Comparison of the Clinical Characteristics and Prognosis Between Clear Cell Carcinomas and High-grade Serous Ovarian Carcinomas

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Research Article

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Abstract

Objectives: To compare the clinical characteristics and prognosis of women with clear cell versus high-grade serous ovarian carcinoma.

Methods: Retrospective analysis of the clinical data of 50 cases patients with ovarian clear cell carcinoma (OCCC) and 103 cases with high-grade serous ovarian carcinoma (HGSOC), who were initially treated and completed standardized therapy in Affiliated Hospital of Qingdao University from January 2013 to December 2017.

Results: There were significant differences in age, gravidity (G > 1), chief complaint, with ovarian endometriosis, tumor diameter, unilateral or bilateral, cystic and solid tumor, CA125, HE4, CA199, lactate dehydrogenase (LDH), and FIGO stage between the two groups. The differences in the prognosis between OCCC patients and HGSOC patients with early stage (FIGO I-II) were not statistically significant. The 5-year overall survival and progression-free survival of OCCC patients were significantly worse than those of HGSOC patients with advanced stage (FIGO III-IV) ($P < 0.05$). FIGO stage and non-R0 resection were independent risk factors affecting the prognosis of patients with ovarian clear cell carcinoma, screening by Cox regression analysis. FIGO stage, the lowest value of CA125, and non-R0 resection were independent risk factors affecting the prognosis of patients with high-grade serous ovarian cancer.

Conclusions: The clinical characteristics and prognosis of OCCC are different from those of HGSOC. OCCC patients have a significantly worse prognosis than those with HGSOC in the advanced stage (FIGO □-□). Satisfactory tumor resection is an essential factor related to the prognosis of patients with OCCC and HGSOC.

Introduction

Epithelial ovarian cancer (EOC) is one of the most lethal malignancies in gynecological tumors. According to 2014 WHO diagnostic criteria[1], the primary tissue types of EOC include seven types (serous carcinoma, endometrioid carcinoma, clear cell carcinoma, mucinous carcinoma, serous mucinous carcinoma, malignant Brenner tumor, and undifferentiated carcinoma), each of which has its unique clinical characteristics and biological behavior. Ovarian clear cell carcinoma (OCCC) is a kind of EOC with unusual biological behavior. Although most OCCC can be detected in the early stage, it still has a high tendency of recurrence after chemotherapy.[2] Compared with high-grade serous ovarian carcinoma (HGSOC), OCCC has different clinical characteristics and prognoses. A series of large clinical studies on patients with EOC have also excluded patients with clear cells in recent years. As a result, there has been little progress in the treatment of OCCC in the last 30 years. This paper retrospectively analyzed the clinical and follow-up data of 50 patients with OCCC and 103 cases with HGSOC. They were initially treated and completed standardized therapy in the Affiliated Hospital of Qingdao University from January 2013 to December 2017. We compared the differences in clinical characteristics and prognosis between

the two groups. And we evaluated the risk factors affecting the prognosis. We wish we could provide some specific clinical basis for the further study of patients with OCCC.

Materials And Methods

Patients

From January 2013 to December 2017, 99 patients with OCCC and 194 patients with HGSOC were registered and treated by the Affiliated Hospital of Qingdao University. The detailed clinical data were collected by reviewing medical charts and clinical follow-up visits. Patients were eligible if they fulfilled the following: (1) had histologically confirmed pure-type OCCC or HGSOC, (2) operations were performed at the Affiliated Hospital of Qingdao University, (3) standard treatment was completed, (4) did not complicate with other primary malignancies or serious complications that affect survival, (5) postoperative follow-up was standardized and complete. Finally, 50 patients with OCCC and 103 patients with HGSOC were enrolled in the current study. Figure 1 shows the data acquisition process. All the patients included had provided written informed consent for the use of their clinical data. The study was approved by the ethics committee at the Affiliated Hospital of Qingdao University in Shandong, China. (Ethical approval number: QYFY WZLL 26500)

All the operation was performed by the gynecologic oncologist of Affiliated Hospital of Qingdao University to achieve optimal cytoreduction as far as possible, which was defined as no residual macroscopical lesion after primary debulking surgery. Staging was performed according to the FIGO staging system (FIGO,2014). Most of the patients received platinum-based chemotherapy regimens as the postoperative first-line treatment.

Follow-up

All patients were routinely followed up for disease progression by telephone or outpatient examinations until December 2020 or mortality. The Overall Survival (OS) was defined as the time from the diagnosis to death or the last follow-up time. Progression-Free Survival (PFS) was defined as the time from therapy initiation to the time of disease progression, relapse, or the last follow-up time. Disease progression or relapse was defined according to the Gynecologic Cancer Intergroup, GCIG.[3] Patients with ovarian cancer after the treatment initiation appeared the following conditions: (1) elevated CA125; (2) a clinically palpable mass; (3) a mass found based on computed tomography, magnetic resonance imaging, or ultrasound; (4) hydrothorax or ascites; (5) Ileus with unknown causes; if 2 out of 5 items are satisfied, it is considered as clinical recurrence; If the patient has only elevated CA125 without clinical manifestations and radiographic evidence, it is a biochemical recurrence. Elevated CA125 was defined as two consecutive occasions when CA125 was greater than the normal upper limit (35U/mL) in patients with normal CA125 or in patients whose values were normalized during treatment. For patients who never normalized CA125, it was greater than twice the nadir on two consecutive measurements.

Statistical Analysis

Statistical Package for Social Science (SPSS) statistical software (Version 20.0, SPSS Inc, Chicago, Ill) was used for all analyses. T-test was used for the measurement data following a normal distribution. A nonparametric test was used for data that did not conform to normal distribution. The Pearson's chi-squared test, Yate's correction for continuity, or Fisher exact test was used to analyze the enumeration data. Kaplan-Meier curves were used to analyze the distribution of OS and PFS by groups. The log-rank test examined the comparison of patient survival among subgroups. Multivariate survival analysis was performed using the Cox regression model, including prognostic factors that were significant in univariate analysis by Logistic regression. All of the P values reported were 2-sided, and a value of P< 0.05 was considered statistically significant.

Results

Patients' Characteristics

The patients' characteristics between the two groups are summarized in Table 1. Among the patients with malignant ovarian cancer who visited our hospital (n=697) from January 2013 to December 2017, 99 patients (14.2%) were diagnosed with OCCC, and 194 patients (27.8%) were diagnosed with HGSOC. There were 50 patients in the group of OCCC with the average age of 51.3 years old and 103 patients in the HGSOC group with the average age of 56.1 years old included in the present analysis. Patients with confirmed OCCC were younger than HGSOC (P<0.05). Most of the OCCC showed a large unilateral cystic solid tumor. The proportion of asymptomatic patients was higher in the OCCC group than in the HGSOC group. Compared with HGSOC, OCCC patients had fewer pregnancies and more patients with ovarian endometriosis. There is a great difference between OCCC and HGSOC in terms of tumor markers. The values of CA125, HE4, and LDH in the OCCC group were lower than that in the HGSOC group, while the CA199 values were higher than that in the HGSOC group. Among the patients with CA125 < 1000, 45.7% of the patients in the OCCC group had CA199 > 27, while only 18.6% in the HGSOC group (P < 0.003). At the same time, the proportion of patients in stages Ⅰ-Ⅱ was 74% in the OCCC group and only 22.3% in the HGSOC group (P < 0.0001).

Prognosis of Patients in the 2 Groups with Different stages.

During the median follow-up time of 44 months (range, 6-93 months), 15 patients (30.0%) in the OCCC group and 52 patients (50.5%) in the HGSOC group were dead (P=0.017). Figure 2 depicts the OS and PFS of each group. In patients with FIGO stages Ⅰ-Ⅱ, the 5-year OS and PFS rates of patients with OCCC (83.8% and 89.2%, respectively) were higher than those of patients with HGSOC (67.2% and 87.0%, respectively). However, this was not statistically significant (P = 0.786 and P =0.194, respectively). In patients with FIGO stages Ⅲ-Ⅳ, the 5-year OS and PFS rates of patients with OCCC (15.4% and 0.0%, respectively) were significantly lower than those of patients with HGSOC (34.1% and 11.4%, respectively; P <0.001 and P<0.001, respectively). The median OS and PFS for the two groups with FIGO stages Ⅲ-Ⅳ were: OCCC (OS/PFS), 20/7 months; HGSOC (OS/PFS), 53/16 months.

In the univariate survival analysis by Logistic regression, significant prognostic factors for OCCC were the lowest value of CA125, lactate dehydrogenase, bilateral tumors, R0 resection, and FIGO stage. Significant prognostic factors for HGSOC were age, menopausal status, intrauterine device use, the lowest value of CA125, R0 resection, and FIGO stage (Table 2). Multivariate Cox regression analyses revealed that R0 resection and FIGO stage were independent risk factors for the prognosis of patients with OCCC. And the lowest value of CA125, R0 resection, and FIGO stage were independent risk factors for the prognosis of patients with HGSOC (Table 3).

Discussion

Ovarian clear cell carcinoma accounts for 5% to 25% of EOC with obvious regionality. OCCC incidence was markedly higher in Asia than in other regions.[4] The rate of early detection of OCCC is also higher than that of HGSOC. However, although a high proportion of patients with OCCC are detected early, much literature has reported that the prognosis of patients with OCCC is similar to or worse than that of patients with HGSOC.[5-9] Compared with other histologic types of EOC, OCCC is more aggressive and less sensitive to platinum-based chemotherapy.[10]

Oliver et al. enrolled 544 patients with OCCC and 7054 patients with serous carcinoma. They found that patients with OCCC were younger and had a higher proportion of early stage.[4] FIGO stages □-□ accounted for more than 50% (57-81%) of patients with OCCC. OCCC also has some special clinical features, such as frequent presentation as a large pelvic mass, association with endometriosis, vascular thrombotic events, and hypercalcemia.[2] Although no patients with OCCC were found to have hypercalcemia in our study, this may be related to our relatively small sample size. The lower incidence of bilaterality of OCCC compared to HGSOC observed in this study has been confirmed by other authors.[11] Strong evidence for an association between ovarian endometriosis and OCCC has been established in many studies.[11-14] Patients with ovarian endometriosis have a higher risk of developing ovarian cancer, and the risk was particularly elevated in subjects with a long-standing history of ovarian endometriosis.[12] Park et al.[14] even proposed that ovarian endometriosis may be a precancerous lesion of OCCC. In the present study, 36% of OCCC patients were complicated with ovarian endometriosis, compared with 1.0% of HGSOC patients ($P<0.01$), which fully demonstrated the association between ovarian endometriosis and OCCC.

Compared with other types of EOC, OCCC lacks effective tumor biomarkers. CA125, which plays a vital role in other types of ovarian cancer, has less clinical significance in OCCC.[15] In recent years, some scholars have studied the clinical significance of CA199 in OCCC. Nakagawa et al.[16] reported that 54% of OCCC patients were associated with elevated CA199. Zhu et al.[17] suggested that CA199 may help to distinguish the prognosis of patients. The clinical value of CA199 in patients with OCCC is worthy of further investigation. Hypercalcemia is one of the most common paraneoplastic syndromes in malignant tumors. However, ovarian cancer with hypercalcemia is rarely reported. Japanese scholars Fujino et al.[18] proposed that OCCC is most closely related to hypercalcemia in patients with ovarian cancer. For patients with OCCC complicated with hypercalcemia, recurrence is often accompanied by an increase in serum

calcium. However, none of the 50 OCCC patients included in this study were complicated with hypercalcemia, which is inconsistent with the above reports and may be related to the insufficient sample size.

OCCC has been generally accepted as unfavorable when compared with other types of EOC, which has been supported by several retrospective studies.[19-21] However, Oliver et al.[4] found that patients with OCCC had a better overall prognosis compared with serous carcinoma. Oliver et al. believed that this difference was related to younger age, earlier stage, and better performance status of patients with OCCC. The study also found that, after adjusting the age, stage, and performance status, the prognosis of OCCC was significantly better than serous carcinoma in stages I–II. At the same time, it was significantly worse in stages □-□. In our study, we used HGSOC as the control group. We found no statistically significant difference in OS and PFS between the two groups in stages I–II. However, in stages □-□ patients, OCCC patients displayed worse OS and PFS.

The factors affecting the prognosis of patients with OCCC continue to be a topic of hot debate in medicine. The sample size of the clinical studies on OCCC by Nasioudis et al. was relatively large. Nasioudis et al.[22] evaluated the effect of chemotherapy on prognosis in 2325 OCCC patients with stage I. They found that the survival benefit of chemotherapy on patients with OCCC in the early stage might only be apparent when the lesion was confined to the ovary. Jenison et al.[11] found that incomplete capsules had a significant adverse effect on the prognosis of patients with OCCC in stage I. Therefore, to improve the prognosis of patients with OCCC, we should try our best to avoid iatrogenic upgrading.

In conclusion, there are many differences in clinical features and prognosis between OCCC and HGSOC. Most of the OCCC showed a large unilateral cystic solid tumor. The detection of CA199 is more critical in patients with OCCC than in patients with HGSOC. OCCC has a high incidence of early stage. OCCC patients have a significantly worse prognosis than those with HGSOC in the advanced stage (FIGO □-□). Clinically, we should try to maintain the integrity of the tumor envelope during surgery. R0 resection is an essential factor that can improve the prognosis of patients with both OCCC and HGSOC.

Our study was a retrospective single-center study; a larger prospective multi-center study is needed for further prospective external validation.

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee at the Affiliated Hospital of Qingdao University in Shandong, China. (Ethical approval number: QYFY WZLL 26500).

Consent for publication

Not applicable.

Availability of data and materials

The data during the current study are available from the corresponding author on reasonable request. An additional movie file shows the data in more detail [see Additional file 1]

Competing interests

The authors declare that there are no competing interests in this study.

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Authors' Contributions

S.D. clinical data collection, manuscript writing, manuscript revision, and corrections; F.Y. manuscript revision and paper supervision; Y.L., X.S., W.W. and X.Y. clinical data collection and follow-up; Y.W. intellectual mentorship and paper supervision. All authors have read and approved the final manuscript.

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Tables

TABLE 1. Patients' characteristics between the 2 groups.

	OCCC	HGSOC	
Characteristics	（N=50）	（N=103）	*P*
Age, mean (SD), yrs	51.3 (7.8)	56.1 (8.9)	0.001†
≤50 yrs, n (%)	24 (48.0)	31 (30.1)	0.030‡
>50 yrs, n (%)	26 (52.0)	72 (69.9)	
Menopausal status, n (%)			
No	21 (42.0)	35 (34.0)	0.334‡
Yes	29 (58.0)	68 (66.0)	
Gravidity, times			
≤ 1 time, n (%)	19 (38.0)	19 (18.4)	0.009‡
>1 time, n (%)	31 (62.0)	84 (81.6)	
Intrauterine device use, n (%)			
No	39 (78.0)	83 (80.6)	0.709‡
Yes	11 (22.0)	20 (19.4)	
Chief complaint, n (%)			0.001§
Abdominal distension	12 (24.0)	63 (61.2)	
Abdominal pain	16 (32.0)	40 (38.8)	
Menstrual alterations or post-menopausal vaginal bleeding	10 (20.0)	10 (9.7)	
Asymptomatic	16 (32.0)	13 (12.6)	
With ovarian endometriosis, n (%)			
No	32 (64.0)	102 (99.0)	<0.001‡
Yes	18 (36.0)	1 (1.0)	
Tumor diameter, mean (SD), cm	11.6 (4.3)	8.4 (4.2)	<0.001†
≤10 cm, n (%)	19 (38.0)	69 (67.0)	0.001‡
>10 cm, n (%)	31 (62.0)	34 (33.0)	
Bilateral tumors, n (%)			
No	41 (82.0)	36 (35.0)	<0.001‡
Yes	9 (18.0)	67 (65.0)	

Cystic solid tumor, n (%)			
No	12 (24.0)	46 (44.7)	0.013‡
Yes	38 (76.0)	57 (55.3)	
CA125, mean (SD), U/ml	288.5 (435.2)	1570.4 (2068.1)	<0.001†
≤1000 U/ml, n (%)	46 (92.0)	59 (57.3)	<0.001‡
>1000 U/ml, n (%)	4 (8.0)	44 (42.7)	
The nadir of CA125 after treatment, mean (SD), U/ml	37.1 (127.5)	30.5 (113.9)	0.748†
≤10 U/ml, n (%)	29 (58.0)	50 (48.5)	0.272‡
>10 U/ml, n (%)	21 (42.0)	53 (51.5)	
He4, mean (SD), pmol/L	153.0 (205.1)	689.9 (778.6)	<0.001†
≤140 pmol/L, n (%)	37 (74.0)	20 (19.4)	<0.001‡
>140 pmol/L, n (%)	13 (26.0)	83 (80.6)	
CA199, mean (SD), U/ml	51.6 (80.8)	23.3 (47.9)	0.025†
≤27 U/ml, n (%)	29 (58.0)	84 (81.6)	0.002‡
>27 U/ml, n (%)	21 (42.0)	19 (18.4)	
Blood calcium, mean (SD), mmol/L	2.2 (0.2)	2.2 (0.2)	0.824†
≤2.52mmol/L, n (%)	50 (100.0)	100 (97.1)	0.551§
>2.52mmol/L, n (%)	0 (0.0)	3 (2.9)	
Lactate dehydrogenase, mean (SD), U/L	191.3 (61.4)	253.4 (166.4)	0.001†
≤250 U/L, n (%)	43 (86.0)	67 (65.0)	0.007‡
>250 U/L, n (%)	7 (14.0)	36 (35.0)	
Platelet to lymphocyte ratio, mean (SD)	216.5 (104.5)	242.3 (132.2)	0.229†
≤200, n (%)	24 (48.0)	46 (44.7)	0.697‡
>200, n (%)	26 (52.0)	57 (55.3)	
R0 resection, n (%)			
No	7 (14.0)	28 (27.2)	0.069‡
Yes	43 (86.0)	75 (72.8)	
FIGO stage, n (%)			<0.001‡

□-□	37 (74.0)	23 (22.3)
□-□	13 (26.0)	80 (77.7)

† t Test.

‡Pearson's chi-squared test.

§Fisher exact test.

R0 resection, complete resection; SD, standard deviation.

TABLE 2. Univariate analyses of prognosis by Logistic regression

	OCCC			HGSOC		
Variable	OR	95%CI	*P*	OR	95%CI	*P*
Age	0.500	0.146-1.712	0.270	2.940	1.211-7.137	0.017
>50 (vs ≤50)						
Menopausal status	0.348	0.100-1.210	0.097	4.038	1.673-9.751	0.002
Yes (vs No)						
Intrauterine device use	2.417	0.603-9.678	0.213	0.255	0.085-0.768	0.015
Yes (vs No)						
The lowest value of CA125	6.875	1.766-26.765	0.005	3.775	1.669-8.534	0.001
>10 (vs ≤10)						
Lactate dehydrogenase	22.667	2.411-213.102	0.006	0.971	0.432-2.182	0.942
>250 (vs ≤250)						
Bilateral tumors	14.437	2.506-83.168	0.003	2.059	0.901-4.704	0.087
Yes (vs No)						
R0 resection	22.667	2.411-213.102	0.006	14.815	4.090-53.660	<0.001
No (vs Yes)						
FIGO stage	45.375	7.283-282.695	<0.001	10.538	2.889-38.441	<0.001
□-□ (vs □-□)						

CI, confidence interval; OR, odds ratio.

TABLE 3. Multivariate analyses of prognosis by multivariate Cox regression.

	OCCC			HGSOC		
Variable	HR	95%CI	*P*	HR	95%CI	*P*
The lowest value of CA125	2.995	0.727-12.337	0.129	2.087	1.123-3.880	0.020
>10 (vs ≤10)						
R0 resection	7.884	1.689-36.811	0.009	3.693	1.940-7.030	<0.001
No (vs Yes)						
FIGO stage	4.555	1.088-19.071	0.038	3.910	1.186-12.889	0.025
□-□ (vs □-□)						

CI, confidence interval; HR, hazard ratio.

Figures

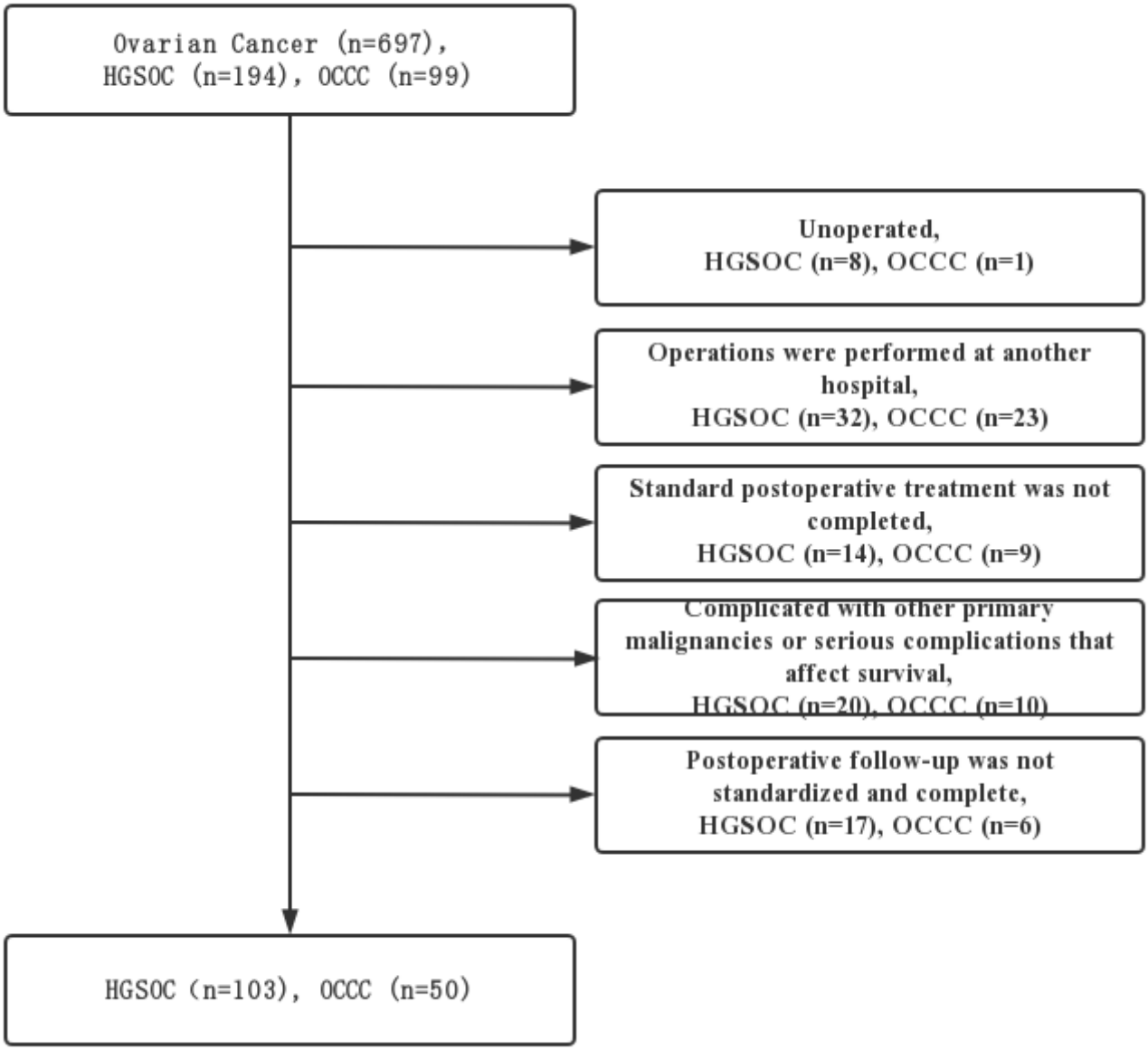

Figure 1

Flow chart of data selection.

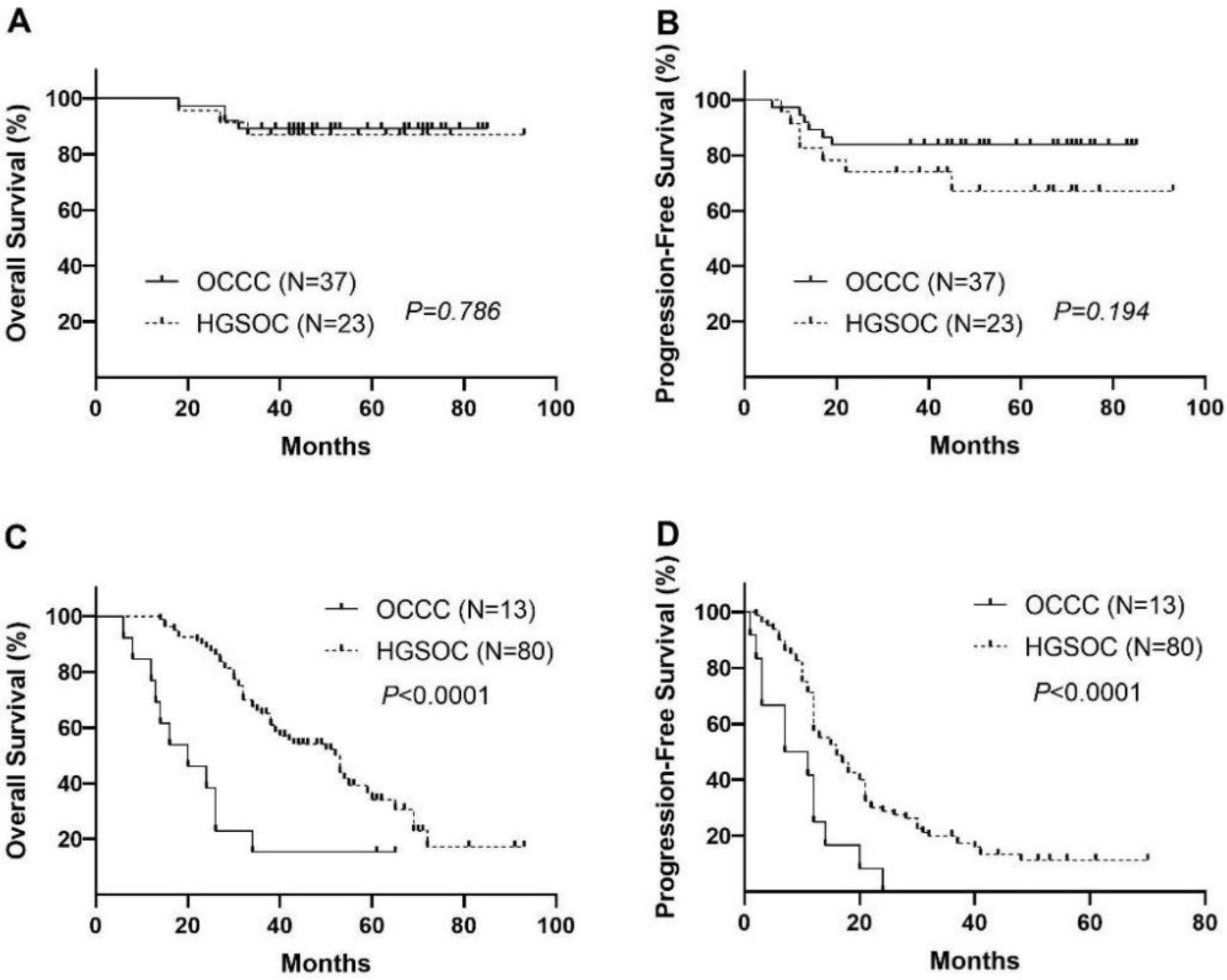

Figure 2

Left, overall survival in the two groups, in FIGO stages Ⅰ-Ⅱ (A), and in FIGO stages Ⅲ-Ⅳ (C). Right, progression-free survival in the two groups in FIGO stages Ⅰ-Ⅱ (B), and in FIGO stages Ⅲ-Ⅳ (D).

Supplementary Files

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