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GYNECOLOGIC ONCOLOGY

Long-term oncologic outcome and its prognostic indicators in reproductive-age women with ovarian clear-cell carcinoma

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Abstract

Background Clear-cell carcinoma (CCC) in reproductive-age women is likely to become an increasingly critical issue regarding possibilities of infertility, hormonal dysfunction, and mortality. The aim of this study was to examine the long-term oncologic outcome and its prognostic indicators based on a multicentric cohort of young patients with CCC.

Patients and methods During the period of 1990–2015, a total of 164 patients aged 45-year-old or younger were enrolled in the study. Clinicopathologic data of these young patients with CCC collected under a centralized pathological review system were subjected to uni- and multivariable analyses to evaluate overall survival (OS).

Results The median follow-up was 73.8 months (range 5.2–244.2) in the surviving patients. Among these patients, 104 (63.4%) had FIGO I disease, and 22 (13.4%), 31 (18.9%), and 7 (4.3%) had II, III, and IV disease, respectively. The 5-year OS rate was 74.5%. On stratification by the FIGO stage, the 5-year OS rates were as follows: stage I (90.2%), stage II (57.9%), and stage III/IV (39.3%), respectively ($P < 0.0001$). Confining analysis to stage I patients, there was no difference in OS between those who underwent fertility-sparing surgery and those who received radical surgery ($P = 0.1593$). In relapsed patients, the median survival after recurrence was 11.6 months. In multivariable analysis of stage I patients, the capsule status was an independent prognostic indicator of OS {IC2/IC3 vs. IA/IC1: HR 4.293 (95% CI 1.140–16.422), $P = 0.0318$}.

Conclusion CCC patients staged greater than IC2/IC3 show a markedly increased risk of mortality. Thus, it is important to diagnose patients staged under IC2/IC3.

Keywords Epithelial ovarian carcinoma · Clear-cell carcinoma · Reproductive-age · Fertility-sparing surgery · Overall survival · Post-recurrence survival

Abbreviations

CCC	Clear-cell carcinoma
FSS	Fertility-sparing surgery
OS	Overall survival
PRS	Post-recurrence survival

Introduction

Clear-cell carcinoma of the ovary (CCC) is a comparatively rare malignancy in Western countries, accounting for approximately less than 10% of all ovarian carcinomas. However, this histological type is very common in East Asia, with CCC being the second most frequent tumor of epithelial ovarian carcinoma in Japan. A Japanese nationwide survey revealed an increasing incidence of CCC as a proportion of all EOCs, now making up more than 25% of EOCs [1]. According to prior studies, resistance to platinum-based chemotherapy and a subsequently poorer clinical outcome has been demonstrated in patients with advanced-stage CCC, compared with serous carcinoma patients. On the other hand, since the majority of CCC patients are diagnosed at an early stage, the prognosis of CCC women without extra-ovarian metastasis is not necessarily poorer than that of those with a non-CCC histology.

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Similarly to other histological types of epithelial ovarian cancer, CCC is primarily a disease of postmenopausal women. However, a close link between CCC and endometriosis, which is a common gynecological inflammatory disease, can be noted in women of reproductive age [2–4]. The malignant transformation of endometriosis is a comparatively rare event, occurring in 0.7–2.5% of cases [5]. Endometriosis is such a common disease in young patients that the risk of CCC is likely to become an increasingly critical issue because of the demographics of patients. Unfortunately, in earlier studies, little is known about CCC in this generation. Furthermore, to our knowledge, no study has focused on the prevalence and mortality of young patients with CCC based on larger series.

Here, we analyzed data on a multicentric cohort of Japanese patients with CCC diagnosed during 1990 and 2015, to further evaluate the long-term oncologic outcome and prognostic indicators in reproductive-age women with this aggressive tumor. This register-based cohort study conducted under central pathological review is one of the largest to date on this topic.

Patients and methods

Patient enrollment

Patients with malignant ovarian tumors have been registered and accumulated by the Tokai Ovarian Tumor Study Group (TOTSG), consisting of 14 collaborating institutions: Nagoya University Hospital, Aichi Cancer Center Hospital, Anjo Kosei Hospital, Toyohashi Municipal Hospital, Toyota Memorial Hospital, Ogaki Municipal Hospital, Nagoya First Red-cross Hospital, Nagoya Second Red-cross Hospital, Nagoya Ekisaikai Hospital, Nagoya Memorial Hospital, Okazaki Municipal Hospital, Handa City Hospital, Komaki City Hospital, and Gifu Prefectural Tajimi Hospital. All histological slides were reviewed by two expert pathologists with no knowledge of the patients' clinical data under a central pathological review system. Between 1990 and 2015, 2744 patients with epithelial ovarian carcinoma and sufficient data on clinical outcomes were identified in this regional population-based registry system. In the present study, eligible criteria were as follows: (1) patients received initial surgery and periodic follow-up at the aforementioned institutions; (2) patients for whom there was sufficient information about the residual tumor at primary surgery, first-line chemotherapy, and date of recurrence or death; and (3) tumors were diagnosed as CCC if typical clear or hobnail cells growing in a papillary, solid, or tubulocystic pattern appeared based on the central pathological review system (the criteria of the World Health Organization). Sixty-six patients were excluded from this study because they had insufficient clinical data or a history of other malignancies, or were lost to follow-up immediately after surgery. Of those remaining, 733 CCC patients who fulfilled the above criteria were extracted. In the present study, 164 reproductive-age patients with CCC were finally enrolled (Fig. 1). This study was approved by the ethics committees of Nagoya University and affiliated institutions. The stage was defined according to the classification of the International Federation of Gynecology and Obstetrics (FIGO, 1988). In addition, stage IC were categorized into three subtypes based on the FIGO (2014) classification [6].

Treatment

Primary laparotomy was conducted in all patients for assessment of the abdominal contents. In principle, standard primary surgical treatment consisted of hysterectomy, bilateral salpingo-oophorectomy, infracolic omentectomy, retroperitoneal lymphadenectomy, or sampling. Twenty-one patients with stage I tumor underwent conservative surgery because they hoped to preserve fertility or were young. In those patients, 15 underwent unilateral salpingo-oophorectomy ± omentectomy, and 6 patients received unilateral salpingo-oophorectomy ± omentectomy and partial resection of the contralateral ovary. Peritoneal washing was routinely carried out in all patients. If any abnormalities were identified, peritoneal biopsies from different sites were appropriately performed. When a residual tumor remained, maximal cytoreductive surgery was performed. If patients were at an advanced stage, or showed severe perioperative complications and/or comorbidity, or underwent conservative surgery, retroperitoneal lymphadenectomy was not performed at each surgeon's discretion. There are 104 patients who were supposed to stage I. In those patients, retroperitoneal lymph node evaluation involved one of the following: (1) lymph node dissection, (2) lymph node sampling, or (3) palpation

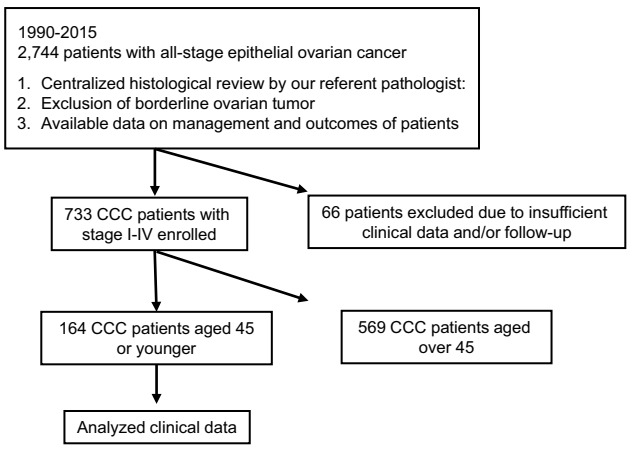

Fig. 1 Patient flowchart

and removal of enlarged lymph nodes. Overall, 72 (69.2%) patients received systemic retroperitoneal lymphadenectomy or sampling. Among them, 4 of 21 (19.0%) of FSS group and 68 of 83 (81.9%) patients underwent those surgical procedure.

As patients with CCC showed poorer clinical outcomes, chemotherapy was in principle recommended for all patients; however, in 16 women, this was not done. Among 104 with stage I tumor, 89 (85.6%) patients underwent postoperative chemotherapy [17/21 (81.0%) in FSS group and 72/83 (86.7%) in non-FSS group, respectively]. Policies on chemotherapeutic agents varied according to the time; however, we basically used the same selection criteria for first-line regimens as TOTSG. Details of the chemotherapy regimen during each period were described previously [7].

Follow-up and analysis

At the end of treatment, all patients underwent strict follow-up, consisting of clinical checkups, such as pelvic examination, ultrasonographic scan, CA125 evaluation, and periodic CT. Radiologic recurrence was defined as recurrence based on CT, and/or magnetic resonance imaging (MRI), and/or ultrasound. Clinical recurrence was defined as the development of ascites, elevated CA125, or a clinically palpable mass. The overall survival was defined as the time interval between the date of surgery and the last date of follow-up or death due to any cause. The post-recurrence survival was defined as the time interval between the date of recurrence and the last date of follow-up or death due to any cause.

Statistics

The distributions of clinicopathologic events were evaluated using Student's *t* test and the Chi-square test. Survival analysis was based on the Kaplan–Meier method. The survival curves were compared employing the log-rank test. Multivariable analysis was performed with the Cox proportional hazards model to evaluate independent factors affecting survival. A P value of < 0.05 was considered significant.

Table 1 Patients' characteristics

	N	(%)
Total	164	
Age		
(Median range) 40 (27–45)		
≤ 34	20	12.2
35–40	68	41.5
≥ 41	76	46.3
FIGO stage		
I	104	63.4
IA	28	17.1
IC1	50	30.5
IC2	10	6.1
IC3	10	6.1
IC *NA*	6	3.6
II	22	13.4
III	31	18.9
IV	7	4.3
Surgery		
FSS	21	12.8
Non-FSS	143	87.2
Ascites volume (mL)		
None	61	37.2
< 100	60	36.6
100–499	22	13.4
500–999	7	4.3
≥ 1000	14	8.5
CA125 value		
≤ 35 U/mL	35	21.3
> 35 U/mL	123	75.0
NA	6	3.7
Chemotherapy		
None	16	9.8
Taxane plus platinum	104	63.4
Platinum-based	44	26.8

FIGO International Federation of Gynecology and Obstetrics, IC substage was defined according to FIGO 2014 classification, *FSS* fertility-sparing surgery, *NA* not applicable

Results

Patients' characteristics

The characteristics of enrolled patients are detailed in Table 1. The median (range) age was 40 (27–45 years) years. The number of patients under 35 was 20 (12.2%). The distribution of the FIGO stage was 63.4% (104/164) in stage I, 13.4% (22/164) in stage II, 18.9% (31/164) in stage III, and 4.3% (7/164) in stage IV. In this study, there was no patient with a stage IB tumor. Based on the stage IC classification of FIGO 2014 [6], there were 50 (30.5%) patients with IC1, 10 (6.1%) with IC2, and 10 (6.1%) with IC3 tumors. In all, there were 21 (12.8%) patients who underwent fertility-sparing surgery [$N = 7$ (IA), 11 (IC1), and 3 (IC2/3)]. Although postoperative chemotherapy was principally recommended for all patients, 16 women (9.8%: 11 with IA, 4 with IC1, and 1 with IIA) did not receive it. In the majority of the patients ($N = 123$; 75.0%), the preoperative CA125 value was elevated to over 35 U/mL.

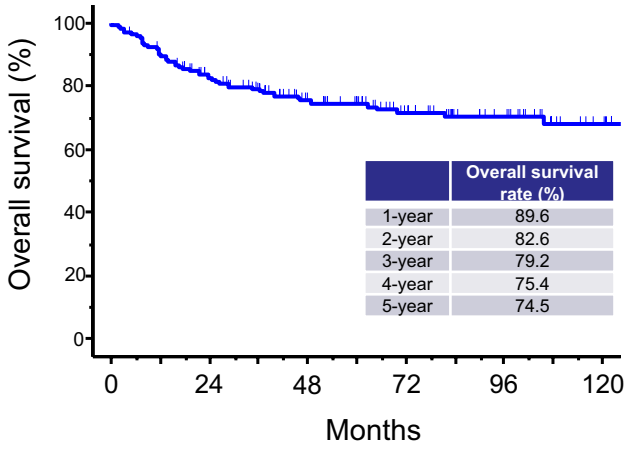

Fig. 2 Kaplan–Meier estimated overall survival of patients with all-stage clear-cell carcinoma (CCC). The overall 5-year survival rate was 74.5%

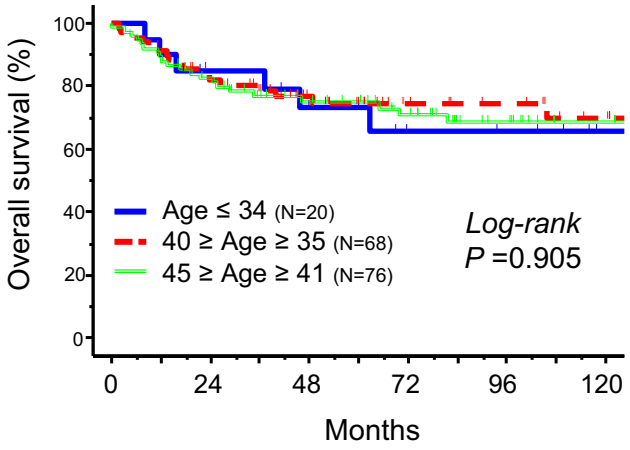

Fig. 4 Kaplan–Meier estimated overall survival of patients with CCC according to age groups (≤34, 35–40, and 41–45). We did not identify a significant difference among the three groups ($P=0.905$)

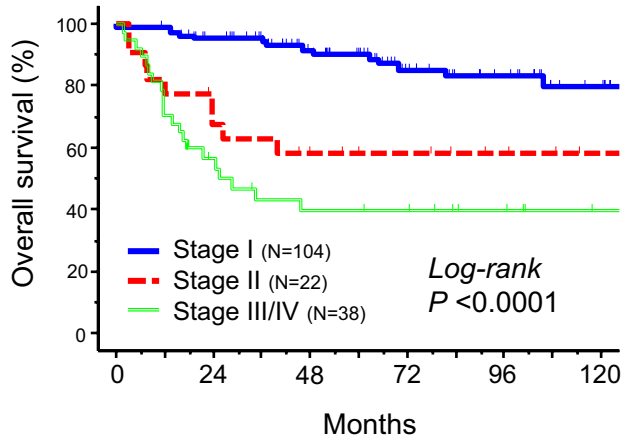

Fig. 3 Kaplan–Meier estimated overall survival of patients with CCC according to the FIGO stage. The 5-year OS rates were as follows: stage I (90.2%), stage II (57.9%), and stage III/V (39.3%) (comparison among three groups: $P<0.0001$). Patients with stage I and II tumors did not reach the median survival time (MST). The MST in patients with stage III–IV tumors was 26.1 months

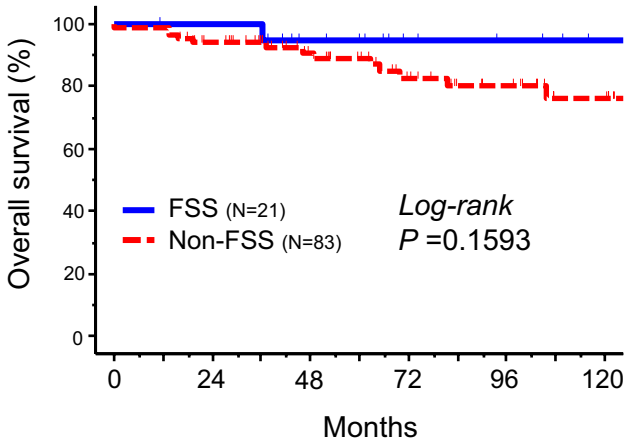

Fig. 5 Kaplan–Meier estimated overall survival of CCC patients at stage I according to the surgical modality (FSS vs. non-FSS). The 5-year OS rates were 95.0% (FSS) and 89.1% (non-FSS). We did not identify a significant difference between the two groups ($P=0.1593$)

Oncologic outcome and overall survival

With a median follow-up of 73.8 months (range 5.2–244.2) in the surviving patients, 59 patients (36.0%) developed recurrence. The median time to recurrence was 11.9 months. Forty-five patients (27.4%) died of their recurrence.

The overall 5-year survival rate was 74.5% (Fig. 2). The overall survival (OS) curves of all patients according to the FIGO stage are shown in Fig. 3. The 5-year OS rates were as follows: stage I (90.2%), stage II (57.9%), and stage III/V (39.3%) ($P<0.0001$). Patients with stages I and II tumors did not reach the median survival time (MST). The MST for patients with stages III–IV tumors was 26.1 months. There was a significant difference in OS rates among patients belonging to each stage ($P<0.0001$: Fig. 3).

Generally, the rate of cancer in women rises with increasing age. Thus, whether the oncologic outcome was different among women of different age groups (≤34, 35–40, and 41–45) was further investigated. Figure 4 shows the OS curves on stratification by the age distribution. No significant difference among the 3 groups ($P=0.905$) was identified. Subsequently, confining analysis to stage I patients, we compared the OS rates between the FSS and non-FSS (radical surgery) groups. The 5-year OS rates were 95.0% (FSS) and 89.1% (non-FSS). As shown in Fig. 5, the patients in the FSS group did not show a poorer OS than those in the radical surgery group ($P=0.1593$).

Multivariable analysis of stage I CCC patients

As the majority of patients had a stage I tumor with known substage, multivariable analysis was subsequently carried out to search for an independent prognostic indicator of OS in stage I CCC patients. As shown in Table 2, the age (≤ 34, 35–40, and 41–45), substage (FIGO IA/IC1 vs. IC2/IC3), type of surgery (FSS vs. non-FSS), volume of ascites (none/< 100 vs. ≥ 100 mL), and presence or absence of adjuvant chemotherapy (Presence vs. absence) were entered into the Cox proportional hazard analysis. Consequently, only substage was an independent prognostic factors unfavorable OS (HR 4.293, 95% CI 1.140–16.422, $P = 0.0318$).

Post-recurrence survival in patients who experienced relapse

As mentioned previously, in our study we identified 59 patients who developed recurrence. Accordingly, the survival rate after recurrence was examined in such patients. Figure 6 shows the Kaplan–Meier curve of post-recurrence survival (PRS). The median PRS was 11.6 months. The 1-, 3-, and 5-year PRS rates were 46.8, 20.5, and 15.6 months, respectively.

Table 2 Multivariable analysis (stage I patients with known substage)

	N	HR	95% CI	*P* value
Age				
≤ 34	11	Ref		
35–40	42	0.903	0.127–18.100	0.9291
≥ 41	98	0.941	0.126–20.374	0.9593
FIGO stage				
IA/IC1	78	Ref		
IC2/IC3	20	4.293	1.140–16.422	0.0318
Sugery				
FSS	21	Ref		
Non-FSS	77	0.450	0.022–3.234	0.4571
Acites volume (mL)				
None/< 100 mL	86	Ref		
≥ 100 mL	12	1.653	0.131–4.294	0.5676
Chemotherapy				
Absent	15	Ref		
Present	83	0.144	0.508–8.87e + 234	0.1436

HR hazard ratio, *FIGO* International Federation of Gynecology and Obstetrics, *FSS* fertility-sparing surgery

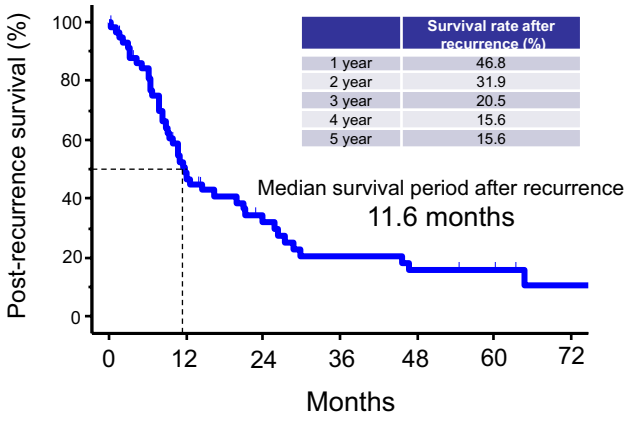

Fig. 6 Kaplan–Meier estimated post-recurrence survival (PRS) of CCC patients who developed recurrence ($N = 59$). The median PRS was 11.6 months. The 1-, 3-, and 5-year PRS rates were 46.8, 20.5, and 15.6 months, respectively

Discussion

In general, CCC is frequently diagnosed postmenopause. Thus, the number of CCC patients at reproductive age is relatively low. However, given the high prevalence of endometriosis in young women, the occurrence of CCC at reproductive age is problematic due to its life-threatening impact as well as the possibility of the loss of fertility. Therefore, it is necessary to understand clinical hallmarks and prognostic indicators of CCC, particularly in this generation. To our knowledge, there have been few reports targeting CCC patients at reproductive age. In the present study, we investigated the clinical features of Japanese patients based on large population-based series under centralized pathological review. Previously, we overviewed the recurrence-free survival and possible prognostic indicators influencing it in young women with CCC [8]. The present study is the subsequent report focusing on long-term overall survival and oncologic outcome in this generation with CCC.

In the present study, the patients' stage distributions were 63.4% (104/164) in stage I, 13.4% (22/164) in stage II, 18.9% (31/164) in stage III, and 4.3% (7/164) in stage IV. Therefore, the majority of patients had stage I tumors. This is consistent with the previous data regarding patients of all ages [9]. With regard to the oncologic outcomes, the 5-year OS rates were as follows: stage I (90.2%), stage II (57.9%), and stage III/V (39.3%), respectively. Since CCC is considered an aggressive tumor, postoperative systemic chemotherapy has been basically recommended in clinical practice to eliminate occult metastatic clones as thoroughly as possible. At present, taxane plus platinum combination is considered standard chemotherapy based on prior studies demonstrating a higher response rate than with conventional platinum-based chemotherapy (22–56% vs. 11–27%,

respectively) [10, 11]. In our series, the majority of patients (90.2%) underwent postoperative cytotoxic chemotherapy. However, patients with disease more advanced than IC with preoperative capsule rupture/positive washing showed an unfavorable oncologic outcome. Moreover, in multivariable analysis, we could not identify a survival advantage in patients who received chemotherapy. By overviewing the current data, we re-recognized the limitation of conventional cytotoxic chemotherapy regarding its power to eliminate invisible micrometastasis.

For reproductive-age patients, child-bearing is a crucial consideration. Normally, the standard surgical treatment for CCC patients consists of hysterectomy, bilateral salpingo-oophorectomy, and omentectomy with surgical staging. However, if we use such surgical procedures for these young women, the reproductive functions as well as female-specific endocrine system will be permanently lost. Occasionally, conservative surgery, at least including the uterus and contralateral ovary, is considered as a surgical option for young patients with early-stage CCC. Nevertheless, the indication in clinical practice is now controversial. The number of women over 40 years of age seeking infertility treatment has been steadily increasing [12]. In our earlier preliminary report, we could not identify a survival disadvantage in early-stage CCC patients under 40 who underwent FSS, compared with those who underwent conventional surgery [13]. However, the population of women in their early 40s requiring assisted reproductive technology increased significantly from 10–15% in the 2000s to 20–25% in 2009 [12, 14, 15]. Furthermore, reflecting on the fact that the majority of women with ovarian cancer in their 40s (51.4%, 507/986) have stage I tumors [16], we considered the necessity of reassessing the possibility of FSS based on a larger number of patients, expanding the age up to those in their early 40s. In this study, the stage I patients in the FSS group did not show a poorer overall survival than those in the conventional surgery group [$P=0.1593$: 5-year OS rates: 95.0% (FSS) and 89.1% (conventional)]. Here, we would like to suggest a reason why a poorer oncologic outcome was not observed in the FSS-group, in spite of the fact that FSS is a limited surgery. Based on summarized data from five representative studies, there were 12 patients with CCC who experienced recurrence after receiving FSS [17–21]. Among these patients, 91.7% (11/12) showed an extra-ovarian/uterine recurrence, including the peritoneal cavity, retroperitoneal lymph nodes, and distant parenchymal organs. We suggest that the contralateral ovary and uterus are uncommon organs as sites of FSS-related recurrence, reflecting the highly aggressive/metastatic hallmarks of CCC. However, we should keep a careful attitude toward the selection of FSS, despite the fact that the FSS-related recurrence is rare in women with early-stage CCC. Irrespective of this, a woman who selects FSS receives the marked benefit of preserving the ability to have a child. It is necessary for the patient and physician to share risk-and-benefit information before selecting this surgery.

In the current study, we consequently identified 59 patients who developed recurrence. We noted extremely poor survival after recurrence in such patients (median post-recurrence survival: 11.6 months). Regardless of a reproductive or non-reproductive age, the therapeutic strategy for recurrent CCC is a marked challenge in clinical practice.

Several reports indicated that younger women have a more favorable tolerance of intensive chemotherapeutic agents, which may lead to a better outcome in these patients [22, 23].

However, given the clearly limited benefit of cytotoxic drugs, with response rates of less than 10% [24], there is now marked interest in the development of either monotherapy or combination with other molecular targeted/cytotoxic agents for the treatment of recurrent CCC. Prognostic improvement in patients with CCC is anticipated through preclinical data, including angiogenesis-modulating agents and inhibitors of PI3K-Akt-mTOR pathway [25–27]. Kikuchi et al. reported that 3 out of 6 patients with CCC showed a response to temsirolimus, which is a targeted agent inhibiting mammalian target of rapamycin (mTOR) [28]. In addition, the emergence of immune checkpoint inhibitors has revolutionized multiple cancer strategies and encouraged us regarding the improvement of patient outcomes. Regarding the introduction of immune checkpoint inhibitors, including nivolumab and avelumab studies, it is noteworthy that 4 of the 5 patients showing durable responses had CCC [29–31]. Given the rarity of and geographical difference in the prevalence of CCC, most previous clinical trials failed to include sufficient numbers of patients with this tumor. Further international collaborative studies are essential to enroll adequate patient numbers.

The limitations of the current report are those associated with any retrospective study, involving the possibility of selection bias and treatment heterogeneity, particularly in relapsed cases. The absence of a significant difference may merely reflect a type II error based on the small patient number. In addition, we lacked detailed clinical information on the prevalence of endometriosis and reproductive outcome reflecting patients' hope to conceive. Furthermore, one of the major weaknesses of the current study was that not all of the patients underwent systematic lymphadenectomy in spite of the fact that all received peritoneal staging, including ascites/washing cytology, and had information on the capsule state. In those patients, we may have missed nodal occult metastases. On the other hand, the strengths of our study included the centralized pathological review by expert pathologists in gynecologic malignancy. Thus, reassessment of the pathological findings contributed to appropriate diagnosis and reduced intraobserver variability on determining the histological type. Additionally, the initial surgery and

chemotherapy were carried out based on the same criteria and protocol in an identical study group (TOTSG group).

In summary, this is one of the largest regional population-based studies to evaluate the demographic and clinicopathologic prognostic factors associated with the oncologic outcome of reproductive-age women with CCC using detailed pathologic information. Although the retrospective data suggest that FSS may be considered for reproductive-age women, patients should be appropriately counseled with sufficient explanation of the risks. Due to the unsatisfactory treatment outcome with cytotoxic chemotherapy, further clinical trials are anticipated for the identifications of optimal combination with molecular targeted/cytotoxic agents.

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Author contributions HK: data analysis and interpretation, drafting paper; SS, NY, KN, MK: data collection; KS: revising manuscript; FK: supervising and funding.

Compliance with ethical standards

Conflict of interest All authors declare that there are no conflicts of interest.

References

1. Committee Japanese Gynecologic Cancer (2012) Annual report on Japanese gynecologic cancer committee. Acta Obstet Gynecol Jpn 64:1029–1141
2. Giudice LC, Kao LC (2004) Endometriosis. Lancet 364:1789–1799
3. Mogensen JB, Kjaer SK, Mellemkjaer L, Jensen A (2016) Endometriosis and risks for ovarian, endometrial and breast cancers: a nationwide cohort study. Gynecol Oncol 143(1):87–92
4. Kim HS, Kim TH, Chung HH, Song YS (2014) Risk and prognosis of ovarian cancer in women with endometriosis: a meta-analysis. Br J Cancer 110:1878–1890
5. Gadducci A, Lanfredini N, Tana R (2014) Novel insights on the malignant transformation of endometriosis into ovarian carcinoma. Gynecol Endocrinol 30:612–617
6. Zeppernick F, Meinhold-Heerlein I (2014) The new FIGO staging system for ovarian, fallopian tube, and primary peritoneal cancer. Arch Gynecol Obstet 290:839–842
7. Suzuki S, Kajiyama H, Shibata K, Ino K, Nawa A, Sakakibara K, Matsuzawa K, Takeda A, Kinoshita Y, Kawai M, Nagasaka T, Kikkawa F (2008) Is there any association between retroperitoneal lymphadenectomy and survival benefit in ovarian clear cell carcinoma patients? Ann Oncol 19:1284–1287
8. Kajiyama H, Mizuno M, Shibata K, Umezu T, Suzuki S, Yamamoto E, Mitsui H, Sekiya R, Niimi K, Kawai M, Nagasaka T, Kikkawa F (2014) A recurrence-predicting prognostic factor for patients with ovarian clear-cell adenocarcinoma at reproductive age. Int J Clin Oncol 19:921–927
9. Chan JK, Teoh D, Hu JM, Shin JY, Osann K, Kapp DS (2008) Do clear cell ovarian carcinomas have poorer prognosis compared to other epithelial cell types? A study of 1411 clear cell ovarian cancers. Gynecol Oncol 109:370–376
10. Takano M, Sugiyama T, Yaegashi N, Sagae S, Kuzuya K, Udagawa Y, Tsuda H, Suzuki M, Kigawa J, Goto T, Tsuda H, Moriya T, Kikuchi Y (2010) Less impact of adjuvant chemotherapy for stage I clear cell carcinoma of the ovary: a retrospective Japan Clear Cell Carcinoma Study. Int J Gynecol Cancer 20:1506–1510
11. Utsunomiya H, Akahira J, Tanno S, Moriya T, Toyoshima M, Niikura H, Ito K, Morimura Y, Watanabe Y, Yaegashi N (2006) Paclitaxel–platinum combination chemotherapy for advanced or recurrent ovarian clear cell adenocarcinoma: a multicenter trial. Int J Gynecol Cancer 16:52–56
12. Cabry R, Merviel P, Hazout A, Belloc S, Dalleac A, Copin H, Benkhalifa M (2014) Management of infertility in women over 40. Maturitas 78:17–21
13. Kajiyama H, Shibata K, Mizuno M, Hosono S, Kawai M, Nagasaka T, Kikkawa F (2011) Fertility-sparing surgery in patients with clear-cell carcinoma of the ovary: is it possible? Hum Reprod 26:3297–3302
14. Ferraretti AP, Goossens V, Kupka M, Bhattacharya S, de Mouzon J, Castilla JA, Erb K, Korsak V, Nyboe Andersen A, European IVFMCftESoHR Embryology (2013) Assisted Reproductive Technology in Europe, 2009: results generated from European registers by ESHRE. Hum Reprod 28:2318–2331
15. Nyboe Andersen A, Gianaroli L, Nygren KG, European IVFmp, European Society of Human R (2004) Embryology assisted reproductive technology in Europe, 2000. Results generated from European registers by ESHRE. Hum Reprod 19:490–503
16. Yamagami W, Aoki D (2015) Annual report of the Committee on Gynecologic Oncology, the Japan Society of Obstetrics and Gynecology. J Obstet Gynaecol Res 41:1861–1869
17. Fruscio R, Corso S, Ceppi L, Garavaglia D, Garbi A, Floriani I, Franchi D, Cantu MG, Bonazzi CM, Milani R, Mangioni C, Colombo N (2013) Conservative management of early-stage epithelial ovarian cancer: results of a large retrospective series. Ann Oncol 24:138–144
18. Kajiyama H, Shibata K, Suzuki S, Ino K, Nawa A, Kawai M, Nagasaka T, Kikkawa F (2010) Fertility-sparing surgery in young women with invasive epithelial ovarian cancer. Eur J Surg Oncol 36:404–408
19. Morice P, Leblanc E, Rey A, Baron M, Querleu D, Blanchot J, Duvillard P, Lhomme C, Castaigne D, Classe JM, Bonnier P, GCCLCC, SFOG (2005) Conservative treatment in epithelial ovarian cancer: results of a multicentre study of the GCCLCC (Groupe des Chirurgiens de Centre de Lutte Contre le Cancer) and SFOG (Societe Francaise d'Oncologie Gynecologique). Hum Reprod 20:1379–1385
20. Park JY, Kim DY, Suh DS, Kim JH, Kim YM, Kim YT, Nam JH (2008) Outcomes of fertility-sparing surgery for invasive epithelial ovarian cancer: oncologic safety and reproductive outcomes. Gynecol Oncol 110:345–353
21. Satoh T, Hatae M, Watanabe Y, Yaegashi N, Ishiko O, Kodama S, Yamaguchi S, Ochiai K, Takano M, Yokota H, Kawakami Y, Nishimura S, Ogishima D et al (2010) Outcomes of fertility-sparing surgery for stage I epithelial ovarian cancer: a proposal for patient selection. J Clin Oncol 28:1727–1732
22. Chan JK, Loizzi V, Lin YG, Osann K, Brewster WR, DiSaia PJ (2003) Stages III and IV invasive epithelial ovarian carcinoma in younger versus older women: what prognostic factors are important? Obstet Gynecol 102:156–161
23. Thigpen T, Brady MF, Omura GA, Creasman WT, McGuire WP, Hoskins WJ, Williams S (1993) Age as a prognostic factor in ovarian carcinoma: the Gynecologic Oncology Group experience. Cancer 71:606–614
24. Takano M, Sugiyama T, Yaegashi N, Sakuma M, Suzuki M, Saga Y, Kuzuya K, Kigawa J, Shimada M, Tsuda H, Moriya T, Yoshizaki A, Kita T et al (2008) Low response rate of second-line chemotherapy for recurrent or refractory clear cell carcinoma of

the ovary: a retrospective Japan Clear Cell Carcinoma Study. Int J Gynecol Cancer 18:937–942
25. Anglesio MS, Carey MS, Kobel M, Mackay H, Huntsman DG, Vancouver Ovarian Clear Cell Symposium S (2011) Clear cell carcinoma of the ovary: a report from the first Ovarian Clear Cell Symposium, June 24th, 2010. Gynecol Oncol 121:407–415
26. Miyazawa M, Yasuda M, Fujita M, Kajiwara H, Hirabayashi K, Takekoshi S, Hirasawa T, Murakami M, Ogane N, Kiguchi K, Ishiwata I, Mikami M, Osamura RY (2009) Therapeutic strategy targeting the mTOR-HIF-1alpha-VEGF pathway in ovarian clear cell adenocarcinoma. Pathol Int 59:19–27
27. Rahman M, Nakayama K, Rahman MT, Nakayama N, Ishikawa M, Katagiri A, Iida K, Nakayama S, Otsuki Y, Shih IM, Miyazaki K (2012) Clinicopathologic and biological analysis of PIK3CA mutation in ovarian clear cell carcinoma. Hum Pathol 43:2197–2206
28. Kikuchi Y, Kudoh K, Talano M, Kikuchi R, Kita T, Hamada Y (2010) Effect of treatment by temsirolimus on patients with clear cell carcinoma of the ovary. J Clin Oncol 28(15):5086. https://doi.org/10.1200/jco.2010.28.15_suppl.5086 (**Abstract 5086**)
29. Disis ML, Patel MR, Pant S, Hamilton EP, Lockhart AC, Kelly K, Beck JT, Gordon MS, Weiss GJ, Taylor MH et al (2016) Avelumab (MSB0010718C; anti-PD-L1) in patients with recurrent/refractory ovarian cancer from the JAVELIN solid tumor phase Ib trial: safety and clinical activity. J Clin Oncol 34(15):5533. https://doi.org/10.1200/JCO.2016.34.15_suppl.5533 (**suppl; abstr5533**)
30. Hamanishi J, Mandai M, Ikeda T, Minami M, Kawaguchi A, Murayama T, Kanai M, Mori Y, Matsumoto S, Chikuma S, Matsumura N, Abiko K, Baba T et al (2015) Safety and antitumor activity of anti-PD-1 antibody, nivolumab, in patients with platinum-resistant ovarian cancer. J Clin Oncol 33:4015–4022
31. Gaillard SL, Secord AA, Monk B (2016) The role of immune checkpoint inhibition in the treatment of ovarian cancer. Gynecol Oncol Res Pract 3:11