Outcomes After Fertility-sparing Surgery of Early-stage Ovarian Cancer: a Nationwide Population-based Study

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Abstract

Here we investigated the outcomes of early-stage epithelial ovarian cancer (EOC) following fertility-sparing surgery (FSS)or radical comprehensive staging surgery (RCS), as well as the suitability of FSS.Our analysis included 1297 early-stage EOC cases in the Taiwan Cancer Registry (TCR) database, which were newly-diagnosed between 2009–2017. Based on site-specific surgery codes, patients were divided into two groups:FSS (401 patients) and RCS (896 patients). Cancer-specific survival (CSS) was evaluated using the Kaplan–Meier method with log-rank testing and Cox models. Compared to the FSS group, patients in the RCS group were older ($p < 0.001$) and more commonly received adjuvant chemotherapy ($p<0.001$). Independent poor prognostic factors for CSS includedstage ($p<0.001$)and histologic grade ($p< 0.001$), but not histologic type ($p= 0.13$).CSS was similar between women who underwent FSS and those who underwent RCS ($p=0.75$).FSS group did not show significantly poorer CSS compared with RCS group in serous, mucinous, or endometrioid histologic type. Whereas, among clear cell carcinoma, FSS group had better CSS (HR: 0.28, 95% CI: 0.06–0.82, $p=0.040$) than RCS group. Endometrioid ovarian cancer patients had the highest frequency of developing second malignancies.FSS canbe a safe alternative procedure in selected young women with early-stage EOC who wish to preserve fertility regardless histologic type. Patients who receive FSS must undergo regular surveillance to detect disease recurrence and second malignancies.

Background

Ovarian cancer affects women of all ages, and is the ninth most common newly diagnosed malignancy among women worldwide[1]. In 2018, there were 295,414 new cases of ovarian cancer, and 184,788 deaths from ovarian cancer globally[1]. In Taiwan, there are approximately 1446 new cases ofovarian cancer and 624 deaths from ovarian cancer annually[2], and the incidence rate keeps raising[3]. At the time of ovarian cancer diagnosis, 23.1% of patients are between 20–45 years of age[2]. These patients are still of reproductive agewhen diagnosed, and may not havecompleted their family planning[4]. Loss of fertility due to malignancy treatment can result in grief, stress, sexual dysfunction, and depression among patients of reproductive age[5]. Therefore, treatments that preserve fertility-especially without compromising oncologic outcomes-are important for these young patients.

For early-stage epithelial ovarian cancer (EOC), the standard surgical treatment has traditionally been total hysterectomy, bilateral salpingo-oophorectomy (BSO), plus peritoneal and lymph-node sampling[6]. Reproductive-age patients with early-stage disease may have the option of fertility-sparing surgery (FSS), although the recommended indications remain controversial[6]. According to the ESMO clinical practice guidelines, FSS can be considered for patients with stage IA or IC disease, favorable histology (non-clear cell, i.e., mucinous, serous, endometrioid, or mixed histology), and grade 1 or 2 disease[7]. Additionally, patients with stage IA clear cell carcinoma are considered acceptable candidates according to Satoh et al[6], and the ASGO international workshop 2014[8]. Moreover, the NCCN clinical practice guidelines state that patients with stage IB disease who desired FSS canreceive BSO to preserve the uterus[9]. Limited available evidence shows that FSS can be a safe procedure for selected young women with early-stage EOC[8].

Due to the difficulty of designing and performing prospective randomized clinical trials, it has not yet been clearly demonstrated whether patients with early-stage EOCand hope for future reproduction can safely undergo FSS rather than radical comprehensive staging surgery (RCS). Investigationsof this subject have mainly been retrospective with limited patient numbers[10–17]. In the present study, we aimed to survey the oncologic outcomes of early-stage EOC patients who underwent FSS or RCS,and to analyze factors influencing their oncologic outcomes. Based on our findings, we propose selective criteria for FSS in cases of early-stage EOC.

Methods

Study design and data source

We conducted a retrospective study using data from the nationwide Taiwan cancer registry (TCR) database. This study was approved by the Institutional Review Board of the National Taiwan University Hospital and the informed consent was waved by the institutional review board due to lack of personal information and secondary data in the study. All research was performed in accordance with relevant guidelines/regulations. The TCR is one of the highest-quality cancer registries in the world, and records clinical data, such as cancer staging, laboratory values, and detailed treatment information for patients with newly diagnosed malignancies in Taiwan[18].

Flowchart of patient selection in this study is shown in Fig. 1.We retrieved information regarding patients who were newly diagnosed with ovarian cancer (ICD-O-3, code: C56) from 2009 to 2017. Women between 20–44 years of age were considered fertile and potentially in need of fertility preservation. FSS candidates were patients with early-stage EOC-e.g., stage I and II, according to the American Joint Committee on Cancer staging guidelines (6th edition in 2009, and 7th edition in 2010–2017). The four main histological types of EOC were serous, mucinous, endometrioid, and clear cell carcinomas. This study also includedmixed cell adenocarcinoma and unspecified types of carcinoma/adenocarcinoma. Patients were excluded if they had been diagnosed with other malignancies more than 3 months prior to their EOC diagnosis. For included patients, we collected the following data:age at diagnosis, year of diagnosis, histology, cancer stage, tumor grade, surgical types, and adjuvant chemotherapy.

Patients who underwent unilateral or bilateral salpingo-oophorectomy (USO or BSO) without hysterectomy were regarded as undergoing FSS, regardless of whether they received total, partial, or no omentectomy. Patients with surgery codes, such as USO or BSO and hysterectomy with or without omentectomy, debulking surgery, or pelvic exenteration, were classified into the RCS group.

Statistical analysis

Descriptive analysis was used to present the patients' basic characteristics, including age at diagnosis, histology, stage, grade, adjuvant chemotherapy, and second malignancy. The age difference between groups was analyzed by one-way ANOVA, andbetween-group differences in other categorical parameters were analyzed by Chi-square test. The main outcome measure was cancer-specific survival (CSS). All cases were followed-up through data linkage to the Death Registration Database until December 31, 2018. Cumulative

CSS plots were generated using the Kaplan-Meier method. CSS was compared between the two groups using the log-rank test. Univariate and multivariate Cox proportional hazards models were used to evaluate the factors associated with survival, with adjustment for potential confounders. A p value of < 0.05 was interpreted as indicating statistical significance. All analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC).

Results

Basic characteristics of 1297 early-stage EOC patients

This study included a total of 1297 early-stage EOC patients: 401 in the FSS group and 896 in the RCS group. Table 1 presents theclinico-pathologic characteristics of the FSS and RCS groups. The median age at diagnosis was 33 years (range, 20–44 years) for the FSS group, and 40 years (range, 20–44 years) for the RCS group. Patients in RCS group were significantly older than patients in the FSS group ($p < 0.001$). In the FSS group, the most common histologic type was mucinous carcinoma (167/401, 41.5%). In the RCS group, the most common histologic types were endometrioid carcinoma (289/896, 32.3%), followed by clear cell carcinoma (259/896, 28.9%). The majority of patients had stage I disease. Stage II disease was diagnosed in 5.2% (21/401) of patients in the FSS group, and 13.7% (123/896) patients of the RCS group ($p < 0.001$, chi-square test). In the FSS group, there were more low-grade tumors (grade 1 and 2, 184/401, 45.9%) than high-grade tumors (grade 3, 109/401, 27.2%). In the RCS group, the proportions of low-grade and high-grade tumors were 44.2% (396/896) and 42.6% (382/896), respectively. The percentage of high-grade tumors was higher in the RCS group than in the FSS group ($p < 0.001$,chi-square test). Adjuvant chemotherapy was more common in the RCS group than in the FSS group: 77.9% (698/896) vs. 53.6% (215/401) ($p < 0.001$) (Table 1).

Table 1
Basic characteristics of 1297 patients with early-stage EOC treated with FSS or RCS

Characteristics	FSS (N = 401) (%)	RCS (N = 896) (%)	*p*
Age, median (range)	33 (20–44)	40 (20–44)	**< 0.001**
Age			
< 35 years	249 (62.1)	157 (17.5)	**< 0.001**
35–39 years	107 (26.7)	253 (28.3)	
≥ 40 years	45 (11.2)	486 (45.2)	
Histology			
Serous carcinoma	42 (10.5)	81 (9.0)	**< 0.001**
Mucinous carcinoma	167 (41.5)	198 (22.1)	
Endometrioid carcinoma	75 (21.5)	289 (32.3)	
Clear cell carcinoma	70 (17.5)	259 (28.9)	
Others*	36 (9.0)	69 (7.7)	
Stage			
IA + IB	212 (52.9)	365 (40.8)	**< 0.001**
IC	168 (41.9)	408 (45.5)	
II	21 (5.2)	123 (13.7)	
Grade			
1 + 2	184 (45.9)	396 (44.2)	**< 0.001**
3	109 (27.2)	382 (42.6)	
Unknown	108 (26.9)	118 (13.2)	
Adjuvant chemotherapy			
No	186 (46.4)	198 (22.1)	**< 0.001**
Yes	215 (53.6)	698 (77.9)	

EOC epithelial ovarian cancer, *FSS* fertility-sparing surgery, *RCS* radical comprehensive staging surgery, *N* number of patients. *Others included mixed cell adenocarcinoma; adenocarcinoma, not otherwise specified (NOS); and carcinoma, NOS.

Stage and tumor grade influenced the cancer-specific survival (CSS) of early-stage EOC patient

CSS was analyzed with stratification according toclinico-pathologic factors. As shown in Fig. 2A, CSS was associated with disease stage, with stage IA/IB diseases showingbetterCSSthan stages IC/II diseases ($p < 0.0001$, Fig. 2A). CSS did not significantly differ between stage IC and stage II diseases ($p = 0.54$, Log-rank test). Additionally, CSS was better in women with grade 1/2 tumors than those with grade 3 tumors ($p < 0.0001$, Fig. 2B). CSS did not significantly differ among different histologic types ($p = 0.13$, Fig. 2C).

Adjuvant chemotherapy, regardless of surgical procedure, correlated with CSS among early-stage EOC patients

We further evaluated whether surgical procedure or adjuvant chemotherapy influenced outcome among the total analyzed group of 1297 patients with early-stage ovarian cancer. CSS was similar between women who underwent FSS and those who underwent RCS ($p = 0.75$, Fig. 2D).CSS was significantly worse in patients who received adjuvant chemotherapy than in those who did not ($p = 0.009$, Fig. 2E).

Stage and tumor grade were two independent risk factors affecting the outcome of early-stage EOC patients

Multivariate analysis was performed to analyze factors that were correlated with CSS among the 1297 early-stage ovarian cancer patients. As shown in Table 2, the independent poor prognostic factors for CSS included stage (stage IC, HR2.40, 95% CI 1.47–4.05, $p < 0.001$; stage II, HR3.60, 95% CI 1.86–6.93, $p < 0.001$)and histologic grade(grade 3, HR 3.19, 95% CI 1.79–5.65, $p < 0.001$). After adjustment,theother tested variables did not significantly affect CSS, including age at diagnosis, histology, type of surgery, and adjuvant chemotherapy.

Table 2
Multivariate analysis of the influence of clinic-pathologic factors on cancer-specific survival (CSS) among 1297 patients with early-stage ovarian cancer

Variables	Cancer-specific survival		*p*
	HR	95% CI	
Age			
< 35 years	1.00	Reference	
35–39 years	0.88	0.52–1.49	0.64
≥ 40 years	0.71	0.41–1.22	0.20
Histology			
Serous	1.00	Reference	
Mucinous	1.67	0.82–3.60	0.17
Endometrioid	0.94	0.46–2.02	0.87
Clear cell	0.81	0.41–1.70	0.55
Others*	0.72	0.25–1.87	0.51
Stage			
IA + IB	1.00	Reference	
IC	2.40	1.47–4.05	**< 0.001**
II	3.60	1.86–6.93	**< 0.001**
Grade			
1 + 2	1.00	Reference	
3	3.19	1.79–5.65	**< 0.001**
Unknown	1.25	0.64–2.33	0.50
Type of surgery			
RCS	1.00	Reference	
FSS	1.09	0.66–1.77	0.73
Adjuvant chemotherapy			
No	1.00	Reference	
Yes	1.03	0.59–1.88	0.92

HR hazard ratio, *CI* confidence interval, *RCS* radical comprehensive staging surgery, *FSS* fertility-sparing surgery. *Others included mixed cell adenocarcinoma; adenocarcinoma, not otherwise specified (NOS); and carcinoma, NOS

Different histologic types had different various factors correlated with the CSSof early stage EOCs

We further analyzed the factors that correlated with outcomes of ovarian cancer of different histologic types. Table 3 shows the multivariate analyses of various clinico-pathologic factors with regards to CSS in cases of four histologic types. Among patients with serous carcinoma, there was no obvious poor prognostic factor. In cases of mucinous carcinoma, poorer CSS was associated with stage II (HR 7.44, 95% CI: 1.49–29.39, p = 0.007) or IC (HR 4.00, 95% CI: 1.55–11.11, p = 0.006) disease compared to stage IA/IB disease, and with grade 3 tumor(HR 3.33, 95% CI: 1.27–7.89, p = 0.009) compared to grade 1/2tumor. Among patients with endometrioid carcinoma, worse CSS was associated with grade 3 tumor (HR 4.37, 95% CI: 1.46–12.89, p = 0.007) compared to grade 1/2 tumor. In clear cell carcinoma, CSS was worse among patients with stage II (HR 4.32, 95% CI: 1.24–14.40, p = 0.016) or IC (HR 3.08, 95% CI: 1.34–8.31, p = 0.014) disease compared to patients with stage IA/IB disease.

Table 3
Multivariate analyses of the influence of various clinico-pathologic factors on cancer-specific survival (CSS) among patients with early-stage ovarian cancer, according to four histologic types

	Serous (N = 123)		**Mucinous (N = 365)**		**Endometrioid (N = 375)**		**Clear cell (N = 329)**	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Age								
< 35 years	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
35–39 years	1.07 (0.12–8.20)	0.95	1.07 (0.43–2.49)	0.88	0.99 (0.31–3.27)	0.99	0.75 (0.27–2.25)	0.58
≥ 40 years	0.70 (0.07–7.21)	0.76	0.65 (0.20–1.75)	0.42	0.76 (0.21–2.84)	0.67	0.73 (0.30–2.06)	0.52
Stage								
IA + IB	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
IC	5.07 (0.77–101.58)	0.15	4.00 (1.55–11.11)	**0.006**	0.45 (0.15–1.37)	0.15	3.08 (1.34–8.31)	**0.014**
II	4.69 (0.52–109.19)	0.22	7.44 (1.49–29.39)	**0.007**	1.17 (0.31–4.14)	0.81	4.32 (1.24–14.40)	**0.016**
Grade								
1 + 2	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)			
3	4.91 (1.00–36.33)	0.07	3.33 (1.27–7.89)	**0.009**	4.37 (1.46–12.86)	**0.007**	N/A	N/A
Unknown	1.92 (0.22–16.82)	0.53	0.89 (0.33–2.015	0.80	2.33 (0.63–7.04)	0.16		

CSS cancer-specific survival, *HR* hazard ratio, *CI* confidence interval, *C/T* chemotherapy, *N/A* not available

	Serous (N = 123)		Mucinous (N = 365)		Endometrioid (N = 375)		Clear cell (N = 329)	
Type of surgery								
RCS	1.00 (Reference)	0.48	1.00 (Reference)	0.17	1.00 (Reference)	0.13	1.00 (Reference)	**0.040**
FSS	2.02 (0.28–14.80)		1.76 (0.78–4.03)		2.27 (0.75–6.48)		0.28 (0.06–0.82)	
Adjuvant C/T								
No	1.00 (Reference)	0.31	1.00 (Reference)	0.81	1.00 (Reference)	0.36	1.00 (Reference)	**0.020**
Yes	3.14 (0.51–62.47)		1.12 (0.44–3.07)		1.81 (0.54–7.18)		0.32 (0.13–0.95)	

CSS cancer-specific survival, *HR* hazard ratio, *CI* confidence interval, *C/T* chemotherapy, *N/A* not available

Adjuvant chemotherapy did not influence the outcome of patients with serous, mucinous, or endometrioid type. Whereas, clear cell carcinoma patients undergoing adjuvant chemotherapy (HR: 0.32, 95% CI 0.13–0.95, p = 0.020) had better CSS than those without in multivariate analysis (Table 3).

Patients underwent FSS did not have poorer CSS than those with RCS in different histologic types

We furtherevaluated if FSS would influnce the CSS of early stage ovarian cancer patients in different histologic type. As shown in Table 3, FSS group did not show significantly poorer CSS compared with RCS group in serous (HR: 2.02, 95% CI 0.28–14.80, p = 0.48), mucinous (HR: 1.76, 95% CI 0.78–4.03, p = 0.17) or endometrioid (HR: 2.27, 95% CI 0.75–6.47, p = 0.13) histologic type in multivariate analysis. Whereas, among clear cell carcinoma, FSS group had better CSS (HR: 0.28, 95% CI: 0.06–0.82, *p* = 0.040) than RCS group.

Second malignancies among women with early-stage EOC who underwent FSS

Of the 401 EOC patients who underwent FSS, 22 developed a second malignancy. As shown in Table 4, a second malignancy was defined as any type of cancer that was diagnosed more than 3 months after the diagnosis of EOC. The most common second malignancy was uterine cancer (n = 14), followed by ovarian cancer over the contralateral ovary (n = 3). Among all histological types, patients with endometrioid ovarian cancer had the highest frequency of developing second malignancies (8/75, 10.7%).

Table 4
Patients with second malignancy in FSS group (N = 22)

Histology of EOC	Second malignancy	Total cases
Serous		1
	Colon	1
Mucinous		8
	Uterine corpus	4
	Ovary	1
	Colon	2
	Breast	1
Endometrioid		8
	Uterine corpus	7
	Ovary	1
Clear cell		3
	Uterine corpus	2
	Retroperitoneum	1
Others		2
	Uterine corpus	1
	Ovary	1
FSS: fertility-sparing surgery; EOC: epithelial ovarian cancer.		

Discussion

In this study, weused a nationwide registry to evaluate the outcomes of early-stage EOC patients who underwent FSS and RCS. Patients in the FSS group were younger and mostly had stage I disease. The RCS group included more cases of stage II and high grade (grade 3) disease, and more frequent adjuvant chemotherapy. The most common histologic type was mucinous carcinoma in the FSS group, compared to endometrioid and clear cell carcinomas in the RCS group. Stage was a risk factor for poor outcome for mucinous and clear cell histologies, but not for serous or endometrioid histology. Patients with grade 3 endometrioid ovarian cancer had a poorer prognosis compared to patients with grade 1/2 tumors. Among

patients with early-stage clear cell carcinoma, CSS was non-inferior and even better after FSS compared to RCS, yet adjuvant chemotherapy was necessary.We also foundthat22 of the 401 women who underwent FSS developed a second malignancy later in life.

Several previous retrospective studies have compared the oncologic outcomes of early-stage EOC patients who undergo FSS or RCS, and have reported comparable results[10–17]. The majority of these prior studies have only enrolled patients with stage I disease, and have found that FSS is adequate treatment for stage I EOC, without compromising survival outcomes [10, 12–15]. Ditto et al.[11] and Bogani et al.[16]analyzed the outcomes of FSS in patients with stage I disease, and small numbers of patients with stage II and III disease. Theyreportedthat FSS did not influence the progression-free survival (PFS) compared to complete staging surgery, among women with high-risk ovarian cancer, with FIGO stage IA/IB grade 3 or stage IC/II diseases[11]. Bogani et al. also reported that the type of surgery did not affect the disease-free survival (DFS) or overall survival (OS) of patients with grade 3 tumors or stage IC/II diseases after over 10 years of follow-up[16]. Similar to these past studies, in our present series,we found that FSS can be a safe procedure for patients with early-stage EOC who had a desire for fertility preservation (FSS vs. RCS, HR of CSS 1.09, $p = 0.73$, Table 2).

We found that disease stage was an independent risk factor affecting outcome in patients with early-stage EOC. Our previous results showedworse 5-year overall survival (OS) instage II disease compared to stage IA/IB disease[4]. Ditto et al. also reported poorer OS in stage IC/II diseases than stage IA/IB diseases[11].In the present study, we found that stage IC and II disease were poor prognostic factors for CSS, withHR values of 2.40 and 3.60 relative to stage IA/IB diseases. We further demonstrated that stage was an independent risk factor for poor CSS in cases of mucinous and clear cell histologies, but not cases of the serous or endometrioid type. Kajiyama et al. also reported that stage IC disease was associated with poorer OS than stage IA/IB disease in cases of the mucinous carcinoma and clear cell carcinoma histologies[19,20]. This indicates that the capsule status during operation significantly influences the outcomes, especially in mucinous and clear cell carcinomas[19,20]. Therefore, we recommend that surgeons should remove ovarian tumors as carefully as possible to avoid intraoperative tumor rupture, especially for patients undergoing FSS.

Tumor grade was another risk factor for poor outcome in early-stage EOC patients. In our study, grade 3 tumors were associated with worse CSS than grade 1/2 tumors, especially in mucinous and endometrioid types (Table 3). Chen et al. also found that grade 3 tumors were a poor prognostic factor compared to grade 1/2 in cases of ovarian endometrioid carcinoma[21]. Among cases of stage I endometroid carcinoma, Chao at el. also found that grade 3 tumors were an independent poor prognostic factor in terms of PFS[22]. However, it remains controversial whether grade correlates with unfavorable survival outcomes in mucinous carcinomas[23]. Moreover, the grading system for ovarian mucinous carcinomasis globally inconsistent[23].Busca et al. compared two widely used grading systems: the International Federation of Gynecology and Obstetrics (FIGO) system[24], which was the same grading system used for endometrioid carcinoma, and the Silverberg grading system[25]. They found that only the Silverberg grading system appeared to correlate with outcome in cases of mucinous carcinoma[23].

There is long-standing debate regarding the safety of using FSS to treat patients with early-stage ovarian cancer, especially clear cell carcinoma. Clear cell histology was considered a contraindication for FSS due to

its relativelyworse outcome compared to other histologic types[26].However, many recent retrospective studies have compared the outcomes of FSS and RCS for stage I clear cell carcinoma, and the results reveal non-inferior survival outcomes following FSS compared to RCS, although with limited patient numbers[20,27–30].Nasioudis et al. used the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database to evaluate cases of stage I clear cell carcinoma treated with uterus- or ovary-preserving staging surgery[31]. Their study included a total of 741 patients with ovarian clear cell carcinoma, including 96 with uterus preservation. The five-year cancer-specific survival rates did not significantly differ between patients with or without uterus preservation (90.8% vs. 87.7%, $p = 0.29$)[31].Moreover, uterine preservation was not associated with worse survival even after controlling for the disease sub-stage[31]. However, in their review article, Satoh and Yoshikawa reported a higher cumulative relapse rate for patients with stage IC clear cell carcinoma (22.6%) compared to patients with stage IA clear cell carcinoma (11.1%)[32].Thus, they did not recommend FSS for stage IC clear cell carcinoma[32], and this indication remains controversial. Our present study included a large series obtained from the nationwide database, and our results showed that patients who underwent FSS for early-stage clear cell carcinoma had survival outcomes similar to those of patients treated without fertility preservation. Within our nationwide database, the patients of reproductive age who underwent FSS were significantly younger than the patients who underwent RCS; however, our results showed no effect of age. Notably, among clear cell carcinoma patients, the FSS group even showed a significantly better survival outcome than the RCS group (HR 0.28, 95% CI: 0.06–0.82, $p = 0.040$).Further subgroupanalysisrevealedthat the FSS and RCS groups had similarly good CSS rates in stage IA/IB (Fig. 3A, p = 0.19) and stage II (Fig. 3C, p = 0.06) clear cell carcinomas.In contrast, among stage IC clear cell carcinomas, the FSS group had better CSS than the RCS group (Fig. 3B, p = 0.006). A likely explanation is that the FSS patients may have been selected by surgeons during surgery, rather than randomly selected. Surgeons may choose the most suitable and low-risk patients to undergo FSS, such as patients with an intact capsule and with minimal pelvic adhesion, to avoid potential spreading of cancer during surgery.

Patients who undergo FSS might develop second malignancies in the uterine corpus or the contralateral ovary.In our study, ovarian endometrioid carcinoma was the histology most likely to develop second malignancies. Of the eight second malignancies in cases of ovarian endometrioid cancer, seven were uterine cancer. These cases illustrated the risk of uterus preservation with this histologic type. It is difficult to distinguish whether the second malignancy was a metastatic endometrioid endometrial cancer from the ovary or a synchronous cancer. Zhao et al. reported thatpatients with stage I ovarian endometrioid carcinoma had a 19.3% rate of synchronous early stage and well-to-moderate differentiated endometrial carcinoma[22]. Notably, in our study, uterine cancer also developed in patients with ovarian cancerof the other histologies. Three patients developed ovarian cancer in the contralateral ovary. During surgery, biopsy of the contralateral ovary was usually not recommended in the absence of gross abnormalities, based on the low risk of microscopic involvement in a contralateral ovary with normal appearance[13], and concerns about infertility caused by postoperative adhesions on the remaining ovary[33,34]. However, patients should be informed that there is a risk of recurrence in the preserved contralateral ovary. Bentivegna et al. reported an 11.6% recurrence rate following FSS in patients with stage I–II disease. Among these recurrences, 38% were isolated in the spared ovary, and 62% occurred at an extraovarian site, which was associated with a worse survival outcome[35]. Based on these findings, we suggest regular postoperative surveillance of the remaining ovary

and of the endometrium using sonography or computerized tomography. Additionally, we recommend theperformance of endometrial biopsy before or during FSS to identify synchronous endometrial and ovarian carcinomas, particularly in patients with ovarian endometrioid carcinoma with clinical symptoms, such as abnormal vaginal bleeding.

The present study had several strengths. The first strength was that it was a nationwide population-based study performed using the TCR database, which includes over 90% of cancer patients in Taiwan[18]. The database is periodically subjected to field data audits,and is thus a high-quality and reliable data source[18]. Additionally, this study has a large sample size, providing sufficient statistical power. Due to ethical problems, it is almost impossible to perform a prospective study comparing the outcomes of FSS and RCS[12]; therefore,we think that our study providesimportantnew insights on this issue. Taiwan exhibits a higher incidence of clear cell carcinoma than many other countries[36].Thus, this study was able to includea large number of ovarian clear cell carcinoma patients, enabling comparison of outcomes after FSS or RCS specifically among ovarian clear cell carcinoma patients. We used cancer-specific survival (CSS) as the main outcome measure, instead of overall survival (OS), because the proportion of death from other causes is relatively high in patients with early-stage cancers[37].Therefore, CSS more precisely reflects the survival outcome related to early-stage ovarian cancer.

One limitation of this study was its retrospective nature. There may have been some unavoidable difficulties in the coding and grouping of the patients, such as an inaccurate diagnosis or cancer staging, and loss of patients to follow-up, which may lead to systemic bias. Additionally, we lacked details of the pathologic findings, information regarding tumor recurrence, chemotherapy regimen and dosage, and the subsequent pregnancy records due to the nature of the TCR system.

Declarations

DATA AVAILABILITY

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

AUTHORS' CONTRIBUTION

CYL and WFC designed the study concept.

WCL obtained, generated data important for the analyses.

CJC designed the analytical strategy and WFC helped to interpret the findings.

CJC did the statistical analyses.

YLC, YCC, YJT, HCH and CYW conducted the literature review and helped to prepare the Introduction and Methods sections of the text.

CYLwrote the manuscript. WFC revised the manuscript.

All authors reviewed the manuscript.

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ETHICS APPROVAL DETAILS

This study was approved by the institutional Research Ethics Committee at the National Taiwan University Hospital (approval No.201907088RIN).All of the patients' data were fully anonymized before we accessed them and the Research Ethics Committee waived the requirement for informed consent.

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Figures

Figure 1

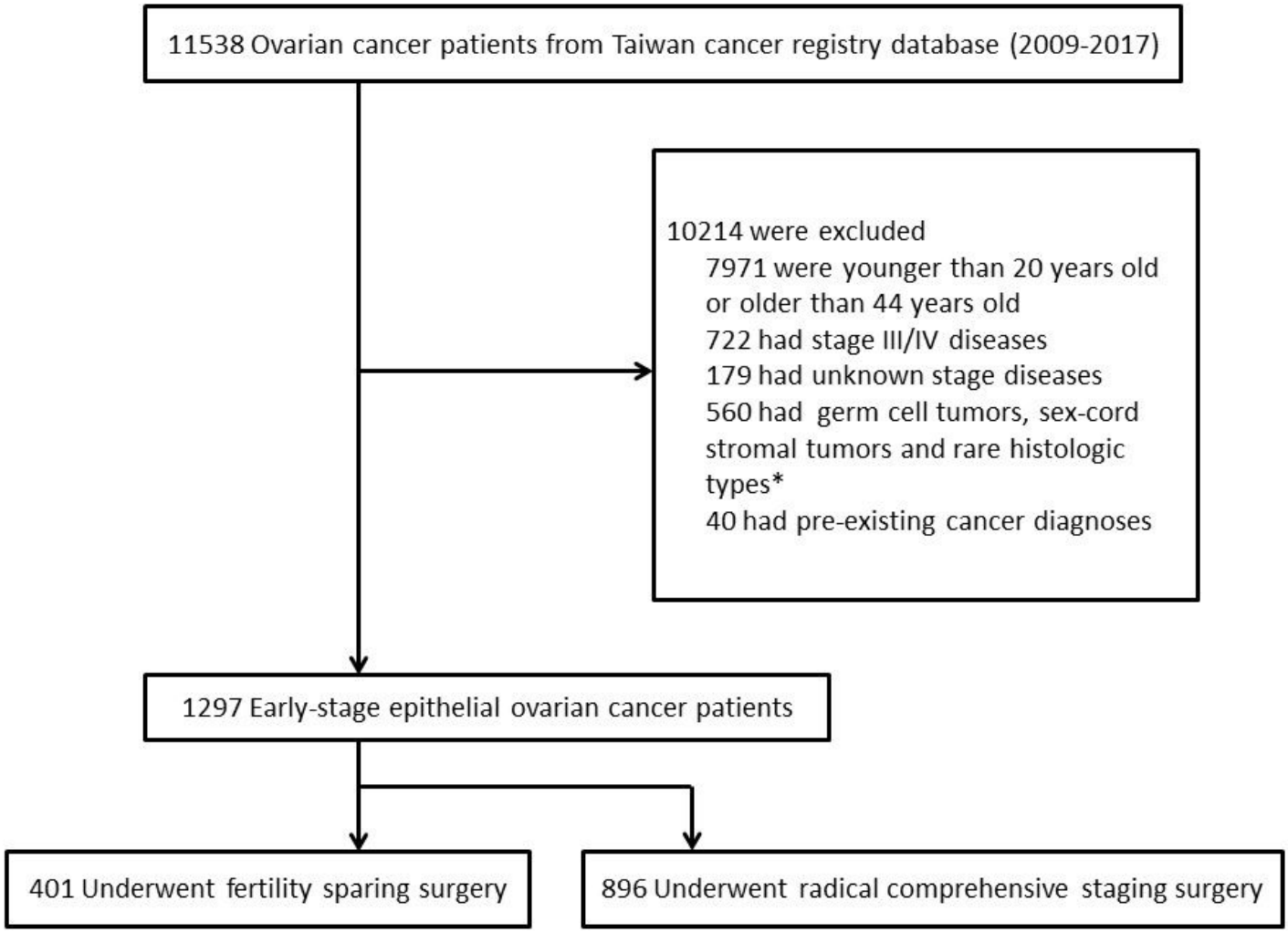

Figure 1

Flowchart of patient selection in this study. *Rare histologic types included large cell neuroendocrine carcinoma, small cell carcinoma, and carcinosarcoma.EOCepithelial ovarian cancer.

Figure 2

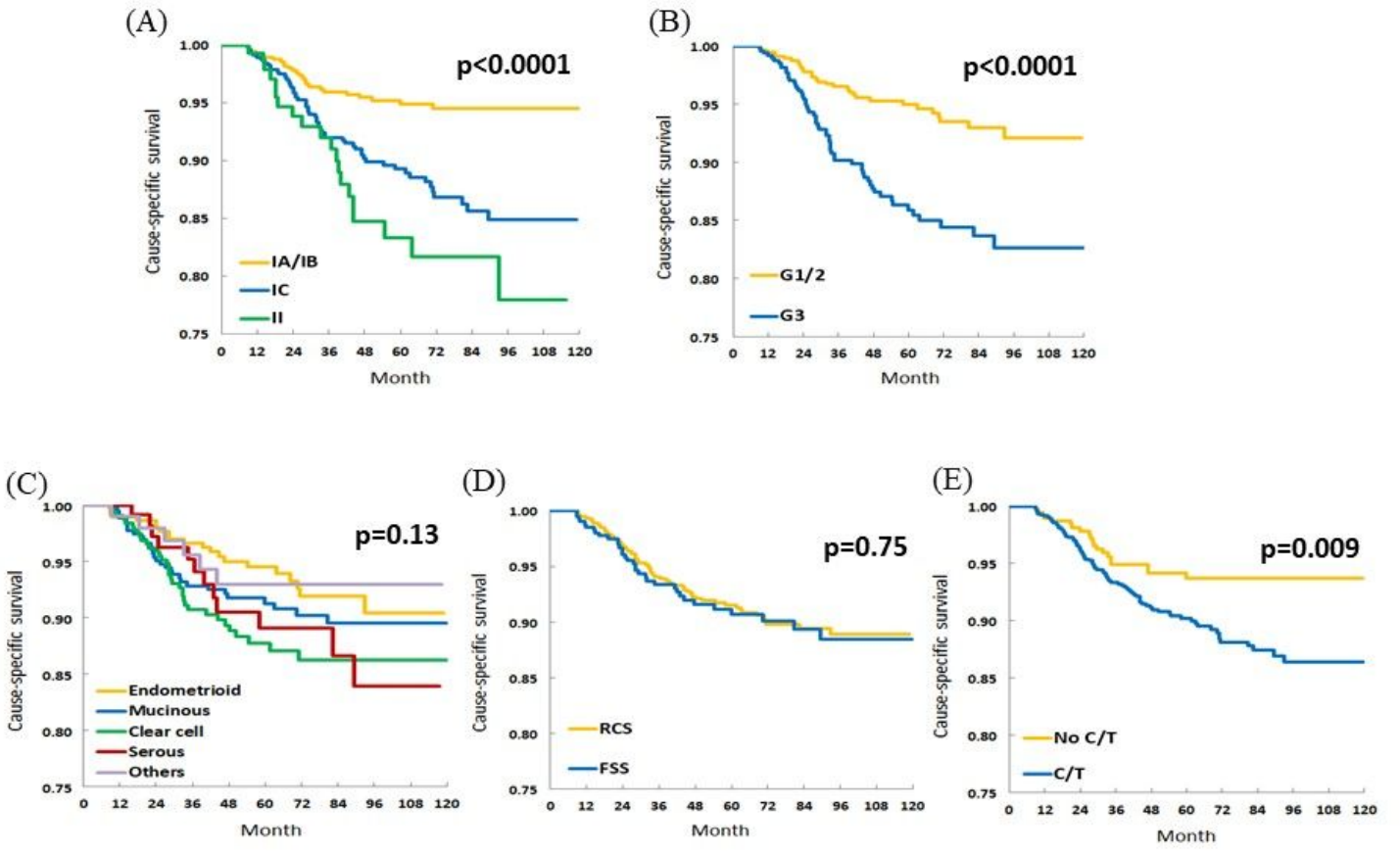

Figure 2

Kaplan-Meier analyses of cancer-specific survival (CSS) among 1297patients with early-stage ovarian cancer stratified according to different clinico-pathologic characteristics: **(A)** stage, **(B)** tumor grade, **(C)** histologic type, **(D)** surgical procedure, and **(E)** adjuvant chemotherapy.

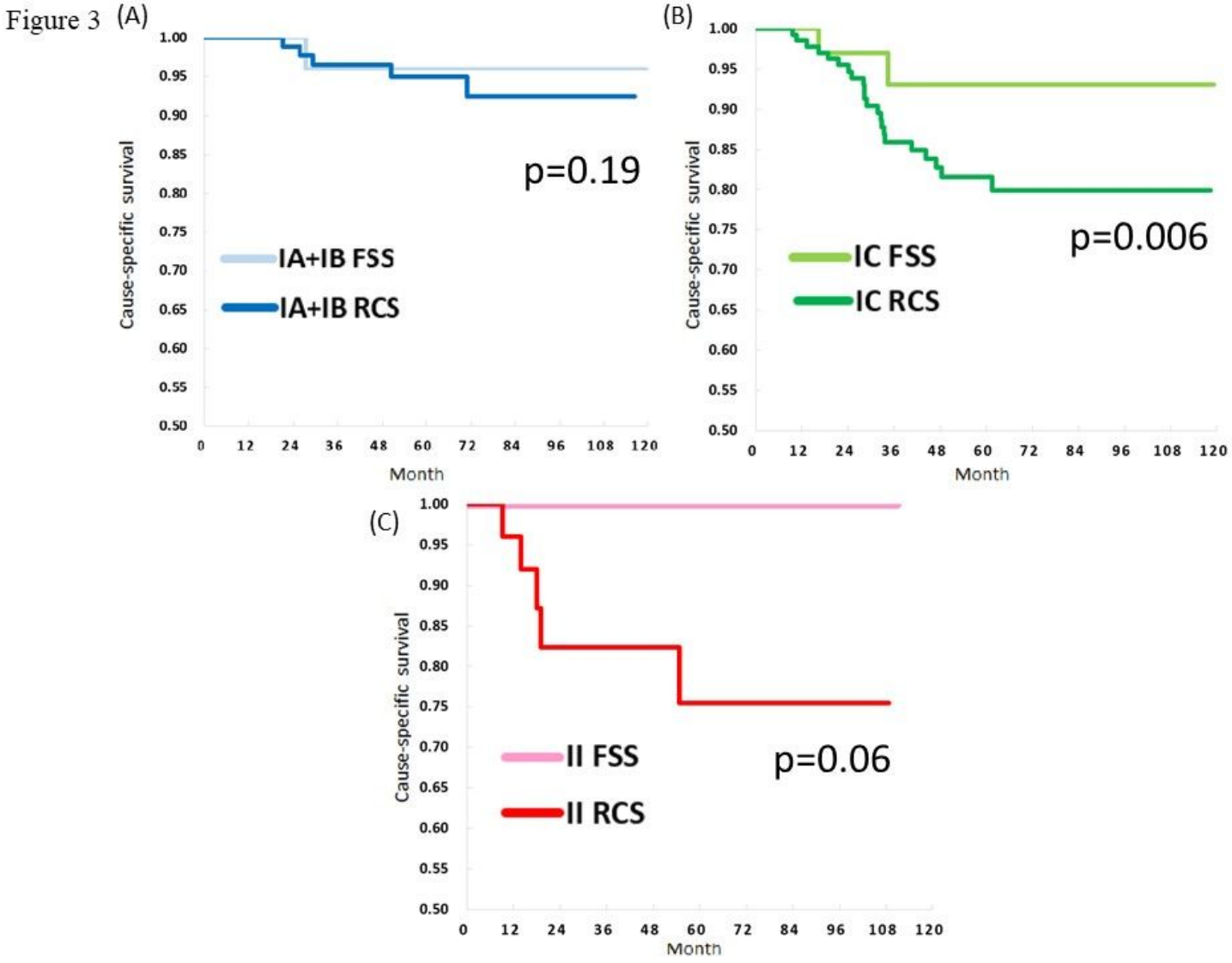

Figure 3

Kaplan-Meier analyses of cancer-specific survival (CSS) among patients with clear cell carcinoma stratified according to different type of surgical procedures in various stages: **(A)** stages IA/IB, **(B)** stage IC, and **(C)** stage II.