



Tumor Size Is an Independent Prognostic Factor for Stage I Ovarian Clear Cell Carcinoma: A Large Retrospective Cohort Study of 1,000 Patients

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Objective: The aim of this study was to investigate the prognostic value and stratification cutoff point for tumor size in stage I ovarian clear cell carcinoma (OCCC).

Methods: This was a retrospective cohort study using the Surveillance, Epidemiology, and End Results database (version: SEER 8.3.9). Patients diagnosed with stage I OCCC from 1988 to 2018 were included for further analysis. X-Tile software was used to identify the potential cutoff point for tumor size. Stratification analysis, propensity score matching, and inverse probability weighting analysis were used to balance the potential confounding factors.

Results: A total of 1,000 stage I OCCC patients were included. Of these 1,000 patients, median follow-up was 106 months (95% confidence interval [CI]: 89–112 months). Multivariate analysis showed that tumor size, age at diagnosis, and stage IC were significantly associated with stage I OCCC patients. Eight centimeters is a promising cutoff point that can divide stage I OCCC patients into a good or a poor prognosis group. After controlling potential confounding factors with propensity score matching and inverse probability weighting, we demonstrated that stage I OCCC patients with tumor size ≤ 8 cm enjoyed a significantly better 5-year overall survival (OS, 89.8% vs. 81%, $p < 0.0001$). Tumor size ≤ 8 cm was an independent prognostic factor of stage I OCCC patients (hazard ratio [HR] 0.5608, 95% CI: 0.4126–0.7622, $p = 0.0002$).

Conclusions: Tumor size is an independent prognostic factor for stage I OCCC, and 8 cm is a promising cutoff point for tumor size for risk stratification. However, using tumor size in the stratification management of stage I OCCC patients warrants further investigation.

Keywords: ovarian clear cell carcinoma (OCCC), tumor size, prognosis factor, early stage, propensity score matching, inverse probability weighting analysis

INTRODUCTION

Ovarian clear cell carcinoma (OCCC) is a relatively rare (incidence: 3%–10%) but distinct histological type of epithelial ovarian cancer (1, 2). Unlike high-grade serous adenocarcinoma (HGSOC), stage I OCCC accounts for 56.3%–65.5% (3). Moreover, many OCCC cases were diagnosed during minimally invasive surgery for ovarian cyst excision (4). It was reported that minimally invasive surgery was a promising therapeutic option in early-stage ovarian epithelial cancer (5–7). Endometriosis was regarded as a precursor of OCCC, and one single-center retrospective study revealed that OCCC with concurrent endometriosis accounts for 45% of all OCCC cases (8). Moreover, clear cell carcinoma was frequently mixed with other histological types of cancer (9) and was associated with a poorer prognosis (10).

Even though OCCC is diagnosed at an early stage and in younger patients, the prognosis of OCCC seems unfavorable (3, 11, 12). A previous large retrospective cohort study showed that OCCC patients have a significantly worse 5-year overall survival compared with patients with HGSOC in every sub-FIGO stage analysis (3). It seems that prognosis of early-stage OCCC is heterogeneous (11, 12). Many stage IA CCC patients have quite a favorable disease-free survival rate, while a subset of OCCC patients progress quickly and experience recurrence (13).

Tumor size is considered a tumor burden parameter, and this parameter is used to evaluate clinical response or prognosis (14, 15). Tumor size also reflects the complexity of the tumor ecosystem (16). During tumor growth, intra-tumoral heterogeneity is dramatically increased, with cancer stem cells and a number of driver mutations (17–19). However, the prognostic effect of tumor size in early-stage OCCC has not been well explored. Thus, we asked whether tumor size in stage I OCCC can predict prognosis. In the current study, we used the largest public database, the Surveillance, Epidemiology, and End Results (SEER) database, to evaluate the prognostic value of primary tumor size in patients with OCCC.

METHOD AND MATERIALS

We conducted this retrospective cohort study according to the STROBE statement and used the high-quality open access database, the SEER database (version 8.3.9).

Data Extraction and Screening

After registration and approval by the SEER team, we downloaded the SEER*Stat 8.3.9 software and established a local OCCC database by extracting the raw clinical information and pathological information from 1998 to 2018. According to the ICD-O-3 coding system, we identified malignant OCCC using the following codes: 8310-3, 8312-3, and 8313-3. Clinical information, such as race, year of diagnosis, sequence of diagnosis, age, survival (months), and vital status, was extracted. Tumor characteristics, such as TNM stage, histological type, and grade (20, 21), were extracted (Table S1). Next, we narrowed the target research objects using the following

including criteria: (1) T1N0M0 (FIGO Stage I) OCCC, (2) diagnosed as primary tumor, (3) with known tumor size information, and (4) with follow-up and survival time information. Patients with advanced stage disease, multiple primary cancer, missing tumor size, and follow-up information were excluded. The workflow is shown in Figure 1. The baseline information of included patients was evaluated using the “tableone” R package and is shown in Table 1.

Cutoff Point Definition

To determine the best cutoff point for tumor size, we used the X-Tile software (22), according to the manufacturer’s guidelines. Briefly, the cutoff point was defined as the risk score that generated the largest value of χ^2 in the Mantel Cox test.

Survival Analysis

We conducted survival analysis using the “survival” package in R. Kaplan–Meier curves were used to evaluate overall survival between different groups. Log-rank *p*-values were calculated with hazard ratios and 95% confidence interval (CI) using the *cox.ph* function.

Balancing the Possible Confounding Factors

To balance these possible confounding factors, namely, age at diagnosis, T stage, and degree of tumor differentiation, we used three different methods: stratification analysis, propensity score matching, and inverse probability weighting (IPW) analysis. Propensity score matching analysis was performed using the R “MatchIt” package with the parameters “method = ‘nearest’, ratio = 1”. Moreover, we further performed IPW analysis (23) using the RISCAs (24) package in R.

RESULTS

Basic Clinicopathological Characteristics of Stage I OCCC Patients

A total of 3,035 OCCC cancer patients were identified using ICD-O-3 codes 8310/3, 8312/3, and 8313/3. Then, we screened the candidates by using the including and excluding criteria as described in the *Method and Materials* section. A total of 1,000 stage I OCCC cases were included in the subsequent analyses. Among them, 19.6% (196/1,000) of OCCC cases were diagnosed before 45 years old (Figure S1). Mean tumor size of included patients is 11.24 cm (range from 0.11 to 98.9 cm, Figure S2). The patients’ basic clinicopathological characteristics are listed in Table 1.

Tumor Size Is a Promising Prognostic Factor in Stage I OCCC Patients

Of these 1,000 included patients, median follow-up was 106 months (range from 1 to 366 months; 95% CI: 98–114). The 5-year overall survival rate for all included patients was 84.0% [standard error (SE) 1.26%]. The 5-year overall survival rate was 87.3% (SE 1.52%) for patients with stage IA disease and 78.6% (SE 2.22%) for patients with stage IC disease. Older age (age > 45

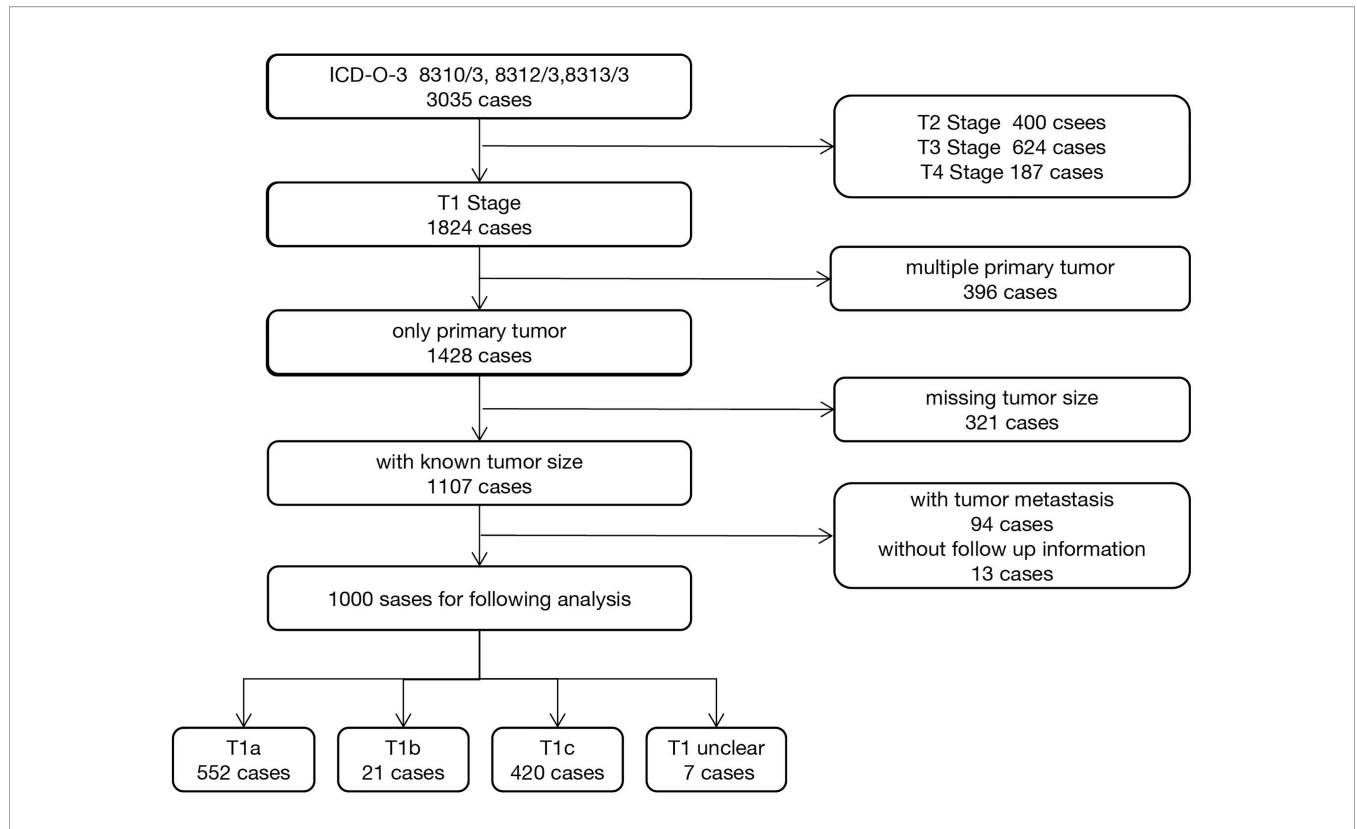


FIGURE 1 | Workflow of 1,000 ovarian clear cell carcinoma patients' selection from the Surveillance, Epidemiology, and End Results (SEER) database.

TABLE 1 | Basic clinicopathological characteristics of 1,000 included stage I ovarian clear cell carcinoma.

Characteristics	Total (N=1000)
Age at diagnosis [mean (SD)]	54.85 (11.05)
Race (%)	
American Indian/Alaska Native	11 (1.1)
Asian or Pacific Islander	196 (19.6)
Black	27 (2.7)
Unknown	3 (0.3)
White	763 (76.3)
T_sub_class (%)	
T1	7 (0.7)
T1a	552 (55.2)
T1b	21 (2.1)
T1c	420 (42.0)
Grade* (%)	
I	15 (1.5)
II	83 (8.3)
III	297 (29.7)
IV	202 (20.2)
Unknown	403 (40.3)
tumor_size [mm, mean (SD)]	112.38 (74.75)

*The definition of tumor grade is according to coding manual of SEER database. (https://seer.cancer.gov/archive/manuals/2021/SPCCSM_2021_MainDoc.pdf).

years old) was associated with inferior overall survival (**Figure S3**, $p = 0.0099$). Younger patients (age ≤ 45 years old) and the older age group had a 5-year overall survival rate of 85.4% (SE 2.71%) and 83.4% (SE 1.43%), respectively.

On univariate analysis (**Table 2**), age of diagnosis (HR 0.608, 95% CI: 0.4152–0.8910, $p = 0.0107$), stage IC (HR 1.5783, 95% CI: 1.2025–2.0716, $p = 0.001$), and tumor size (HR 1.0020, 95% CI: 1.0008–1.0033, $p = 0.0008$) were associated with prognosis. However, race, tumor differentiated degree, and stage IB were not associated with prognosis. In the multivariate analysis, age of diagnosis (HR 0.6425, 95% CI: 0.4383–0.9419, $p = 0.0234$), stage IC (HR 1.5086, 95% CI: 1.1488–1.9809, $p = 0.0031$), and tumor size (HR 1.0021, 95% CI: 1.0008–1.0033, $p = 0.0012$) were independently associated with overall survival.

Among 1,000 stage I OCCC patients, we identified 8 cm as the best cutoff point criteria according to the X-Tile software (**Table S2**). This cutoff was also observed in the T1a and T1c subgroup analysis (**Tables S3, S4**). Thus, we choose 8 cm as the cutoff point, and divide the patients into two subgroups. **Table 3** lists the baseline information between the two groups before and after the potential confounding factors were balanced. Then, we compared the overall survival between the two groups. As shown in **Figure 2**, OCCC patients with tumors ≤ 8 cm enjoy a significantly better prognosis than patients with a tumor > 8 cm (HR 0.5608, 95% CI: 0.4126–0.7622, $p = 0.0002$). The 5-year overall survival rate of patients with tumor size > 8 cm was 80.6%, while that for patients with tumors ≤ 8 cm was 90.2% ($p < 0.0001$). After PSM and IPW, we also found that patients with tumors ≤ 8 cm enjoyed a significantly better prognosis (**Figure 2**). We further performed subgroup analysis in stage 1a and stage 1c OCCC patients, respectively. As shown in **Figures S4, S5**, 8 cm could divide

TABLE 2 | Univariate and multivariate analysis of the included 1,000 OCCC patients.

	Univariate analysis				Multivariate analysis			
	HR	95% CI		P value	HR	95% CI		P value
		Lower	Upper			Lower	Upper	
Age_of_diagnosis								
>45	Reference				Reference			
<=45	0.608	0.4152	0.891	0.0107	0.6425	0.4383	0.9419	0.0234
Grade								
I	Reference							
II	0.738	0.278	1.9587	0.542				
III	0.8411	0.3381	2.0921	0.71				
IV	0.6776	0.2639	1.7394	0.418				
Unkonwn	0.8235	0.3345	2.0277	0.673				
Race								
American Indian/Alaska Native	Reference							
Asian or Pacific Islander	1.6522	0.2264	12.0532	0.62				
Black	2.9722	0.3576	24.7	0.313				
White	2.0221	0.2831	14.4418	0.483				
Unknown	1.61E-06	0	Inf	0.994				
Sub_stage								
IA	Reference				Reference			
IB	1.5817	0.6447	3.8809	0.3167	1.4434	0.5877	3.5451	0.4234
IC	1.5783	1.2025	2.0716	0.001	1.5086	1.1488	1.9809	0.0031
INOS	3.62E-07	0	Inf	0.9921	2.93E-07	0	Inf	0.9922
Tumor_size	1.002	1.0008	1.0033	0.0008	1.0021	1.0008	1.0033	0.0012

TABLE 3 | Baseline information of all T1 OCCC patients between the two groups before and after balancing the confounding factor.

Characteristics	Unmatched			Propensity Score Match			Inverse Probability Weighting		
	tumor size >8cm n=645	tumor size <=8cm n=355	p value	tumor size >8cm n=355	tumor size <=8cm n=355	p value	tumor size >8cm n=996.4	tumor size <=8cm n=1000	p value
Age (mean (SD))	55.58 (10.89)	53.52 (11.24)	0.005	53.88 (10.95)	53.52 (11.24)	0.665	54.93 (11.63)	54.86 (10.96)	0.93
Race (%)			0.15			0.933			0.839
American Indian/Alaska Native	9 (1.4)	2 (0.6)		1 (0.3)	2 (0.6)		9.6 (1.0)	11.0 (1.1)	
Asian or Pacific Islander	125 (19.4)	71 (20.0)		70 (19.7)	71 (20.0)		197.1 (19.8)	196.7 (19.7)	
Black	22 (3.4)	5 (1.4)		6 (1.7)	5 (1.4)		25.8 (2.6)	26.9 (2.7)	
Unknown	3 (0.5)	0 (0.0)					0.0 (0.0)	3.0 (0.3)	
White	486 (75.3)	277 (78.0)		278 (78.3)	277 (78.0)		763.9 (76.7)	762.4 (76.2)	
T (%)			0.103			0.702			0.986
T1	6 (0.9)	1 (0.3)		0 (0.0)	1 (0.3)		7.5 (0.8)	7.0 (0.7)	
T1a	340 (52.7)	212 (59.7)		215 (60.6)	212 (59.7)		554.9 (55.7)	553.0 (55.3)	
T1b	16 (2.5)	5 (1.4)		7 (2.0)	5 (1.4)		17.1 (1.7)	20.6 (2.1)	
T1c	283 (43.9)	137 (38.6)		133 (37.5)	137 (38.6)		416.8 (41.8)	419.4 (41.9)	
Grade (%)			0.061			0.969			1
I	10 (1.6)	5 (1.4)		4 (1.1)	5 (1.4)		15.5 (1.6)	15.1 (1.5)	
II	47 (7.3)	36 (10.1)		32 (9.0)	36 (10.1)		80.1 (8.0)	81.9 (8.2)	
III	209 (32.4)	88 (24.8)		90 (25.4)	88 (24.8)		296.3 (29.7)	297.2 (29.7)	
IV	133 (20.6)	69 (19.4)		66 (18.6)	69 (19.4)		201.8 (20.2)	202.1 (20.2)	
Unknown	246 (38.1)	157 (44.2)		163 (45.9)	157 (44.2)		402.8 (40.4)	403.7 (40.4)	

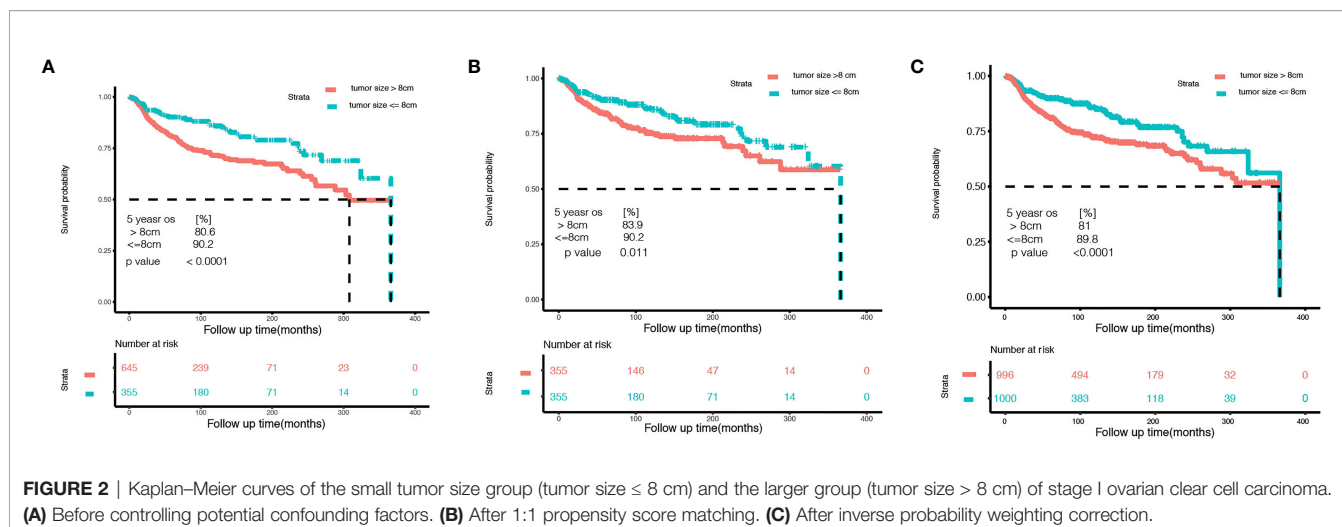
patients into two significantly different prognosis groups in both stage Ia and stage Ic OCCC patients.

DISCUSSION

In this retrospective cohort study, we demonstrated the effect of tumor size on the prognosis of stage I OCCC and found that

8 cm was a promising cutoff point for tumor size. We used the cutoff to divide stage I OCCC patients into two groups and found a significant difference in prognosis.

However, limited to the clinicopathologic information we can obtain from the SEER database, we failed to obtain information on surgery approach (such as minimally invasive surgery or traditional transabdominal operation), adjuvant therapy, and disease-free survival time. Thus, in the current study, we can



hardly establish the relationship between tumor size and disease-free survival. Even though we performed stratification analysis, propensity score matching, and IPW analysis to balance the potential confounding factors, such unavailable information may serve as potential confounding factors in the current study.

The majority of OCCC cancer patients are diagnosed at an early stage. However, stage I OCCC patients have a highly heterogeneous prognosis. Oseledchik et al. (25) reported that stage IA/B patients have a significantly better prognosis than stage IC patients. However, another single-center study (26) from Japan showed no significant difference in prognosis between stage IA and rupture-only stage IC disease. Many prognostic factors in CCC have been investigated, while tumor size was seldom mentioned (8, 27, 28). Chan et al. (3) analyzed 1,411 patients with clear cell ovarian cancers and identified disease stage, age at diagnosis, and tumor grade as predictors of cancer-specific survival. Furthermore, Matsuo et al. (29) reported that lympho-vascular space invasion was an independent predictor of prognosis of stage I OCCC.

Tumor size is considered as an independent prognostic factor of clear renal cell carcinoma, and is significantly associated with lympho-vascular space invasion (30, 31). For some gynecological malignancies, the tumor size is incorporated into the FIGO stage, such as cervical cancer (32), vulvar tumor (33), and uterine sarcoma (34). In ovarian cancer, it has been widely accepted that residual tumor size after primary cytoreductive surgery is one of most important clinical predictors of patients' prognosis (35, 36). However, the prognostic value of primary tumor size in early-stage ovarian cancer has not been well explored. Our previous single-center retrospective study (8, 37) has taken tumor size into consideration. Limited to the small population size and analysis method, we failed to find the prognosis value of primary tumor size of OCCC progression-free survival and overall survival. In this manuscript, we found that tumor size is an independent prognostic factor of stage I OCCC. A recent study reported that tumor size was independently associated with lympho-vascular space invasion in stage I OCCC (29). The odds ratio of the tumor size ≥ 15 cm group was 5.11 (95% CI: 1.37–19.1, $p = 0.015$) when

compared with the tumor size < 10 cm group (29). This finding may help explain why the large tumor size group is associated with worse prognosis. In the report, the authors divided patients into three groups (< 10 cm, 10–15 cm, and > 15 cm), but they found that tumor size group was not significantly associated with disease-free survival and overall survival in stage I OCCC patients.

Another notable matter is fertility preservation of unexpected OCCC during ovarian cyst excision. Many OCCC patients are diagnosed at a younger age and are eager to get pregnant (4). In the current study, we found that 19.6% (196/1,000) of OCCC cases were diagnosed before 45 years old, and they enjoyed a significantly better prognosis (**Figure S3**). Several studies have reported the safety of fertility-sparing surgery among young early-stage OCCC patients. The single-center retrospective study reported by Park et al. (38) showed that there was no significant difference in 5-year disease-free survival and 5-year overall survival between the fertility-preservation group and the radical survival group. A recent systematic review also confirmed that fertility-sparing surgery is safe and feasible in low-risk early-stage OCCC patients (39). These observations suggest that further stratification management should be considered for stage I OCCC, and a fertility-preservation strategy can be considered in certain low-risk stage I OCCC patients. Our findings may provide a stratification management strategy for stage I OCCC patients. However, due to the limited high-quality evidence available, in the current version of the National Comprehensive Cancer Network (NCCN) guidelines (<https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1453>), patients with OCCC are not recommended to undergo fertility-preserving treatment strategies, even for stage IA to IC OCCC patients. An ongoing prospective clinical research (study number: JCOG-1203) conducted by the Japan Clinical Oncology Group (JCOG) will provide high-quality evidence of the safety of the fertility-sparing strategy in stage I OCCC patients (<https://jrct.niph.go.jp/latest-detail/jRCTs031180178>).

CONCLUSION

Tumor size is an independent prognostic factor for stage I OCCC. Additionally, 8 cm is a promising cutoff point for tumor size for risk stratification. However, the use of tumor size in the stratification management of stage I OCCC patients warrants further investigation.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/**Supplementary Material**.

AUTHOR CONTRIBUTIONS

LW, HS, and HZ designed the study. Data collection: LW and SS. Data analysis and interpretation: LW, HS, and HZ. Manuscript writing and figure preparation: LW and SS. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fonc.2022.862944/full#supplementary-material>

Supplementary Figure 1 | Age distribution of included stage I ovarian clear cell carcinoma. x-axis: age of diagnosis (years old), y-axis: number of cases.

Supplementary Figure 2 | Tumor size distribution of included stage I ovarian clear cell carcinoma. x-axis: tumor size (in millimeters), y-axis: number of cases.

Supplementary Figure 3 | Kaplan–Meier curves of young (age \leq 45 years old) and old (age $>$ 45 years old) group stage I ovarian clear cell carcinoma.

Supplementary Figure 4 | Kaplan–Meier curves of the small tumor size group (tumor size \leq 8 cm) and the larger group (tumor size $>$ 8 cm) of stage Ia ovarian clear cell carcinoma. **(A)** Before controlling potential confounding factors. **(B)** After 1:1 propensity score matching. **(C)** After inverse probability weighting correction.

Supplementary Figure 5 | Kaplan–Meier curves of the small tumor size group (tumor size \leq 8 cm) and the larger group (tumor size $>$ 8 cm) of stage Ic ovarian clear cell carcinoma. **(A)** Before controlling potential confounding factors. **(B)** After 1:1 propensity score matching. **(C)** After inverse probability weighting correction.

Supplementary Table 1 | Detailed clinical pathological information of the included 1,000 OCCC patients.

Supplementary Table 2 | Cutoff value screen of 1,000 stage I OCCC tumor size by X-tile software.

Supplementary Table 3 | Cutoff value screen of stage Ia OCCC tumor size by X-tile software.

Supplementary Table 4 | Cutoff value screen of stage Ic OCCC tumor size by X-tile software.

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