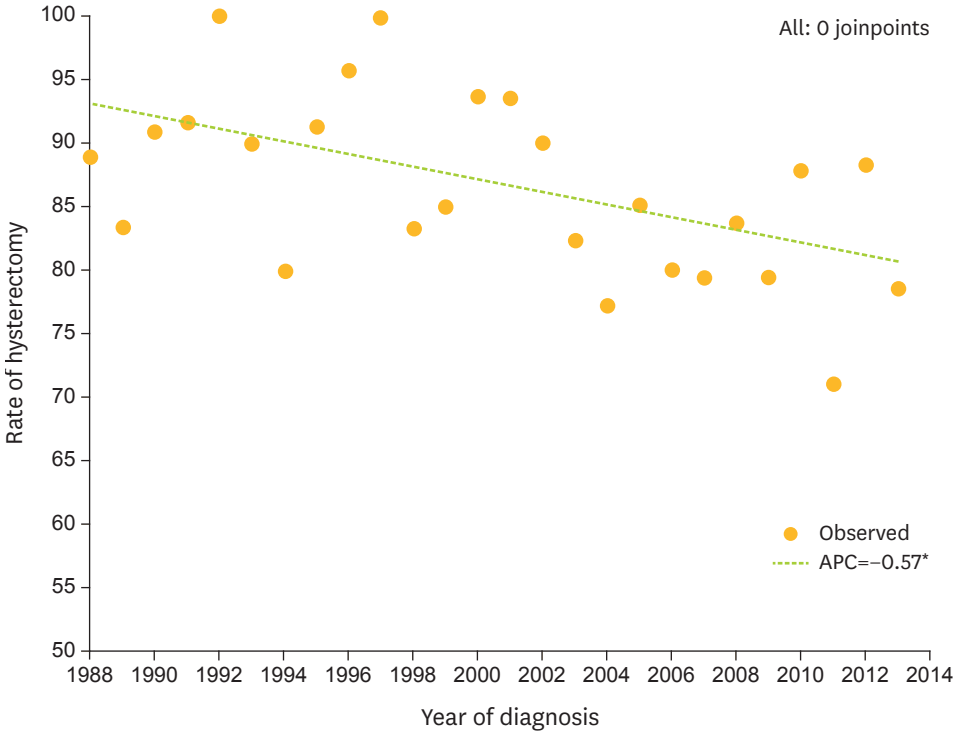

Fig. 2. Rate of hysterectomy among premenopausal women with unilateral CCC confined to the ovary per year of diagnosis (final selected model: 0 joinpoints).
APC, annual percent charge; CCC, clear cell carcinoma.
*The APC is significantly different from zero at alpha=0.05.

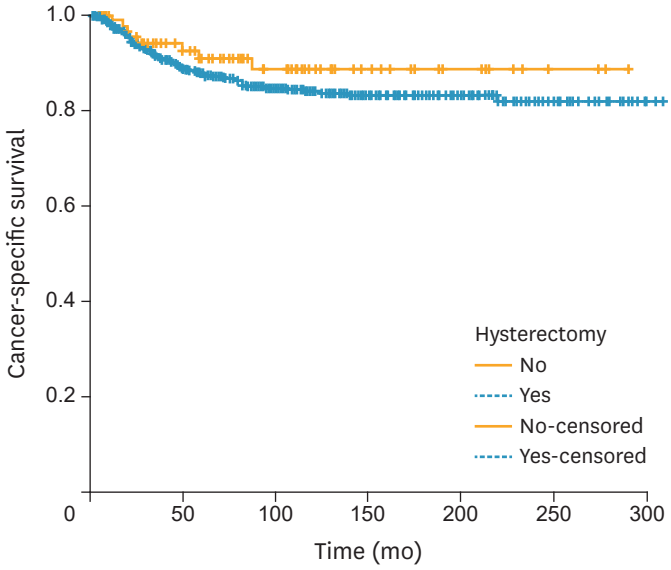

Fig. 3. CSS of premenopausal women with unilateral CCC confined to the ovary stratified by performance of hysterectomy (n=564 and n=94 in the hysterectomy and uterine preservation groups, respectively; p=0.290 from the log-rank test).
CCC, clear cell carcinoma; CSS, cancer-specific survival.

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(**Fig. 4**). The rate of OP was 18.5% for women diagnosed between 1988–2003 compared to 36.6% for those diagnosed between 2004–2013 (p=0.001). OP was performed similarly for women with stage IA (27.2%, 49 cases) and stage IC (30.1%, 22 cases) disease (p=0.640). Moreover, no difference in the performance of LND was noted (47.9% vs. 59.1% in the OP and BSO groups, respectively; p=0.110). However, women with OP were younger compared with those who underwent BSO (median age, 41 vs. 45 years; p<0.001). According to the reverse Kaplan-Meier method, median follow-up of the OP group was 89 months. Five-year CSS rates in the OP and BSO groups were 92.6% and 85%, respectively (p=0.060 from log-rank test) (**Fig. 5**). Similarly, 5-year OS rates in the OP and BSO groups were 90.8% and 85%, respectively (p=0.100 from log-rank test). Following stratification by disease sub-stage, 5-year OS and CSS rates for women who had unilateral salpingo-oophorectomy (USO) (n=47) were 91.7% and 94.4% compared with 90.7% (p=0.400) and 90.7% (p=0.220) for those who had BSO (n=130). For women with stage IC disease, 5-year OS and CSS rates in the USO group (n=22) were 88.7% and 88.7% compared with 70% (p=0.090) and 70% (p=0.100) in the BSO (n=51) group. After controlling for disease sub-stage (IA vs. IC), OP was not associated with a worse cancer-specific (HR, 0.36; 95% CI, 0.13, 1.02) or overall mortality (HR, 0.44; 95% CI, 0.17, 1.13).

Lastly, from a total of 643 premenopausal women with stage I apparent OCCC who underwent LN sampling/LND, rate of LN positivity was 4.4% (28/643); 3.8% and 4.8% for those with stage IA and IC disease, respectively. While not statistically significant, a trend for an increase in the rate of LN metastasis based on the number of LN removed was also observed; 3.6%, 4.3%, and 5.1% for those who had 1–10, 11–20, and >20 LNs removed.

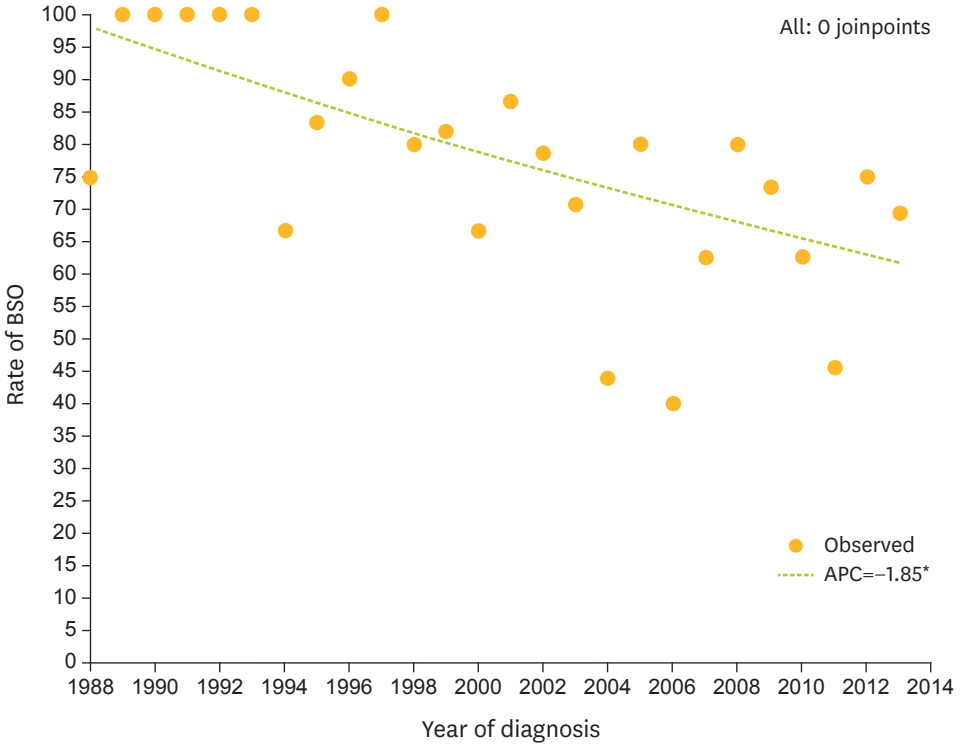

Fig. 4. Rate of BSO among premenopausal women with unilateral CCC confined to the ovary per year of diagnosis (final selected model: 0 joinpoints).
APC, annual percent charge; BSO, bilateral salpingo-oophorectomy; CCC, clear cell carcinoma.
*The APC is significantly different from zero at alpha=0.05.

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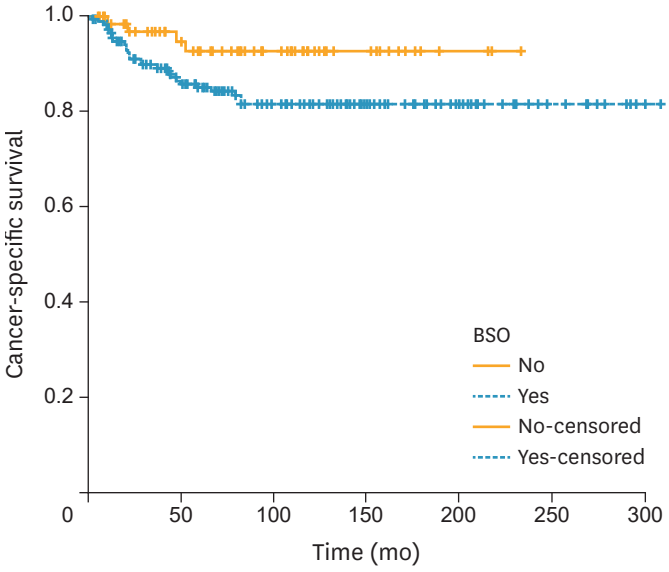

Fig. 5. CSS of premenopausal women with unilateral CCC confined to the ovary stratified by performance of BSO (n=69 and n=181 in the USO and BSO groups, respectively; p=0.060 from the log-rank test).
BSO, bilateral salpingo-oophorectomy; CCC, clear cell carcinoma; CSS, cancer-specific survival; USO, unilateral salpingo-oophorectomy.

DISCUSSION

To our knowledge this is the first population-based study focusing on the safety of FSS for women with FIGO stage I OCCC. Even after controlling for disease sub-stage neither uterine nor OP was associated with a worse overall or cancer-specific mortality. In addition, we demonstrated that the prevalence of regional LN metastasis in this population can be as high as 5.1%.

During the past years an increasingly number of reports on FSS for EOC has been published [6]. In accordance to this trend, we observed a significant increase in the rate of uterine and OP per study period. The selection criteria for FSS have not been yet definitively established given the lack of evidence from randomized trials. Current clinical guidelines of the European Society of Medical Oncology (ESMO) suggest that premenopausal women with stage IA or IC unilateral tumors and favorable histological characteristics, such as mucinous, serous, endometrioid or mixed histology and grade 1 or 2, are candidates for FSS only following a thorough staging procedure that includes lymphadenectomy [7].

Clear cell histology has long been considered a contra-indication for FSS given that it can be associated with poorer outcomes compared to other histologic subtypes [8]. However, several retrospective studies have investigated the safety of FSS for premenopausal women with stage I OCCC, most in terms of recurrence rate [6]. Only 2 studies have evaluated the long-term survival of these women [10,12]. In a recent case-control study, Park et al. [10] compared the oncologic outcomes of 22 premenopausal women (mean age, 36.5 years) with stage I OCCC who had FSS to a group of 25 patients who had radical surgery (mean age, 40.9 years). Similar to our results, after a median follow-up of 72 months no difference was noted in disease-free survival (DFS) or OS between the 2 groups, even following stratification by disease sub-stage [10]. Moreover, all women in the FSS group resumed normal menstruation and 27% had a

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live birth [10]. A major advantage of that study was that the majority of patients in the FSS group underwent thorough staging that included lymphadenectomy (86%) and omentectomy (91%) [10]. In another retrospective case-control study, Kajiyama et al. [12], compared the OS and progression free survival of 16 premenopausal women (median age, 35 years) to that of 205 women of all ages (median age, 54 years) who had radical surgery and did not find any differences. However, in the radical surgery group only 17 patients were ≤40 years and as in other case-series, LND and omentectomy were optional for patients undergoing FSS and rarely performed [11,12].

A recent comprehensive literature review identified a total of 115 women with early stage OCCC who had FSS with a cumulative relapse rate of 17% [6]. While authors suggested that FSS could potentially be offered to women with stage I CCC, they noted that the majority of recurrences were at an extra-ovarian location occurring within the first 2 years following initial surgical staging, a finding with significant implications for the management of these patients [6]. Whether the preserved ovary or uterus is the source of the recurrence remains in question [6]. Consistent with these results, in the present cohort the majority of cancer-related deaths in the uterine (88%) and OP (100%) group occurred within 5 years from initial tumor diagnosis.

An important clinical question is the safety of FSS in women with stage IC OCCC. There remains significant variability in treatment recommendations for this group. In their systematic review Satoh and Yoshikawa [18], calculated a cumulative relapse rate of 22.6% (7/31) for women with stage IC compared with 11.1% (3/27) for those with stage IA disease. The authors concluded that FSS should not be recommended for stage IC disease, due to poor recurrence-free survival rates. Likewise, the Gynecologic Cancer Intergroup (GCIG) consensus committee on OCCC suggests that FSS should be considered only for women with stage IA disease [19]. On the other hand, the National Cancer Network guidelines pose no limitation on the use of FSS by disease sub-stage (IA or IC) [20]. The key consideration in this scenario is not whether patients with stage IC disease have lower survival compared with stage IA, but whether FSS has an independent negative oncologic impact. In our sub-analysis, while 5-year OS and CSS rates of women who underwent FSS were lower compared to those with stage IA disease (all were below 90% and as low as 77.5% for women with a preserved uterus), they were comparable to those who underwent radical surgery. The small number of patients included in each analysis stratified by disease sub-stage, however, limited the power and increased the likelihood of a type II error.

While our findings support the safety of FSS in women with both stage IA and IC diseases, we believe the total number of cases published is insufficient and the clinical heterogeneity too significant to draw firm conclusions on the safety of FSS for any sub-stage of OCCC. Prospective multi-institutional collaborations can potentially shed light on the safety of this approach. With great interest, we await the primary results of the Japan Clinical Oncology Group Study (JCOG) non-randomized phase III trial that recruits adequately staged patients with stage IA CCC who undergo FSS and receive standard adjuvant carboplatinum-paclitaxel chemotherapy [21].

Another important clinical question is the role of LND for women undergoing FSS for EOC [22]. In our cohort of FIGO stage I OCCC, LND was not associated with improved OS or CSS, refuting a therapeutic benefit of lymphadenectomy. The procedure, however, still plays an important role in the assessment of disease spread and guiding adjuvant treatment. Even though occult LN metastases for women with apparent stage I mucinous tumors are

extremely rare [23], in our study the calculated incidence of LN metastasis for premenopausal women with stage I apparent OCCC was not negligible (ranging from 3.6%–5.1% depending on the extent of LND).

A major strength of the present study is the large number of women undoing fertility-preserving surgical procedures. In addition, follow-up of the FSS cases was long enough (median follow-up 6.8 and 7.4 years in the uterine and OP groups, respectively) to investigate the long-term CSS and OS impact. However, several limitations should be noted. First, due to the lack of central pathology review, tumor misclassification remains a possibility. Moreover, even though all patients with OCCC routinely receive chemotherapy, according to major guidelines, we can hypothesize that women with uterine and OP should have been even more likely to receive adjuvant chemotherapy. Nevertheless, the SEER database does not report information on the use of chemotherapy, as such we could not control for its administration. Lastly, we could not verify whether all staging procedures were performed in high volume centers.

In the present retrospective population-based cohort of premenopausal women with stage IA or IC OCCC, uterine and OP did not have a negative impact on oncologic outcomes, especially for those with stage IA disease. Selection criteria for FSS could potentially be expanded to include women with stage IA OCCC. A large number of cases should be accumulated before making any final recommendations. Providers should understand the limitations of the current evidence and proceed with FSS only for women with a strong desire to perceive fertility, following extensive counseling. The creation of an international registry of women with EOC and high-risk characteristics, such as OCCC, who undergo FSS could further elucidate the safety of this approach.

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