Original Article

The surgical, histopathological characteristics, and survival outcome of ovarian clear cell carcinoma: a retrospective case series sharing the experience of a tertiary cancer centre

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Background: Ovarian clear cell carcinoma (OCCC) is a rare and distinct subtype of epithelial ovarian cancer (EOC). It is unique in several biological aspects. This study analyzes the clinicopathological features and survival outcome of patients with OCCC, aiming to identify factors affecting recurrence, progression-free survival (PFS) and overall survival (OS).

Methods: A retrospective study included 49 women with OCCC between January 2009 and December 2021 at Oxford Cancer Center. All demographic and pathological characteristics, pre-operative biomarkers, surgical procedure, complications, hospital stay, chemotherapy regimen, and disease status on follow-up, were collected from electronic medical records.

Results: No residual disease (R0) was achieved in 39 out of 49 women who underwent cytoreductive surgery. The follow-up time had a mean of 8.75 years. The 3-year OS was 73.4%, and the 3-year PFS was 81.3% [95% confidence interval (CI): 84.63–118.93]. Women with stage 1 disease had the best outcome. There was a marked difference (P<0.001) in OS in the presence of residual disease. No residual disease conferred a 3-year OS of 88.6% (95% CI: 108.6–141.8), compared to only 12.5% in the presence of residual disease (95% CI: 4.48–32.11). In multivariant analysis, the International Federation of Gynecology and Obstetrics (FIGO) stage was the only independent prognostic indicator of OS with (P<0.05), including carbohydrate antigen (CA) 125, hemoglobin, albumin, associated endometriosis, ascites, residual disease and FIGO staging.

Conclusions: Surgery to achieve no residual disease is necessary to improve the prognosis in advanced OCCC. The true challenge is to predict which patients with early-stage disease at higher risk of recurrence and would most benefit from adjuvant treatments.

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Introduction

Ovarian clear cell carcinoma (OCCC) is a rare and distinct subtype of epithelial ovarian cancer (EOC). It is unique in several biological aspects, starting with its significant prevalence variation according to geographic distribution, where it is rare accounting for only 5–10% of all EOC in the United States and Western countries. It has a higher prevalence in Asian countries, especially Japan, where it reaches 25–30%, but the cause of this variation is unclear (1).

Highlight box

Key findings

- The 3-year overall survival (OS) was 73.4%, and the 3-year progression-free survival was 81.3%. Women with stage 1 disease had the best outcome. In comparing OS in respect to absence or presence of residual disease, the 3-year OS was 88.6% [95% confidence interval (CI): 108.6–141.8], compared to 12.5% (95% CI: 4.48–32.11) respectively (P<0.001). In multivariant analysis, the International Federation of Gynecology and Obstetrics (FIGO) stage was the only independent prognostic indicator of OS with (P<0.05), including carbohydrate antigen 125, hemoglobin, albumin, associated endometriosis, ascites, residual disease and FIGO staging.

What is known and what is new?

- The standard therapeutic treatment for ovarian clear cell carcinoma (OCCC) according to the National Comprehensive Cancer Network guidelines (version 1.2020) is optimal cytoreduction combined with systemic chemotherapy. Patients with OCCC tend to be less sensitive to conventional platinum-based chemotherapy, where only 11–27% of patients with OCCC respond to platinum-based chemotherapy, resulting in poorer outcomes.
- This paper confers a long-term follow-up of over 8 years and reinforces the importance of radical cytoreductive surgery with the intention to achieve no residual disease R0 in rare subtypes of epithelial ovarian cancers which are notoriously not chemo-sensitive.

What is the implication, and what should change now?

- Surgery to achieve no residual disease is necessary to improve the prognosis in advanced OCCC. The true challenge is to predict which patients with early-stage disease are at higher risk of recurrence and would most benefit from adjuvant treatments.

While OCCC is type 1 ovarian cancer, it does not fit typically for this subtype as it is considered a high grade at presentation, regardless of its stage (2). It behaves aggressively, especially in advanced stages, unlike other type 1 tumors. OCCC is associated with endometriosis, suggesting that retrograde menstruation is the origin of these tumors (3). The ovary's atypical endometriosis and atypical adenofibroma have been considered precancerous lesions (4,5). Another distinctive feature is the association between thromboembolism and a poor prognosis in OCCC (6,7), but the biological mechanism of hypercoagulation in OCCC remains unclear (8). Carbohydrate antigen (CA) 125, the standard tumor marker for high-grade serous carcinoma, is elevated only in about 57% of OCCC (9).

OCCC characteristically contains clear or hobnail cells with eccentric, rounded, bulbous nuclei, multiple complex papillae, densely hyaline basement membrane material, and hyaline bodies. Compared with other types of EOC, the frequency of mitoses is lower [usually <5/10 high power field (HPF)] (10). No single immunohistochemistry marker has been reported to be beneficial in distinguishing between high-grade serous and clear-cell ovarian carcinoma. A four-marker immunohistochemical panel [WT1/p53/napsin A/progesterone receptor (PR)] can distinguish EOC subtypes with high accuracy, and additional immunohistochemical markers can be used if needed. WT1 is the most critical marker diffusely expressed in almost all high-grade and low-grade serous ovarian cancers and is virtually absent in almost all OCCCs and mucinous ovarian cancers (11-14). Fadare *et al.* recommended a panel of immuno-histochemical markers, including Napsin-A, hepatocyte nuclear factor-1 beta (HNF-1β), and alpha-methylacyl-CoA racemase (AMACR), to obtain the highest sensitivity and specificity when OCCC is a diagnostic consideration (15).

Different molecular pathways and genetic alterations have been identified in OCCC, including the most common mutations of AT-rich interaction domain 1A (ARID1A) and phosphatidylinositol-4,5-bisphosphate 3-kinase (PIK3) catalytic subunit alpha (PIK3CA). OCCC shows high frequency of PIK3CA mutation (40%), leading to higher

activity of the phosphoinositide 3 kinase (PI3K)/Akt/mammalian (or mechanistic) target of rapamycin (mTOR) pathway (16). The standard therapeutic treatment for OCCC according to the National Comprehensive Cancer Network (NCCN) guidelines (version 1.2020) is optimal cytoreduction combined with systemic chemotherapy. Patients with OCCC tend to be less sensitive to conventional chemotherapy, as only 11–27% of patients with OCCC respond to platinum-based chemotherapy, resulting in poorer outcomes (17). OCCC chemoresistance might be attributed to the increased antioxidant capacity of cancer cells that are able to neutralize the effects of platinum-derived chemotherapeutics (18,19).

This study aimed to have a closer insight into the clinicopathological features and outcome of patients with OCCC, by identifying factors affecting recurrence, progression-free survival (PFS), and OS, through a retrospective review of all OCCC cases diagnosed and treated at Oxford Cancer Centre over 13 years. We present this article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-83/rc).

Methods

Setting and ethical consideration

A retrospective review of all medical records of women diagnosed with primary OCCC between January 2009 and December 2021—with ≥12 months follow-up—at the Churchill Gynecology Oncology Cancer Center, Oxford University Hospitals Foundation Trust was performed. The center is a tertiary hospital receiving referrals from other cancer units in the Thames Valley Cancer Network. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board following Oxford University Hospitals Foundation Trust clinical governance processes and service evaluation number was obtained (registration No. 7049). Informed consent was obtained from all individual participants.

Data collection

All demographic and pathological characteristics, pre-operative biomarkers, surgical procedure, complications, hospital stay, chemotherapy regimen, and disease status on follow-up, were collected from electronic medical records. Patient records and information were anonymized before analysis; thus, consent was not required. The International Federation of Gynecology and Obstetrics (FIGO 2014) staging system was used for all tumor staging. For cases before 2014, the stage of disease was classified retrospectively based on surgical and pathological assessment. PFS was defined as the time from initial surgical staging or cytoreductive surgery to the date of disease progression or recurrence, and overall survival (OS) was defined as the time from surgical staging or cytoreductive surgery to the date of death, or to the last follow-up date, if still alive. Recurrence was documented by histologic evidence of disease in tumour biopsy/or the appearance of new lesions on imaging examination. Exclusion criteria included patients whose data was available only for pathology review, women presented in our center only at the time of recurrence (primary treatment given elsewhere), and women with synchronous malignancy or data lost at follow-up.

Statistical analysis

Statistical analysis was performed using SPSS v.28.0 software (IBM Corp., Armonk, NY, USA). Summary statistics were used to describe the data. Continuous variables were expressed as mean, standard deviation, and range; categorical variables were expressed as percentages. Comparisons between groups were analyzed using the Student's *t*-test or Wilcoxon-Mann-Whitney test according to the data distribution for continuous variables or the χ^2 or Fisher's exact test for categorical variables. Univariate and multivariable Cox regression analyses were performed to identify predictors of PFS and OS. A P value of <0.05 was considered statistically significant, and all P values reported were two-sided.

Results

Two hundred and twenty-seven women were diagnosed with non-high-grade serous epithelial ovarian tumor, and 64 were diagnosed with OCCC between January 2009 and December 2021 at our tertiary Cancer Center. Of 64 women, nine cases were referred for pathology review only, three cases presented at the time of disease recurrence, two had synchronous malignancies, and one was lost from follow-up (due to traveling), leaving 49 cases for this study analysis.

Demographic data and laboratory findings

The mean age at diagnosis was 63 years (range, 37–83 years,

Table 1 Patients and tumor characteristics

Variables	Values (N=49)
Age (years)	
Minimum–maximum	37–83
Mean ± standard deviation	62.6±11.04
<40, n [%]	1 [2]
40–60, n [%]	18 [36.7]
>60, n [%]	30 [61.2]
Menopausal status, n [%]	
Pre-menopausal	11 [22.4]
Post-menopausal	38 [77.6]
Body mass index (kg/m^2)	
Minimum–maximum	16.4–43
Mean	25.86
Underweight <18.5, n [%]	1 [2.6]
Normal 18.5–24.9, n [%]	18 [47.4]
Overweight 25–29.9, n [%]	10 [26.3]
Obese ≥30, n [%]	9 [23.7]
NA	11
Laterality, n [%]	
Right	23 [53.5]
Left	19 [44.2]
Bilateral	1 [2.3]
NA	6
Endometriosis-associated, n [%]	
Yes	28 [57.14]
No	21 [42.86]
Ascites, n [%]	
No	33 [67.35]
Yes	16 [32.65]
FIGO 2014 staging, n [%]	
Stage I	27 [55.1]
IA	9 [18.4]
IB	0 [0.0]
IC	18 [36.7]
IC1	4 [8.2]
IC2	4 [8.2]
IC3	5 [10.2]
IC NA	5 [10.2]
Stage II	9 [18.4]
IIA	5 [10.2]
IIB	4 [8.2]
Stage III	9 [18.4]
IIIA	3 [6.1]
IIIB	2 [4]
IIIC	4 [8.2]
Stage IV	4 [8.2]
IV A	2 [4]
IV B	2 [4]

NA data: not available in medical records. FIGO, International Federation of Gynecology and Obstetrics.

with 77.6% post-menopausal women, and mean body mass index (BMI) of 25.86 kg/m^2 (range, 16.4–43 kg/m^2). More than half of cases presented in early-stage disease, 27 women (55.1%) had stage I, 9 women (18.4%) had stage II, 9 women (18.4%) had stage III, and four women (8.2%) had stage IV; 57.14% were associated with endometriosis, as seen on their histopathology records, and 32.65% had ascites at the time of presentation (*Table 1*). The mean CA 125 was 402 IU/mL, while 20% of women presented with regular CA 125 levels. The mean hemoglobin (HB) level was 122 g/L, while 26.5% were anemic (HB <115 g/L) at the presentation time.

Management data

In our retrospective analysis, five women (10%) were enrolled in clinical trials, and neoadjuvant chemotherapy (NACT) was given to four women (8.2%). Diagnostic laparoscopy was performed in 11 women (22.4%), and all patients had cytoreductive surgery. The summarized details of surgical procedures with intra-and postoperative complications are shown in *Table 2*, with no macroscopic residual disease (R0) being achieved in 39 women (79.59%) of cases. Post-operative adjuvant therapy was offered in 39 women (79.6%); see summary in *Table 3*.

Follow-up, disease progression, survival, PFS, and recurrence

A follow-up time for non-progress survivors ranged

Table 2 Surgical procedures and complications

Variables	Number of patients	Percentage
Neoadjuvant chemotherapy		
Yes	4	8.2
No	45	91.8
Pre-operative laparoscopy		
Not done	36	73.5
Done	11	22.4
Done in separate setting	6	12.2
Done in the same setting	5	10.2
Done as total laparoscopic hysterectomy	2	4.08
Surgical procedure	47 (NA =2)	
Hysterectomy	40+7 hysterectomy	85.1
Bilateral salpingo-ophrectomy	46	97.9
Unilateral salpingo-ophrectomy	1	2.1
Pelvic lymph node sampling	8 (positive in 1)	17 (2.1)
Pelvic lymph node dissection	6 (positive)	12.8
Para aortic lymph node sampling	8 (positive in 1)	17 (2.1)
Infracolic omentectomy	47 (positive in 5)	100 (positive 10.6)
Appendectomy	10 (all negative)	21.3
Falciform ligament resection	3 (all negative)	6.4
Excision of gastric nodule	1 (negative)	2.1
Excision of liver nodule	1 (positive)	2.1
Bladder peritoneum resection	7 (positive in 2)	14.9 (positive 4.3)
Pelvic peritonectomy	8	17
Paracolic peritonectomy	6	12.8
Small bowel resection & end to end anastomosis	2	4.3
Large bowel resection & end to end anastomosis	1	2.1
Colostomy	1	2.1
R0 no residual achieved	39	79.59
R0 not achieved	10	20.41
Intra-operative complications	9	19.1
Post operative complications	40 (NA =9)	
None	24	60
Ileus (all managed conservatively)	6	15
Severe wound infection	2	5
Wound dehiscence and return to theatre	1	2.5
Pelvic collection (readmission)	1	2.5
Peritonitis + pulmonary embolism	1	2.5
Pulmonary embolism	1	2.5
Deep vein thrombosis in left subclavian vein	1	2.5
Ureteric leaking	1	2.5
Lymphocyst	1	2.5
Complete heart block and percutaneous pacing	1	2.5
Need for intensive care unit admission	4	10

NA data: not available in medical records.

Table 3 Adjuvant therapy

Variables	Values
Adjuvant therapy, n	49
Adjuvant offered, n [%]	39 [79.6]
Adjuvant chemotherapy, n [%]	37 [75.5]
Palliative, n [%]	2 [4]
Adjuvant chemotherapy offered but declined or hold, n/N [%]	4/39 [10.3]
Adjuvant chemotherapy types	
Carboplatin ± paclitaxel, n	
Completed 6 cycles	22
<6 cycles	7
Data not clear on medical records, n	10

between 12–144 months, with a mean of 105.5 months [95% confidence interval (CI): 87.25–123.9], with a median of 53 months based on the reverse Kaplan-Meier method. Among our cohort group, residual disease (R0 was not achieved) in 10 women (20.4%), who progressed rapidly over the following months or even weeks, and recurrence occurred in 9 women (18.4%), with a total 14 deaths (28.5%) during follow-up period among the whole cohort, with OS 71.4%. The 3-year OS was 73.4%, and the 3-year PFS was 81.3%, with a mean of 101.7 months (95% CI: 84.63–118.93) (*Figure 1*).

Further stratification of the cohort group concerning endometriosis association was done; for univariant analysis, OCCC was associated with endometriosis, in 27 women (55.1%), and not associated in 22 women (44.8%). The 3-year OS was 68.1% and 79.9% (95% CI: 87.25–123.9) (in endometriosis-associated and non-endometriosis associated respectively), but with no statistically significant difference using log-rank (Mantel-Cox) analysis. Again, 3-year PFS was 84.4% and 77.9% (95% CI: 84.6–119.93) (in endometriosis-associated and non-endometriosis-associated, respectively), but no statistical significance was found in the analysis.

Stratification of our study group based on the FIGO stage, and estimating the impact of the stage on OS, showed a statistically significant difference (P<0.001), with stage I having the best prognosis and stage IV the worst prognosis (*Figure 2*). Univariant analysis using log-rank (Mantel-Cox test), for the impact of residual disease on OS, showed a statistically significant difference (P<0.001), the 3-year OS in no-residual disease group

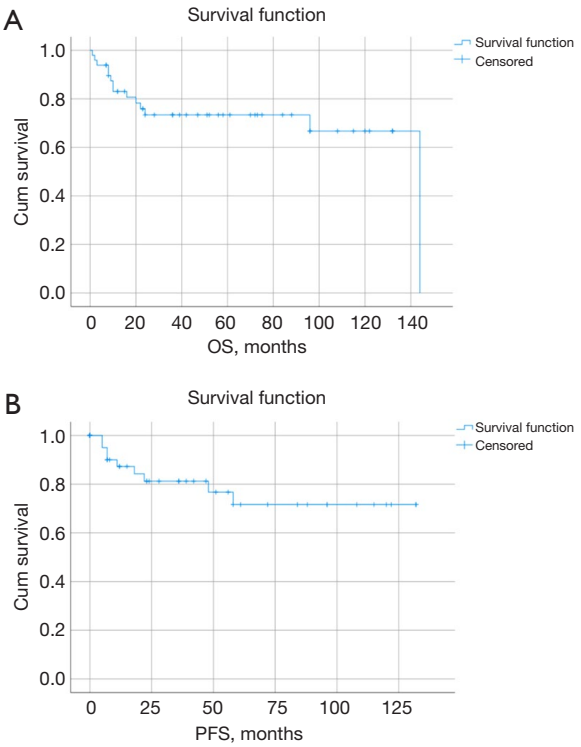

Figure 1 Kaplan Meier survival analysis—OS (A) and PFS (B). OS, overall survival; PFS, progression-free survival.

88.6% (95% CI: 108.6–141.8), compared to 12.5% (95% CI: 4.48–32.11) in the residual disease group (*Figure 3*). In multivariant analysis, CA 125 (<200 IU/mL), HB (<115 g/L), albumin (<40 g/L), endometriosis-association, ascites, residual disease and FIGO staging were included, but only the FIGO stage was an independent prognostic indicator of OS with (P<0.05). None of the other factors had statistical significance (*Table 4*).

Discussion

Our study described OCCC medical data—with a total of 49 women—from a single cancer center in the UK from January 2009 to December 2021. Surprisingly, in our study, the mean age at presentation was 62.6±11.04 years (range, 37–83 years), with >61% presenting above the age of 60 years. This is different from previous retrospective studies that showed a younger mean age at presentation, as a recent publication (20) involving 86 patients stated the median age at diagnosis was 49.21±9.91 years (range, 25–70 years) with only 12% presenting above the age of 60 years. Another recently published study (21), stated

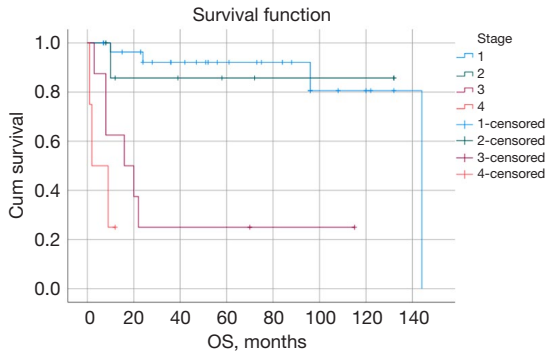

Figure 2 Kaplan Meier survival analysis—stratified by stage. OS, overall survival.

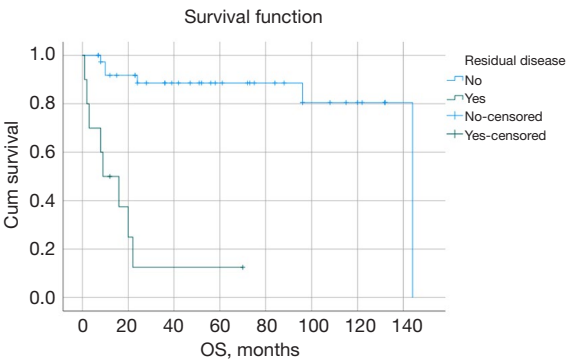

Figure 3 Kaplan Meier survival analysis—stratified by residual disease. OS, overall survival.

Table 4 Multivariant analysis using Cox regression

Predictive factor	Independent covariate	
	HR (95% CI)	P value
CA 125 (>200 IU/mL)	0.3 (0.04–2.341)	0.25
Hemoglobin (<115 g/L)	3.2 (0.804–13.53)	0.09
Albumin (<40 g/L)	1.8 (0.276–12.27)	0.52
Ascites	1.471 (0.250–8.66)	0.66
Endometriosis-association	1.980 (0.367–10.691)	0.42
FIGO stage I	1.213 (0.102–14.462)	0.87
FIGO stage II	18.747 (1.029–341.687)	0.048*
FIGO stage III	234.817 (2.765–19940)	0.01*
Residual disease	0.385 (0.020–7.251)	0.52

*, statistically significant. HR, hazard ratio; CI, confidence interval; CA, carbohydrate antigen; FIGO, International Federation of Gynecology and Obstetrics.

the age of onset had two peaks, namely 36 and 77 years, but in our cohort, only one woman presented below the age of 40 years. These studies were conducted in China, with different disease prevalence and possible genetic basis that may explain the findings. However, the Memorial Sloan Kettering (MSK) experience (22) from the USA, including 176 OCCC patients, had a mean age of 53 years at diagnosis.

Our study diagnosed 36 women (73.5%) at stage I or II. This aligns with prior studies (22,23), in which most women with OCCC present with early-stage disease. Part of this may be due to its tendency to present as a large unilateral pelvic mass, compared to the early peritoneal dissemination, which is common in HGSC.

The histopathology protocol followed in our institution for OCCC diagnosis is based generally on the hematoxylin and eosin (H&E) stain. There are a few well-recognized patterns—solid, papillary, and tubule-cystic. There can be a mixture of these in the same malignancy. The carcinoma cells can be transparent or pink (eosinophilic) and there are characteristic features such as pink globules and hob-nail cells/nuclei seen. If there is a need to differentiate from serous carcinomas or endometrioid carcinomas with secretory changes, then Napsin A is the most widely used immunomarker. Estrogen receptor (ER) and PR should be negative, as should WT1, unless there is a component of serous carcinoma admixed. We tend to use vimentin to look for endometrioid epithelium. AMACR can also be used for clear cell tumours but Napsin A is the best.

During our 13-year retrospective period, five patients have been enrolled in 5 different trials: 1st patient was enrolled in Javelin Ovarian 100, NCT02718417: a phase 3 open-label study on avelumab in previously untreated patients with EOC. The study was terminated based on the results of a planned interim analysis that showed futility of efficacy (24). Another patient was enrolled in the OSI trial, identifier: NCT00889382, a multi-center, randomized, open-label, phase 1/2 study of continuous weekly paclitaxel and escalating doses of intermittent or continuous OSI-906 in patients with recurrent/relapsed ovarian and other solid tumors (25). A 3rd patient was enrolled in Chorus trial identifier: NCT00075712, Timing of Surgery and Chemotherapy in Treating Patients with Newly Diagnosed Advanced Ovarian Epithelial, Fallopian Tube, or Primary Peritoneal Cavity Cancer (26). According to her medical notes, the 4th patient was enrolled in the Ovpsch trial, but no further details were found either on medical records or in

the trust intranet registered trials. A 5th patient was enrolled in the Peacock trial (27); phase II, multicenter, single-arm trial in patients with advanced clear cell gynaecology cancer (CCGC) who had ≥1 prior line of chemotherapy with progression at study entry.

Since OCCC is a high-risk group, adjuvant chemotherapy is recommended even if the stage is Ia, but the guidelines vary slightly between different gynecologic oncology societies. In our study group, where the British Gynecology Cancer Society guideline is followed, adjuvant chemotherapy was not offered in 10 women (20.4%), as the guideline states that low stages Ia /Ib OCCC are excluded from offering adjuvant platinum-based chemotherapy. According to the GOG 157 trial in which OCCC represented one third of cases (n=130), the benefit of using 6 *vs.* 3 cycles adjuvant paclitaxel and carboplatin chemotherapy in early-stage ovarian cancer in reducing recurrence risk was not evident in OCCC group (RFS HR =0.9, 95% CI: 0.43, 1.91) (28,29). ACTION study reported similar PFS for patients with early-stage clear-cell carcinoma with or without adjuvant chemotherapy (30) and two retrospective analyses (31,32) reported no benefit from adjuvant chemotherapy after completing surgical staging for stage IA–B clear-cell carcinoma. On the contrary, other studies suggest a high level of biological heterogeneity among clear-cell tumors that can sometimes justify an aggressive appearance even among patients with stage I disease (33). The true challenge is to predict which patients with early-stage disease are at higher risk of recurrence and would most benefit from additional treatments.

Our study's mean follow-up time was 105.5 months (range, 7–144 months), with 3-year OS 73.4%. The study group showed significant variation in OS for women among stages (P<0.001), 3-year OS rate was 92.1% for stage I, which is consistent with previous studies (21,22,34), 85.7% in stage II, dropping to 25% in stage III, with the worst prognosis for stage IV with 1-year OS 25%.

In our study group, endometriosis was found in 28 women (57.14%), confirmed in the histopathology report; the percentage is consistent with other studies that reported 18% to 43% of women with OCCC have a history of endometriosis (35,36), and a different study has demonstrated that this benign disease is significantly related to the pathogenesis of OCCC, with three-fold increased risk of OCCC [odds ratio (OR) =3.05] when endometriosis being reported (37). In our study, OS and PFS showed no statistically significant difference when Kaplan-Meier analysis stratified by endometriosis. It is unclear in the literature the role of endometriosis on ovarian cancer prognosis. Published studies have generally shown that patients with endometriosis-associated ovarian cancer had higher survival rates. Still, in most series, this finding has been linked to an earlier stage at diagnosis among ovarian cancer cases with endometriosis rather than the association with endometriosis as a prognostic factor or their published data had no statistically significant difference (38,39). Our results agreed with a recently published study that concluded that the presence of endometriosis did not affect either the OS (87.99 *vs.* 75.30, P value =0.25) or the PFS (111.13 *vs.* 117.42, P value =0.48) (40).

In our study, in a univariant analysis, a statistically significant difference (P<0.001) was found when survival analysis was stratified according to the presence of residual disease (suboptimal cytoreduction), showing 3-year OS in no-residual disease group 88.6% (95% CI: 108.6–141.8), compared to 12.5% (95% CI: 4.48–32.11) in residual disease group, keeping suboptimal cytoreduction a significant prognostic predictor for OCCC. The residual disease was linked to advanced stages, and the small number of advanced cases in our cohort (13) did not allow further analysis. In published data, other studies examined the association between residual disease and prognosis in clear cell carcinoma (41,42). In a retrospective cohort study, that examined the association between residual disease and prognosis by histological type of ovarian cancer using data from the National Cancer Database of America, OS differed significantly according to residual disease status not only in patients with high-grade serous carcinoma but also in those with clear cell carcinoma and, while not statistically significantly different, the survival benefit associated with complete cytoreduction was more significant in clear cell carcinoma (HR =0.39, 95% CI: 0.22 to 0.69) than in high-grade serous carcinoma (HR =0.58, 95% CI: 0.49 to 0.68) (42). Different studies have elicited the significance of complete cytoreduction and its impact on survival in ovarian cancer patients (43-62).

In our study, in multivariant analysis, CA 125, HB, albumin, endometriosis-association, ascites, residual disease and FIGO staging were included; only FIGO stage was an independent prognostic indicator of OS with (P<0.05), and none of the remaining factors had statistical significance. A similar analysis in a study published by Park *et al.* (63), found in the univariate survival analysis, significant prognostic factors for both DFS and OS were coexisting endometriosis, elevated preoperative serum CA 125 levels, advanced FIGO stage (stage I *vs.* stages II–IV), ovarian surface involvement,

Table 5 Summarizes similar retrospective studies involving OCCC in the last years

Authors	Year of publication	Study design	Study period	No. of patients	Endometriosis association	Early stage I & II	Residual disease	Recurrence	PFS	OS
Gallego (65)	2022	Retrospective	1992–2013	56	58.9%	40.5%	12.5%	–	–	~60% (3 years)
Tranoulis (64)	2022	Retrospective	2010–2019	94	51%	~50% stage I	25% with endo; 10.9% with no endo	–	39 months (in both groups)	55 months (no endo); 71 months (with endo)
Kim (1)	2016	Retrospective	1999–2018	2,962	–	74%	–	–	–	74.9% (5 years)
Zhu (20)	2021	Retrospective	2010–2022	86	18.6%	68.6%	10.46%	26.53%	3 years, 78.95% (early); 22.2% (advanced)	3 years, 89.47% (early); 44.44% (advanced)
Zhou (21)	2021	Retrospective	1998–2018	91	54%	72.5%	6.2%	17.2%	89.9% (5 years)	88% (5 years)
Park (63)	2018	Retrospective	1991–2012	155	50.3%	76.7%	14.19%	32.9%	5 years, 83% (endo); 51% (no endo)	5 years, 84% (endo); 54% (no endo)
Scarfone (66)	2014	Retrospective	1990–2012	73	36.9%	56.1%	–	–	–	5 years, 60% (no endo); 73% (endo)

OCCC, ovarian clear cell carcinoma; PFS, progression-free survival; OS, overall survival; endo, endometriosis.

positive peritoneal cytology, and suboptimal debulking. In the multivariate analysis, coexisting endometriosis and advanced FIGO stage were significant factors for both DFS and OS.

As a recent review of the literature, we added a table of previously published studies over the last 5 years, involving OCCC in retrospective analysis, and the studies have been summarized as shown in (1,20,21,63-66) (*Table 5*).

Limitations

The main limitations of this study are the small number of patients in our cohort and the retrospective study design, with potential selection and information bias.

Conclusions

The true challenge is to predict which patients with early-stage disease are at higher risk of recurrence and would most benefit from additional treatments. Surgery to achieve no residual tumor is necessary to improve the prognosis in advanced-stage clear cell carcinoma. Due to the rarity of clear cell carcinoma, international collaboration will be essential to power large-scale clinical trials required to answer the many remaining questions regarding the optimal treatment of this disease.

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Footnote

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Innovation (one patent and four pending). He also reports participation on a Data Safety Monitoring Board or Advisory Board: Well-being of Women and The Eve Appeal; and he is a founder, director and consultant of Singula Bio Ltd. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board following Oxford University Hospitals Foundation Trust clinical governance processes and service evaluation number was obtained (registration No. 7049). Informed consent was obtained from all individual participants.

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