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Comparison of Clinical Characteristic and Survival Outcomes between Clear Cell and Non-Clear Cell Ovarian Cancer

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ABSTRACT

Objectives: To compare clinical characteristics and survival outcomes between women with clear cell carcinoma (CCC) and non-clear cell (NCC) epithelium ovarian cancer.

Materials and Methods: A retrospective cohort study was conducted on 220 Epithelial ovarian cancer (EOC) patients at Buddhachinaraj Hospital between January 1999 and May 2017. The patient data were retrieved from medical records. The patient characteristic, operative findings, histologic types, chemotherapy, time of recurrence, and follow-up time were analyzed. The medical records were comprehensively reviewed. The Kaplan-Meier method and Cox regression were employed in the survival analyses.

Results: A total of 220 EOC patients were eligible in the study, comprising 63 cases of CCC and 150 cases of NCC. Patients with CCC were more presented stage I and met optimal cytoreduction ($p < 0.005$). The progression-free survival (PFS) and overall survival (OS) were not statistically different between CCC and NCC when analyzed in all stages. However, PFS and OS were significantly different when classified EOC into three groups: NCC type I, type II EOC, and CCC. In stage I, CCC had better PFS ($p = 0.007$), but OS was no significant difference ($p = 0.279$). In stage II-IV, CCC had a trend toward poorer 5-year OS than type II EOC. The optimal surgery and complete course of platinum-based chemotherapy were associated with better survival outcomes in patients with epithelial ovarian cancer ($p < 0.001$).

Conclusion: The prevalence of CCC was 29.65% of EOC patients, and the majority found stage I. The PFS and OS were not statistically different between CCC and NCC.

Keywords: clear cell adenocarcinoma, epithelial ovarian cancer, survival analysis.

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การเปรียบเทียบลักษณะทางคลินิกและอัตราการรอดชีวิตในผู้ป่วยมะเร็งรังไข่ชนิด Clear Cell (CCC) และ Non-Clear Cell (NCC)

พรสวรรค์ วาสิงหนท์, กอบกาญจน์ ชามพูนท, อรรถยา รัตนแก้ว, พัลลภ พงษ์สุทธิรักษ์

บทคัดย่อ

วัตถุประสงค์: *เพื่อเปรียบเทียบลักษณะทางคลินิกและอัตราการรอดชีวิตในผู้ป่วยมะเร็งรังไข่ชนิด Clear cell (CCC) และ Non-clear cell (NCC)*

วัสดุและวิธีการ: *การศึกษาย้อนหลังที่โรงพยาบาลพุทธชินราช พิษณุโลก ในผู้ป่วยที่ได้รับการวินิจฉัยและรักษาโรคมะเร็งรังไข่ชนิดเยื่อบุผิวตั้งแต่เดือนมกราคม 2542 ถึง ธันวาคม 2560 จำนวน 220 คน โดยเก็บข้อมูลพื้นฐานของผู้เข้าร่วมการวิจัยหรือข้อมูลเกี่ยวกับการดูแลรักษาของผู้ป่วยในด้านการผ่าตัด, ชนิดของมะเร็ง, การให้ยาเคมีบำบัด, ระยะเวลาการตรวจติดตามและระยะเวลาโรคกำเริบโดยการทบทวนแฟ้มเวชระเบียนผู้ป่วยแล้วนำข้อมูลที่ได้มาวิเคราะห์ทางสถิติและเปรียบเทียบอัตราการรอดชีวิต*

ผลการศึกษา: *ผู้ป่วยมะเร็งรังไข่ชนิดเยื่อบุผิวเข้าเกณฑ์การศึกษาทั้งหมด 220 คนประกอบด้วยผู้ป่วยมะเร็งรังไข่ชนิด CCC 63 ราย และชนิด NCC 150 ราย กลุ่มผู้ป่วย CCC พบได้มากในระยะที่ 1 และได้รับการผ่าตัดแบบ optimal cytoreduction ($p < 0.005$) เมื่อวิเคราะห์กลุ่มผู้ป่วย CCC และ NCC ในทุกระยะของโรคไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติของระยะปลอดการลุกลามของโรค (PFS) และอัตราการรอดชีวิตทั้งหมด (OS) อย่างไรก็ตาม PFS และ OS มีความแตกต่างอย่างมีนัยสำคัญจากการจำแนกผู้ป่วยมะเร็งรังไข่ชนิดเยื่อบุผิวออกเป็นสามกลุ่ม ได้แก่ NCC type I, Type II EOC และ CCC เมื่อเปรียบเทียบผู้ป่วยในระยะที่ 1 พบว่ากลุ่มผู้ป่วย CCC มี PFS ดีกว่า ($p = 0.007$) แต่ OS ไม่มีความแตกต่างอย่างมีนัยสำคัญ ($p = 0.279$) เมื่อเปรียบเทียบผู้ป่วยในระยะที่ 2-4 พบว่ากลุ่มผู้ป่วย CCC มีแนวโน้มอัตราการรอดชีวิตที่ระยะ 5 ปีน้อยกว่า Type II EOC ส่วนผู้ป่วยที่ได้รับการผ่าตัดแบบ optimal surgery และได้รับยาเคมีบำบัดสูตรแพลทตินั่มจนครบตามกำหนด พบว่าสัมพันธ์กับการรอดชีวิตมากขึ้นในผู้ป่วยมะเร็งรังไข่ชนิดเยื่อบุผิว ($p < 0.001$)*

สรุป: *ความชุกของผู้ป่วย CCC พบได้ถึงร้อยละ 29.65 ของผู้ป่วยมะเร็งรังไข่ชนิดเยื่อบุผิวและส่วนใหญ่มักพบในระยะที่ 1 อัตราการรอดชีวิตไม่มีความแตกต่างกันระหว่างกลุ่มผู้ป่วย CCC และ NCC อย่างไรก็ตามเมื่อจำแนกผู้ป่วยมะเร็งรังไข่ชนิดเยื่อบุผิวเป็นสามกลุ่ม ได้แก่ NCC type I, Type II EOC และ CCC พบว่าอัตราการรอดชีวิตในกลุ่มผู้ป่วย NCC type I ดีที่สุด ส่วนอัตราการรอดชีวิตที่แย่ที่สุดพบในผู้ป่วยกลุ่ม Type II EOC ส่วนผู้ป่วยกลุ่ม CCC มีอัตราการอดชีวิตอยู่ระหว่างสองกลุ่ม*

คำสำคัญ: *มะเร็งรังไข่ชนิด clear cell, มะเร็งรังไข่ชนิดเยื่อบุผิว, การวิเคราะห์อัตราการรอดชีวิต*

Introduction

Ovarian cancer (OC) is a common gynecologic malignancy, resulting in death in women worldwide[1]. Epithelial ovarian cancer (EOC) accounts for more than 90% and holds different histology, biological behavior, and clinical characteristics. Serous carcinoma was the major subtype (75-80%). Clear cell carcinoma (CCC) was less common with high-grade nuclei mostly found, which made the CCC invasive in nature with significant clinical outcomes[2, 3].

The incidences of CCC vary across countries and ethnic groups. In western countries, North America, and Europe, the prevalence was 3-7%, while it was rising to 18% in Asia[4]. The Surveillance Epidemiology and End Results (SEER) showed a 5.6% prevalence of CCC in the female population of the USA and increased to 13.4% in the Asian women subgroup[5]. The prognostic of CCC is still debatable. Previously, CCC was defined as the high-risk histologic type for recurrence and lethal outcomes[6-8]. However, some reports showed that CCC had more favorable results in the early-stage[9, 10]. In the recent decade, integration of molecular genetics and histopathologic studies that lead to a better understanding of ovarian carcinogenesis. CCC was classified into the type I category, which is low-risk and has a better prognosis than the type II category[11]. However, CCC is still different from other non-clear cells (NCC) epithelium ovarian cancer by the age of onset, clinical course, and molecular genetics[2]. In the current surgical and chemotherapeutic guidelines, EOC can be managed according to disease stage and its histologic grading. If careful exploration of CCC and other NCC, it might be emerging new information for the clinical management of EOC. The purpose of this study was to compare clinical characteristics and survival outcomes between women with CCC and non-clear cell (NCC) epithelium ovarian cancer. The study also explored the survival outcome between NCC type I, type II EOC, and CCC.

The purpose of this study was to compare survival outcomes between women with CCC and NCC epithelium ovarian cancer. The secondary objectives were including 1) to compare clinical characteristic between women with CCC and NCC epithelium ovarian cancer, 2) to compare clinical characteristic between women with CCC, NCC type I, type II epithelium ovarian cancer, 3) to compare survival outcomes between women with CCC, NCC type I, type II epithelium ovarian cancer

Materials and Methods

The retrospective cohort study was conducted on one thousand patients who were diagnosed with epithelial ovarian cancer between January 1999 and May 2017 at Buddhachinaraj Phitsanulok Hospital, Thailand. The inclusion criteria were listed as follows: 1. patients received primary surgical treatment at the institution, 2. pathological confirmation of EOC, 3. complete follow-up information (complete medical record of clinical characteristic, surgery procedure, chemotherapy, date of loss to follow up/death)

The exclusion criteria were patients with histological diagnosis of mixed type OC or borderline and/or incomplete medical records or follow-up information (Fig. 1). The medical records were comprehensively reviewed. Baseline characteristics and clinical outcomes of all patients with EOC were collected for analysis. The variables used were age at diagnosis, risk of malignancy index (RMI) score [The RMI score is calculated based on the serum CA-125 value, menopausal status, ultrasound findings], stage at diagnosis [based on the 2014 International Federation of Gynecology and Obstetrics (FIGO) staging system], lymphovascular space invasion, peritoneal cytology status, type of primary surgery, presence of residual tumor when cytoreductive surgery was performed (categorized as no residual tumor, gross residual tumor < 1 cm, and residual tumor ≥ 1 cm), regimens and date of primary adjuvant chemotherapy completion, the date and site of the first progression or disease recurrence, and date and cause of death.

The standard guidelines for ovarian cancer treatment were complete staging surgery and cytoreductive surgery (CRS) with subsequent adjuvant chemotherapy in patients with high-risk early-stage (IB grade3, IC, II, clear cell) and advanced-stage III-IV disease, respectively. The majority of the patients received paclitaxel and carboplatin chemotherapy regimens from six to nine cycles. Gynaecological

oncologists operated to achieve optimal cytoreduction, which was defined as residual disease less than (or including) 1 cm after primary debulking. The postoperative follow-up consisted of a detailed medical history, physical examination, and serum CA-125 levels (categorized as abnormal if the level > 35 U/ml). Contrast-enhanced computed tomography of the abdomen and pelvis was performed when rising CA-125 or abnormal pelvic mass. The follow-up interval was varied about 3 to 4 months in the first 2 years, every 6 months in the 3rd to 5th year, and once a year thereafter. The platinum-sensitive disease group included patients who had relapsed more than six months after completion of the last platinum-based regimen. The overall survival (OS) was calculated from the date of their primary surgery to the date of death or last contact, and their progression-free survival (PFS) was determined from the date of their primary surgery to the date of first progression or recurrence. Type I EOC includes low-grade serous, mucinous, endometrioid, clear cell, and transitional cell carcinomas, while type II EOC comprises high-grade serous carcinomas, undifferentiated carcinomas, and carcinosarcomas.

The study was approved by the ethical committee of Buddhachinnaraj Hospital, IRB No. 085/61.

Statistical analysis

All descriptive data were shown in percentage, mean or median. Baseline characteristic data was performed with the Mann-Whitney U test (for continuous variables) and Pearson chi-square or Fisher exact tests for categorical variables. PFS and OS times were estimated using the Kaplan-Meier model. Predictors of survival outcomes were initially identified through stratified univariate analyses based on the log-rank test. Multivariate Cox proportional hazard regression models were used to analyze the independent predictors of survival. The histological diagnosis and variables with statistical significance in univariate analyses were entered into the models as covariates. Results were considered statistically significant if $p < 0.05$ (two-sided) and were expressed with their 95% confidence intervals. All statistical calculations were performed using the IBM SPSS statistical software (Version 22.0; IBM Inc., Armonk, NY, USA).

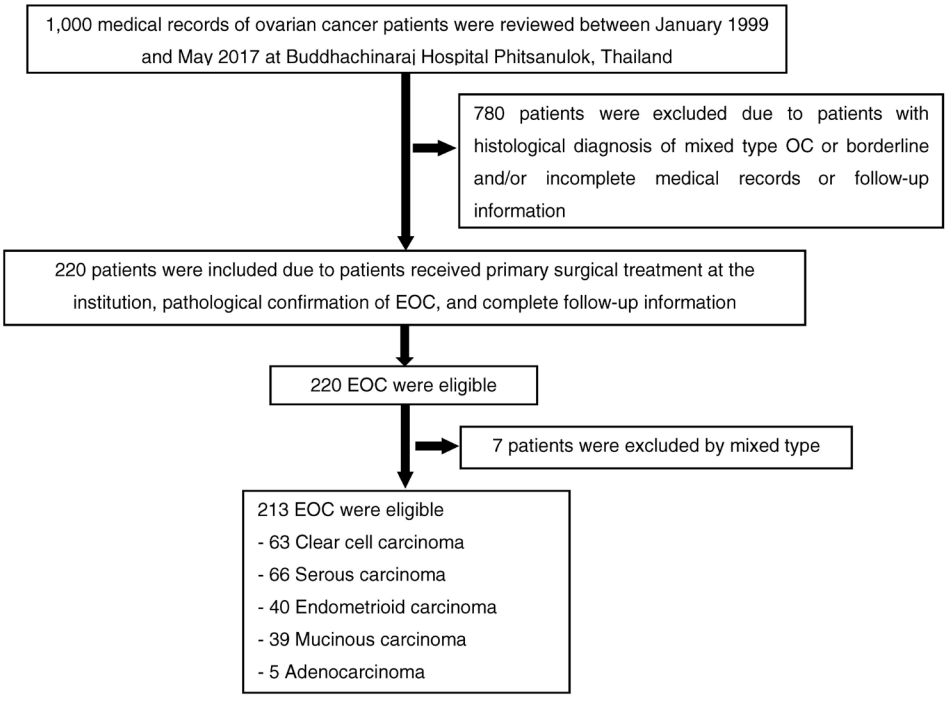

Fig. 1. The diagram of the enrollment patients.

OC: ovarian cancer, EOC: epithelial ovarian cancer

Results

A total of 220 EOC patients were eligible for the study. All 220 EOC were complete surgical staging surgery. However, seven were excluded from the analysis due to mixed histologic cell types. The pathologists had reviewed the pathological reports and slides. There were 63 CCC (29.6%), 66 serous cystadenocarcinoma (31%), 40 endometrioid carcinoma (18.8%), 39 mucinous carcinoma (18.3%) and 5 adenocarcinoma (2.3%); a total of 150 patients with NCC. Clinical characteristics and operative data of patients with CCC and NCC are shown in Table 1. Patients with CCC were more likely presented with pelvic mass compared with the patients with NCC (70.2% vs. 54.5%, p = 0.045). The patients in the CCC group had a lower median value of serum CA-125 and RMI score than the NCC group (198 vs. 496, p < 0.032 and 859 vs. 1,669, p < 0.043, respectively). Patients with CCC more often presented with FIGO stage I when compared with NCC (74.6% vs. 48.7%, p < 0.005). The percentage of optimal surgery in CCC was higher than NCC (87.3% vs. 72.7%, p < 0.021). The frequency of complete adjuvant chemotherapy ≥ six cycles in patients with CCC was also found to be higher (93.7% vs. 76.2%, p < 0.003). Coexisting with endometriosis was found to be more common in CCC than in NCC (41.3% vs. 9.5%, p < 0.001).

Table 1. Clinical characteristics and operative data of the patients.

Variables	CCC (n = 63)		NCC (n = 150)		p value
Age (years), mean (SD)	53.9	(9.0)	51.9	(11.9)	0.198
Oral contraception (%)	5/40	(12.5)	20/74	(27.0)	0.074
Menopausal status (%)					0.059
Premenopause	17/63	(27.0)	61/150	(40.7)	0.011
Postmenopause	46/63	(73.0)	89/150	(59.3)	0.013
Clinical presentation (%)					
Abdominal mass	40/57	(70.2)	72/132	(54.5)	0.045
Vaginal bleeding	3/57	(5.3)	7/57	(5.3)	0.999
Pelvic pain	25/57	(43.9)	51/132	(38.6)	0.502
Abdominal distention	22/57	(38.6)	62/132	(47.0)	0.288
Serum CA-125*, median (range)	198.0	(32.0 - 3,785.0)	496	(5.9 - 14,986.0)	0.032
RMI score*, median (range)	859.0	(0 - 34,065)	1,669	(0 - 134,874)	0.043
Optimal surgery (%)					0.021
No	8	(12.7)	41	(27.3)	
Yes	55	(87.3)	109	(72.7)	
Histopathology (%)					N/A
CCC	63	(100.0)	-		
MC	-		39	(26.0)	
EMC grade 1-2	-		25	(16.7)	
EMC grade 3	-		15	(10.0)	
LGSC	-		5	(3.3)	
HGSC	-		61	(40.7)	
Poorly differentiated denocarcinoma	-		5	(3.3)	
Associated endometriosis	26/63	(41.3)	14/148	(9.5)	< 0.001
FIGO 2014 staging (%)					0.005
I	47	(74.6)	73	(48.7)	
II	2	(3.2)	13	(8.7)	
III	13	(20.6)	1	(35.5)	
IV	1	(1.6)	63	(7.3)	
Lymph node metastasis (%)	8/59	(13.6)	14/115	(12.2)	0.795
Positive peritoneal cytology (%)	17/50	(34.0)	46/108	(42.6)	0.305
Adjuvant chemotherapy (%)	63/63	(100.00)	122/150	(81.3)	< 0.001
Adjuvant chemotherapy ≥ 6 cycles (%)	59/63	(93.7)	93/122	(76.2)	0.003

CCC: clear cell carcinoma, NCC: non-clear cell carcinoma, RMI: Risk of malignancy index, MC: mucinous carcinoma, EMC: endometrioid carcinoma, LGSC: low-grade serous carcinoma, HGSC: high-grade serous carcinoma, FIGO: International Federation of Gynecology and Obstetrics
*Total no. of patients with serum CA-125 and RMI = 127, CCC = 41, NCC = 86

The median follow-up time was 49 months (range 1-232 months). The PFS and OS were not statistically significant differences between CCC and NCC when analyzed in all stages (Table 2 and Fig. 2).

Table 2. Survival outcomes compared CCC and NCC.

Variables	CCC (n = 63)	NCC (n = 150)	p value
Recurrence (%)	26 (41.3)	58 (38.7)	0.723
PFS analysis			0.820
Progression and recurrent rate/1,000 person-month	7.7	7.0	
3-year PFS (%)	68.0	62.4	
5-year PFS (%)	63.6	58.8	
Death (%)	17 (27.0)	46 (30.7)	0.591
OS analysis			0.848
Death rate/1,000 person-month	4.4	4.4	
3-year OS (%)	78.5	79.4	
5-year OS (%)	74.2	70.7	

CCC: clear cell carcinoma, NCC: non-clear cell carcinoma, OS: overall survival, PFS: progression-free survival

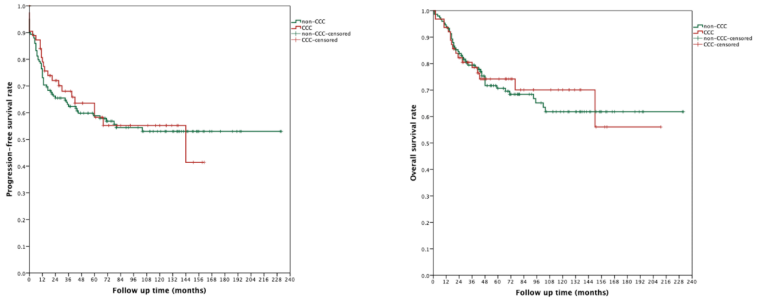

Fig. 2. The PFS and OS curves compared CCC and NCC groups.

OS: overall survival, PFS: progression-free survival, CCC: clear cell carcinoma, NCC: non-clear cell carcinoma

However, the PFS and OS analysis compared NCC type I, type II EOC, and CCC in all stages were significantly different (Table 3 and Fig. 3). The NCC type I EOC had the best prognosis. When comparing stage I, there was a significant difference in PFS but no significant difference in OS among EOC. However, PFS and OS of NCC type I, type II EOC, and CCC in stage II-IV were not significantly different with a trend toward a poorer outcome in CCC and type II EOC (Table 3, Fig. 4, 5).

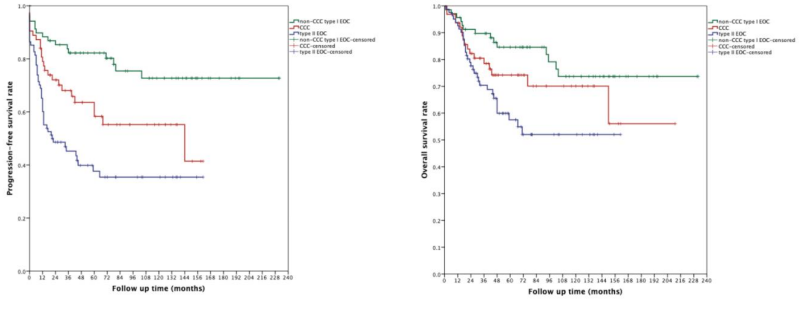

Fig. 3. The PFS and OS curves compared non-CCC type I, CCC, and type II EOC in all stages.

OS: overall survival, PFS: progression-free survival, CCC: clear cell carcinoma, NCC: non-clear cell carcinoma

Table 3. Survival outcomes compared CCC, non-CCC type I, and type II EOC.

	Non-CCC type I EOC	CCC	Type II EOC	p value
All stage	(n = 69)	(n = 63)	(n = 81)	
PFS analysis				< 0.001
3-yr PFS (%)	82.2	68.0	45.2	
5-yr PFS (%)	82.2	63.6	37.6	
OS analysis				0.007
3-yr OS (%)	89.7	78.5	70.4	
5-yr OS (%)	84.6	74.2	57.5	
Stage I EOC	(n = 51)	(n = 47)	(n = 22)	
PFS analysis				0.007
3-yr PFS (%)	93.9	79.5	81.0	
5-yr PFS (%)	93.9	73.7	63.2	
OS analysis				0.279
3-yr OS (%)	98.0	91.4	90.9	
5-yr OS (%)	95.7	85.5	90.9	
Stage II-IV EOC	(n = 18)	(n = 16)	(n = 59)	
PFS analysis				0.475
3-yr PFS (%)	49.4	32.1	31.4	
5-yr PFS (%)	49.4	32.1	28.3	
OS analysis				0.629
3-yr OS (%)	66.2	40.4	62.5	
5-yr OS (%)	53.5	40.4	44.1	

CCC: clear cell carcinoma, EOC: epithelial ovarian cancer, OS: overall survival, PFS: progression-free survival

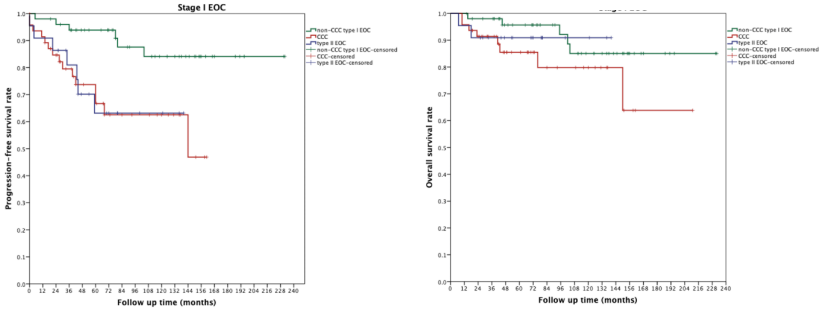

Fig. 4. The PFS and OS curves compared non-CCC type I, CCC, and type II EOC stage I.

OS: overall survival, PFS: progression-free survival, CCC: clear cell carcinoma, NCC: non-clear cell carcinoma

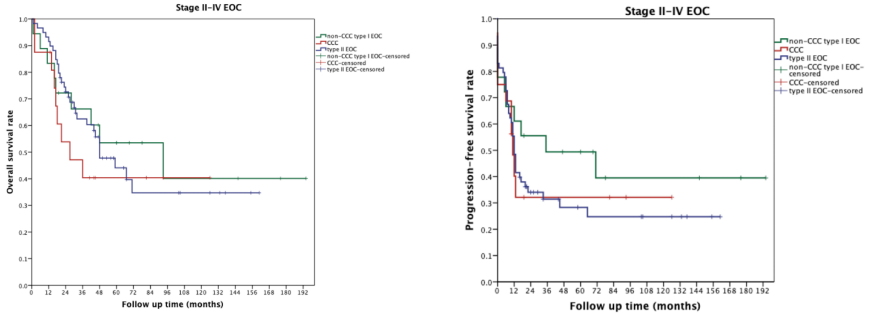

Fig. 5. The PFS and OS curves compared non-CCC type I, CCC, and type II EOC stage II-IV.

OS: overall survival, PFS: progression-free survival, CCC: clear cell carcinoma, NCC: non-clear cell carcinoma

Univariate and multivariate survival analyses for PFS and OS are shown in Tables 4 and 5. The histological subtypes (NCC type I vs. CCC vs. type II EOC) were significant factors associated with PFS in the univariate and multivariate survival analyses. However, the histological subtypes were not significant factors related to OS in the multivariate survival analyses. CA-125 ≥ 200 units/ml, suboptimal surgery, FIGO stage II-IV, node metastasis, positive peritoneal cytology, and chemotherapy less than six cycles were found to be poor prognostic factors for PFS and OS. The coexistence with endometriosis was a significant factor associated with PFS but not a significant factor with OS.

Table 4. Univariate and multivariate survival analysis for progression-free survival.

Variables	n	Event (%)		Univariate analysis			Multivariate analysis		
				cHR	95% CI	p value	aHR	95% CI	p value
Histology									
Non-CCC type I EOC	69	16	(23.2)						
CCC	63	25	(39.7)	2.16	1.15-4.07	0.016	2.38	1.17-4.82	0.016
Type II EOC	81	48	(59.2)	3.91	2.20-6.93	< 0.001	2.20	1.14-4.24	0.019
Age									
< 60 yrs.	164	66	(40.2)						
> 60 yrs.	49	23	(46.9)	1.36	0.84-2.19	0.207			
Nulliparity									
No	131	65	(49.6)						
Yes	82	24	(29.3)	0.48	0.30-0.77	0.002	0.95	0.37-2.43	0.922
Menopausal status									
Premenopause	78	24	(30.8)						
Postmenopause	135	65	(48.1)	1.89	1.18-3.03	0.008	3.57	1.01-12.56	0.048
RMI									
< 200	33	11	(33.3)						
≥ 200	101	53	(52.5)	1.85	0.97-3.55	0.064	0.33	0.07-1.50	0.152
CA125									
< 200	49	13	(26.5)						
≥ 200	78	50	(64.1)	3.40	1.84-6.28	< 0.001	2.69	0.77-9.36	0.118
Optimal surgery									
No	49	36	(73.5)						
Yes	164	53	(32.3)	0.21	0.14-0.33	< 0.001	0.20	0.04-0.89	0.035
FIGO 2014 staging									
Stage I	120	28	(23.3)						
Stage II-IV	93	61	(65.6)	4.85	3.07-7.65	< 0.001	2.76	1.53-4.95	0.001
Associated endometriosis									
No	171	78	(45.6)						
Yes	40	9	(22.5)	0.42	0.21-0.84	0.014	1.08	0.32-3.57	0.895
Node metastasis									
Negative	152	51	(33.5)						
Positive	22	13	(59.1)	2.93	1.57-5.47	0.001	0.77	0.11-5.36	0.792
Peritoneal cytology									
Negative	95	32	(33.7)						
Positive	63	36	(57.1)	2.39	1.48-3.86	< 0.001	0.85	0.30-2.41	0.770
Chemotherapy cycles									
< 6 cycles	33	21	(63.6)						
≥ 6 cycles	152	65	(42.8)	0.47	0.29-0.78	0.003	0.32	0.81-1.28	0.109

cHR: crude hazard ratio, aHR: adjusted hazard ratio, CI: confidence interval, EOC: epithelial ovarian cancer, CCC: clear cell carcinoma, NCC: non-clear cell carcinoma, RMI: risk of malignancy index, FIGO: International Federation of Gynecology and Obstetrics

Table 5. Univariate and multivariate survival analysis for progression-free survival.

Variables	n	Event (%)		Univariate analysis			Multivariate analysis		
				cHR	95% CI	p value	aHR	95% CI	p value
Histology									
Non-CCC type I EOC	69	14	(20.3)						
CCC	63	17	(27.0)	1.69	0.83-3.43	0.150	1.81	0.88-3.69	0.105
Type II EOC	81	32	(39.5)	2.67	1.41-5.05	0.003	1.10	0.56-2.15	0.784
Age									
< 60 yrs.	164	46	(28.0)						
≥ 60 yrs.	49	17	(34.7)	1.49	0.85-2.61	0.161			
Nulliparity									
No	131	48	(36.6)						
Yes	82	51	(62.2)	0.46	0.25-0.83	0.010	0.44	0.13-1.49	0.190
Menopausal status									
Premenopause	78	18	(23.1)						
Postmenopause	135	45	(33.3)	1.65	0.95-2.85	0.074	5.79	1.09-30.73	0.039
RMI									
< 200	33	6	(18.2)						
≥ 200	101	38	(37.6)	2.35	0.99-5.58	0.052	0.10	0.01-1.06	0.056
CA125									
< 200	49	8	(16.3)						
≥ 200	78	37	(47.4)	3.62	1.68-7.81	0.001	7.94	0.92-68.09	0.059
Optimal surgery									
No	49	30	(61.2)						
Yes	164	33	(20.1)	0.20	0.12-0.34	< 0.001	0.47	0.26-0.85	0.012
FIGO 2014 staging									
Stage I	120	15	(12.5)						
Stage II-IV	93	48	(51.6)	6.14	3.41-11.04	< 0.001	4.67	2.28-9.57	<0.001
Associated endometriosis									
No	171	55	(32.2)						
Yes	40	6	(15.0)	0.43	0.19-1.00	0.051	3.43	0.66-17.54	0.140
Node metastasis									
Negative	152	32	(21.1)						
Positive	22	9	(40.9)	2.93	1.38-6.21	0.005	2.89	0.30-27.71	0.356
Peritoneal cytology									
Negative	95	17	(17.9)						
Positive	63	32	(50.8)	3.64	2.02-6.57	< 0.001	1.00	0.26-3.80	0.991
Chemotherapy cycles									
< 6 cycles	33	18	(54.5)						
≥ 6 cycles	152	43	(28.3)	0.37	0.21-0.34	< 0.001	0.15	0.29-0.86	0.033

cHR: crude hazard ratio; aHR: adjusted hazard ratio, CI: confidence interval, EOC: epithelial ovarian cancer, CCC: clear cell carcinoma, NCC: non-clear cell carcinoma, RMI: Risk of malignancy index, FIGO: International Federation of Gynecology and Obstetrics

Discussion

The incidence of CCC was 29.6% in the current study, which was consistent with previous data from Thai and Asian studies[12-15]. Several social and environmental factors may be the causes of higher incidences of CCC among Asians. Also, the increased amounts of endometriosis found in Asian women may have a role in elevating the incidence of CCC in Asia[16-18]. Previous reports have shown that CCC was the most common histologic subtype associated with endometriosis[19, 20] which goes in line with this study. Moreover, 74.6% of CCC presented with stage I that more common than NCC, which was also similar to the data from previous studies[6-9, 12-15].

In this study, CCC had a lower median value of serum CA-125 and RMI score than NCC. Currently, no clear benefit of such screening had been demonstrated in the high-risk group for ovarian cancer[21, 22]. CA-125 blood level elevated in approximately 80% of patients with FIGO stage II-IV but less than 50% with clinically detectable stage I disease[23-26].

Our study found that the PFS and OS in CCC and NCC groups were not significantly different. Many investigators have studied and compared the prognosis of patients with CCC to NCC, but conflicting results have been reported[7-9, 12, 13]. Several works of the literature showed the outcome of CCC being similar to other types of EOC. In contrast, others demonstrated a less successful outcome which a variety of factors could explain studied such as patients, chemotherapeutic regimens, and the proportion of suboptimal treatment[12, 13].

Nowadays, new insights into molecular genetics and histopathology can better understand ovarian carcinogenesis and its role in tumour classification[11]. Type I includes low-grade serous, mucinous, endometrioid, clear cell, and transitional cell carcinomas, while type II comprises high-grade serous carcinomas, undifferentiated carcinomas, and carcinosarcomas. The type I tumours are generally low grade except for CCC, which is usually considered to be a high grade[24]. The grading was used to divide EOC into type I and II, which had clear evidence that influenced the prognosis[11, 27-29]. PFS and OS were significantly different from this study when OC was classified into 3 groups; NCC type I, type II EOC, and CCC. The NCC type I had the best survival outcomes, while type II EOC had the worst. Suppose the NCC group consists of a higher proportion of type II patients, especially the high-grade serous adenocarcinoma, which yields a poor prognosis. In that case, the result may produce better survival outcomes for CCC than NCC.

Similarly, if the NCC group has a higher proportion of type I patients, especially the low-grade serous adenocarcinoma and mucinous carcinoma, which provides a good prognosis, CCC's survival outcomes may be worse than NCC. The findings in this study confirmed this hypothesis that the PFS and OS of CCC and NCC were not statistically different when compared between CCC and NCC. However, if the CCC was separately classified as type I and type II EOC, the prognosis of CCC would change, which might signal physicians to allow more provision during ovarian cancer treatment.

The standard treatment of EOC involves aggressive debulking surgery followed by chemotherapy. Postoperative chemotherapy is indicated in all patients with EOC, except those with surgical pathologic stage I disease with low-risk characteristics[24]. Previously, adjuvant chemotherapy was offered to CCC patients in all stages[24]. In our study, all patients with CCC received adjuvant chemotherapy. Although the PFS of CCC stage I was better than type II EOC, the OS was not statistically different, which concurred with the current recommendation of the European Society for Medical Oncology-European Society of Gynaecological Oncology (ESMO-ESGO) consensus conference and Scottish Intercollegiate Guidelines Network (SIGN) suggesting that the benefit of adjuvant chemotherapy for patients with CCC stage I is uncertain and should be considered on an individual patient basis[30]. A large review of CCC demonstrated a poor outcome of advanced-stage CCC than serous epithelial ovarian cancer, which was also in agreement with the non-profit research organizations (NRG) oncology/ gynecologic oncology group, who reported decreased OS its inherent chemo-resistance of CCC[31].

Moreover, molecular genetics revealed that PIK3CA and AT-Rich Interaction Domain 1A (ARID1A) mutations were found in CCC while BRCA mutation and TP53 mutation were found in HGSC[11]. In our study, the 5-yr OS of CCC displayed a lower amount than in type II EOC. Every patient received paclitaxel and carboplatin chemotherapy for EOC. Therefore, the proper treatment of EOC should incorporate distinct molecular biology as a part of a therapeutic strategy in conjunction with standard chemotherapy to achieve the ultimate goal of therapy.

Advanced stage and suboptimal surgery have been extensively reported as poor prognostic factors[31-32]. In this study, suboptimal surgery, FIGO stage II-IV, node metastasis, positive peritoneal cytology, and received

chemotherapy less than six cycles were found to be poor prognostic factors for both PFS and OS. Therefore, the meticulous exploration of the pelvic and abdominal cavity for an optimal cytoreductive surgery at the first operation combined with proper adjuvant chemotherapy and continuing until six courses are the essential processes for staging and treatment[24].

Conclusion

In conclusion, the study showed that the prevalence of CCC was 29.65% of EOC patients, and the majority was found in the FIGO stage I. The PFS and OS were not statistically different between CCC and NCC. However, PFS and OS of NCC type I EOC was the best, while type II EOC was the worst outcomes when classified EOC into three groups: NCC type I, type II EOC, and CCC. Survival outcomes of CCC were located between NCC type I and type II EOC. This study emphasized the fact that the optimal surgery and complete course of platinum-based chemotherapy were the notable factors associated with better survival outcomes in patients with epithelial ovarian cancer.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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