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The oncological outcome of the patients with ovarian clear cell cancer: Platinum-based adjuvant chemotherapy is not suitable

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The study protocol was approved by Etlik Zubeyde Hanim Women's Health Training and Research Hospital institutional review board. (12.04.2019-07).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Ovarian clear cell cancer (OCCC) is one of the rare histological subtypes of epithelial ovarian cancer with different tumoral biology and prognosis. This study aimed to evaluate the clinical and pathological data of OCCC and define the prognostic factors.
Methods: Sixty-three patients with OCCC were included in this retrospective cross-sectional study. Patients with mixed-type clear cell carcinoma were excluded. Response to chemotherapy was assessed according to the WHO criteria. The survival analysis was performed using the Kaplan-Meier method and survival curves were compared with the log-rank test. Cox proportional hazards model was used in the multivariate analysis.
Results: The mean age of patients was 54.6 (10.7) years. Twenty-three (36.5%) patients were stage III&IV. Systematic lymphadenectomy was performed in 55 (87.3%) patients and 13 (23.6%) had lymph node metastasis. Maximal cytoreduction was performed in 57 (90.5%) patients, optimal cytoreduction, in 1 (1.6%) patient, and suboptimal cytoreduction was performed in 2 (3.2%) patients via primary cytoreductive surgery. The complete clinical response rate following adjuvant treatment was 61.1% in stages III&IV. Five-year failure-free survival was 63% in the entire cohort. According to the multivariate analysis, the stage was an independent risk factor for treatment failure. The probability of recurrence increased 24 times in stages III and IV (95% Confidence interval: 5.561-104.421; $P<0.001$).
Conclusion: The stage of the disease is a prognostic factor for OCCC. The response to platinum-based chemotherapy in OCCC is very low.

Keywords: Ovarian clear cell cancer, Recurrence, Stage, Survival

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Introduction

Epithelial ovarian cancer (EOC) is the second most common gynecological cancer in developed countries and the most common cause of death due to gynecological malignancies [1]. Ovarian clear cell cancer (OCCC) is one of the rare histological subtypes of epithelial ovarian cancer with different tumoral biology and prognosis [2]. Approximately 30% of EOC patients in East Asia and 10% in Europe and America were diagnosed with OCCC [3]. In addition to diagnosis at an early stage and young age, it is often associated with endometriosis [4].

The treatment of OCCC is the same as the other EOC subtypes. Staging surgery is recommended, including total hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic-paraaortic lymphadenectomy, and omentectomy. The purpose of surgical treatment, especially in advanced-stage disease, should be to perform the surgery without leaving any residual tumor [5].

The classical combination of platinum and taxane used in EOC is considered the standard adjuvant therapy for OCCC [6]. However, it has a relatively poor prognosis and increased chemoresistance compared with other EOC subtypes. The 5-year overall survival decreases to 85-90% in stage 1 cases, and 15-20% in stage 4 cases despite conventional treatments [7, 8]. The survival data of OCCC are better than that in high-grade serous ovarian cancer at the early stages and poorer at advanced stages [7]. This might be caused by the partial response to conventional adjuvant therapy [6].

Developing optimal treatment strategies is complicated due to the rarity of OCCC, insufficient data, and increased resistance to chemotherapy compared to the other subtypes. This study aimed to evaluate the clinicopathological data and survival rates of patients with OCCC and identify prognostic factors that determine survival and recurrence.

Materials and methods

A total of 1381 patients with EOC who were treated in the gynecological oncology clinic between 1990-2019 were retrospectively enrolled in this study. Eighty patients were diagnosed with OCCC as a subtype of EOC. Patients with synchronized tumors, secondary malignancies, a tumor with non-epithelial and non-clear cell components, who have received neoadjuvant therapy, who were operated on elsewhere, and those with insufficient data were excluded. A study group was formed with a total of 63 patients.

Demographic characteristics, intraoperative findings, postoperative pathological characteristics, types of adjuvant therapy received, and oncological outcomes of patients were retrieved from the hospital database. The study protocol was approved by Etlik Zubeyde Hanim Women's Health Training and Research Hospital institutional review board (12.04.2019-07).

In our clinic, the routine staging surgery in ovarian cancers includes exploration of the abdomen, peritoneal cytological sampling, total abdominal hysterectomy, bilateral salpingo-oophorectomy, total omentectomy, and systematic retroperitoneal lymphadenectomy. In the presence of a macroscopic tumor, maximal cytoreduction is aimed with cytoreductive surgery techniques in addition to staging surgery. Maximal cytoreduction is defined as no visible tumor, optimal cytoreduction is defined as a residual tumor with ≤1 cm diameter, and suboptimal cytoreduction is defined as >1 cm residual tumor at the end of the surgery. All surgical procedures were performed by experienced gynecological oncology surgeons. Adjuvant treatment options were decided by the gynecologic oncology tumor council.

Patients who had a complete clinical response after completion of the initial treatment were followed up quarterly for the first 2 years, semi-annually up to 5 years, and then annually thereafter with a pelvic examination, abdominal-pelvic ultrasound, complete blood count, blood chemistry, and tumor markers. Chest X-ray screening was performed once a year and if necessary, thoracic and/or abdominal computed tomography was performed.

We defined recurrence distal to the pelvic inlet as pelvic recurrence, between the pelvic inlet and diaphragm as abdominal recurrence, and the remaining types of recurrences as extra-abdominal recurrence. Recurrence in the liver parenchyma, skin, and bone was considered an extra-abdominal recurrence.

The 2014 International Federation of Gynecology and Obstetrics (FIGO) staging criteria were used. For patients treated before 2014, cancer staging was modified according to the FIGO 2014 system using surgical and pathological evaluation. Response to chemotherapy was assessed per the WHO criteria [9]. The response to chemotherapy in patients with measurable lesions was evaluated using clinical, biochemical (CA-125), and imaging (CT or magnetic resonance) parameters one month after the end of adjuvant chemotherapy. Complete clinical response (1) was defined as no visible macroscopic tumor, and partial clinical response (2) was defined as a >50% decrease in macroscopic tumor size. Stable disease (3) was defined as a <50% decrease or <25% increase in macroscopic tumor size and progressive disease (4) as the detection of a new lesion and/or a >25% increase in macroscopic tumor size.

Disease progression during initial adjuvant chemotherapy was defined as a refractory disease. The same adjuvant chemotherapy protocol was administered to the patients with partial clinical response and stable disease. During the adjuvant chemotherapy process, patients were re-evaluated and, finally, they were classified as having complete clinical response or refractory disease. Radiological (detection of new lesions) and laboratory evidence of (increase in CA-125 levels) recurrence in patients with complete clinical response was considered a recurrent disease. Both refractory disease and recurrent disease were defined as disease failure.

The time from the first surgery to death because of the disease or last follow-up visit was defined as overall survival (OS). Failure-free survival (FFS) was defined as the period from initial surgery to proven recurrence or refractory disease with clinical examination and/or radiological imaging or the period from initial surgery to the last follow-up visit in those who did not develop refractory/recurrent disease.

Statistical analysis

SPSS 20.0 (SPSS Inc., Chicago, IL) was used for data review and statistical analysis. Descriptive statistics were expressed as mean (standard deviation) and median (min-max)

for continuous variables and n (%) for categorical variables. The Kaplan-Meier method was used to evaluate survival results. Survival curves were compared in the log-rank test. All variables with a *P*-value of <0.05 in the univariate analysis, except those associated with the stage, were included in the multivariate analysis. Multivariate analysis was conducted by use of the Cox proportional hazards model to assess independent factors affecting survival. All *P*-values less than 0.05 were considered statistically significant.

Results

The mean age of 63 patients included in the study was 54.6 (10.7) years (range: 18-86 years). The median preoperative CA-125 value was 163 IU/ml (range: 5-2165 IU/ml). According to the FIGO 2014 criteria, 37 (58.7%) patients were stages I and II, and 23 (36.5%) were stages III and IV. The data of three patients were inadequate for determining the stage. Ascites was detected in 11 (17.5%) patients and the median ascites volume was 500 ml (range: 100-8500 ml). Systematic lymphadenectomy was performed in 55 (88.3%) patients. The median number of lymph nodes removed in those who underwent lymphadenectomy was 59 (range: 11-112), a median of 41 (range: 1-76) were removed from the pelvic region, and 24 (range: 8-46), from the paraaortic region. Thirteen (23.6%; n=13/55) had lymph node metastasis and the median metastatic lymph node number was 6 (range: 1-14). The tumor was bilateral in 13 (20.6%) patients. Positive peritoneal cytology was present in 17 (27%) patients and omental metastasis was seen in 14 (22.2%). Endometriosis was present in 11 (17.5%) patients. Maximal cytoreduction was achieved in 57 (90.5%) patients, optimal cytoreduction was achieved in 1 patient, and 2 (3.2%) patients were suboptimally cytoreduced. Cytoreduction data of three patients could not be obtained. Detailed clinical, surgical, and pathological characteristics of patients are presented in Table 1.

Table 1: Patients' characteristics

Characteristics			Mean(SD)	Median (range)
Age			54.6(12.29)	54 (18-86)
Ca 125 (IU/ml)			319.2(436.25)	163 (5-2165)
Ca 19-9 (IU/ml)			136.8(116.24)	180 (2-263)
Ascites volume (cc)			2054.6(2976.70)	500 (100-8500)
Number of removed lymph node			59.6(20.07)	59 (11-112)
Number of removed pelvic lymph node			38.2(19.47)	41 (1-76)
Number of removed paraaortic lymph node			24.3(10.06)	24 (8-46)
Number of metastatic lymph node			6.38(3.50)	6 (1-14)
			n	%
FIGO 2014 stage	Stages I-II		37	58.7
	Stages III-IV		23	36.5
	Not determined		3	4.8
Outcome of cytoreductive surgery	Suboptimal (residue tumor > 1cm)		2	3.2
	Optimal (residue tumor ≤ 1cm)		1	1.6
	Maximal (no residue tumor)		57	90.5
	Not determined		4	6.3
Ascites	Present		11	17.5
	Absent		50	79.4
	Not reported		2	3.2
Peritoneal Cytology	Positive		17	27
	Negative		29	46
	Not reported		17	27
Ovarian tumor laterality	Bilateral		13	20.6
	Unilateral	Left	22	34.6
		Right	22	34.6
	Not reported		6	9.5
Omental involvement	Present		14	22.2
	Absent		48	76.2
	Not reported		1	1.6
Peritoneal involvement	Present		8	12.7
	Absent		54	85.7
	Not reported		1	1.6
Endometriosis	Present		11	17.5
	Absent		45	71.4
	Not reported		7	11.1
Lymphadenectomy	Performed		55	87.3
	Not performed		5	7.9
	Not reported		3	4.8
Lymph node metastases [1]	Present		13	23.6
	Absent		41	74.6
	Not reported		1	1.8
Site of metastatic lymph node	Only pelvic		3	4.8
	Only paraaortic		5	7.9
	Pelvic and paraaortic		5	7.9

SD: Standard deviation, [1]: Lymph node metastasis was evaluated in 55 patients who underwent lymphadenectomy

Adjuvant chemotherapy and survival analysis

Due to insufficient data or patients lost to follow-up during the postoperative treatment process, 8 patients were excluded, and survival analysis was performed with a total of 55 patients. Fifty-three (96.4%) patients received chemotherapy, while two patients refused. These two patients were stage IA according to the FIGO 2014 criteria and recurrence did not occur during 41 and 133 months of follow-up. All patients received platinum-based chemotherapy (Table 2).

Progression was detected in 7 (12.7%) patients during adjuvant chemotherapy, which was defined as a refractory disease. All these patients were stages III & IV. Complete clinical response to adjuvant chemotherapy was achieved in 11 (61.1%) of 18 patients with stages III and IV; however, refractory disease was detected in 7 (38.9%).

Following adjuvant chemotherapy, recurrence occurred in 11 (20%) of 48 (87.3%) patients with complete clinical response. The median time to recurrence in this group was 14 months (range: 6-48 months).

Table 2: Adjuvant chemotherapy and disease failure pattern

Characteristics		Mean (SD)	Median (range)
Follow-up (months)		58.7 (56.50)	42 (3-260)
Time to recurrence (month) [1]		19.9 (14.27)	14 (6-48)
		n	%
Adjuvant therapy	Not received	2	3.6
	Received	53	96.4
Type of adjuvant chemotherapy	Cyclophosphamide + Epirubicin+ Cisplatin	1	1.8
	Paclitaxel + Carboplatin	44	80
	Paclitaxel + Cisplatin	7	12.7
	Paclitaxel + Carboplatin + Epirubicin	1	1.8
Response to adjuvant chemotherapy [1]	Complete clinical response	48	87.3
	Progressive disease	7	12.7
Recurrence [1,2]	Negative	37	67.3
	Positive	11	20
Disease failure [1]	Negative	37	67.3
	Positive	18	32.7
Disease failure pattern	Only abdominal	13	23.6
	Only pelvic	1	1.8
	Abdominal and pelvic	1	1.8
	Thoracic	1	1.8
	Thoracic and abdominal	1	1.8
	Thoracic and pelvic	1	1.8

SD: Standard deviation, Disease failure: Progressive disease and recurrence, [1]: Survival analysis was done with 55 patients, [2]: Recurrence in patient with complete clinical response.

Eighteen (32.7%) patients had "disease failure" (Figure 1). The cancer was in the abdomen in 13 (23.6%), in the pelvic region in 1 (1.8%), in the pelvic and abdominal regions in 1 (1.8%), in the thorax 1 (1.8%), in the thorax and abdomen in 1 (1.8%), and in the thorax and pelvis in 1 (1.8%). Detailed information about adjuvant therapy and disease failure is shown in Table 2.

Figure 1: Cohort chart

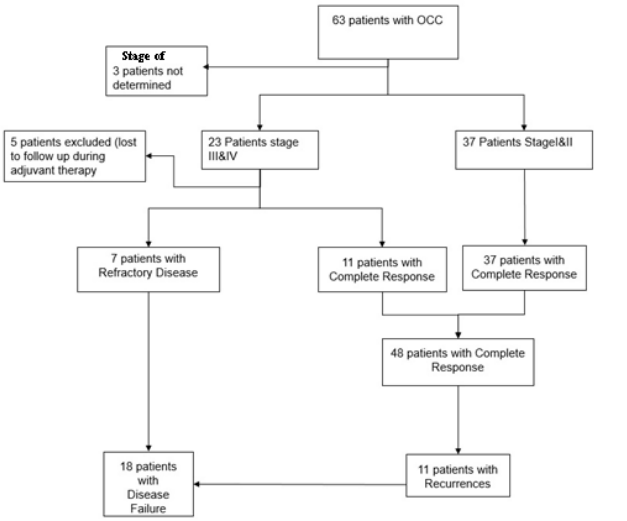
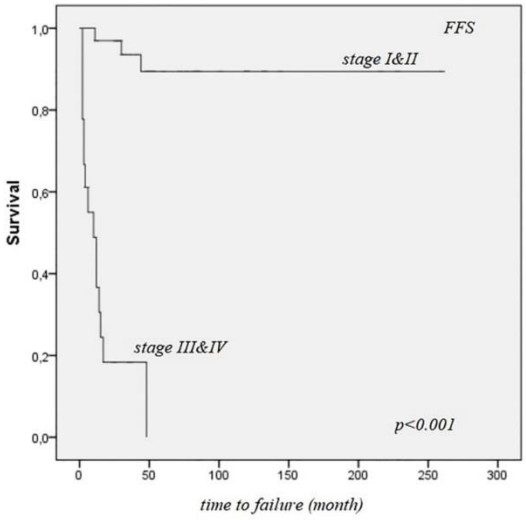


Figure 2: Relationship between failure-free survival and stage Kaplan-Meier Analysis



The median follow-up period of 55 patients who underwent survival analysis was 42 months (range: 3-260 months). Only 2 patients died because of the disease during the follow-up period. Therefore, statistical analysis could not be performed to identify the prognostic factors affecting OS. The 5-year FFS rate was 63%. In univariate analysis, advanced stage, the presence of ascites, lymph node metastases, bilateral ovarian tumors, peritoneal involvement, omental metastasis, rupture of the capsule, surface involvement, and positive peritoneal cytology were unfavorable prognostic factors for FFS (Table 3).

Lymph node metastasis, positive peritoneal cytology, peritoneal spread, and omental metastasis are highly correlated with stage; therefore, a multivariate analysis model was created with the stage (III&IV *vs.* I&II), ascites (present vs. absent), site of ovarian tumor (bilateral vs. unilateral), capsule rupture (positive vs. negative), surface involvement (positive vs. negative) (Table 3). Only stage was an independent risk factor for disease failure (Hazard Ratio; 24.1, 95% Confidence interval: 5.561-104.421; $P<0.001$). In stages I and II, the 5-year-FFS was 89%, and in stages III & IV, it was 0% ($P<0.001$) (Figure 2).

Table 3: Factors predicting failure-free survival

Factors		Univariate Analysis 5-year Failure-Free Survival		Multivariate Analysis Risk of Disease Failure		
		Percentage	*P*-value	Hazard Ratio	95% Confidence Interval	*P*-value
Age [1]	≤54 years	59	0.325			
	>54 years	73				
FIGO 2014 stage	I&II	89	<0.001	1 (ref.)	5.561-104.421	<0.001
	III&IV	0		24.1		
Preoperative CA 125 level (IU/ml)	≤35	83	0.172			
	>35	55				
Ascites	Absent	74	0.001	1 (ref.)	0.552-5.192	0.357
	Present	20		1.693		
Lymph node metastasis	Negative	77	<0.001			
	Positive	20				
Number of removed lymph node [1]	≤59	50	0.072			
	>59	71				
Site of ovarian tumor	Unilateral	79	<0.001	1 (ref.)	0.712-8.738	0.153
	Bilateral	0		2.496		
Peritoneal involvement	Negative	72	0.002			
	Positive	0				
Omental metastasis	Negative	79	<0.001			
	Positive	0				
Capsule rupture	Negative	66	0.004	1 (ref.)	0.409-3.852	0.690
	Positive	27		1.256		
Capsule surface involvement	Negative	77	0.003	1 (ref.)	0.490-5.299	0.387
	Positive	38		1.758		
Peritoneal cytology	Negative	91	<0.001			
	Positive	8				
Endometriosis	Negative	58	0.087			
	Positive	91				

[1]: Median value, ref: reference

Discussion

Ninety percent of ovarian tumors have an epithelial origin. EOC is a heterogeneous group with eight histological subtypes according to the World Health Organization (WHO) classification [10]. Treatment strategies of all histological subtypes are currently similar, and whether adjuvant chemotherapy will be administered is determined by tumor stage and grade rather than tumor subtype. However, each EOC subtype has different clinical and molecular features, and their oncological outcomes are disparate [11]. Liu et al. [7] reported the 5-year disease-specific survival rate in epithelial ovarian cancer as 66.4% in clear cell subtype, 71.4% in mucinous subtype, 80.3% in endometrioid subtype, and 42.4% in the serous subtype. However, in the current study, the oncological outcome of the patients with advanced-stage OCCC was poorer than those with serous and endometrioid type ovarian cancers.

Maximal cytoreduction was achieved in 90.5% of the patients and 96.4% received adjuvant chemotherapy. The univariate analysis revealed that the stage of the disease, presence of ascites, lymph node metastasis, peritoneal involvement, omental metastasis, capsule rupture, surface involvement, and positive peritoneal cytology were significant for disease failure. These results are in line with previous findings in the literature investigating prognostic factors in OCCC [12-15].

In multivariate analysis, the stage was an independent prognostic factor for disease failure in OCCC, and the risk of disease failure increased 24 times in the advanced stage. Five-year FFS rates were 89% in stages I&II and 0% in stages III& IV. Studies show that the prognosis is better in the early stages of OCCC [7, 13-15]. In a study reported by Lee et al, the 3-year relapse-free survival rates were 80%, 47%, 34%, and 30% at stages I, II, III, and IV, respectively [13].

The current treatment strategy for OCCC is aggressive surgery and platinum-based adjuvant chemotherapy. However, poor prognosis is often observed in patients with advanced-stage, which is considered to be mostly due to the resistance to conventional platinum-based chemotherapy [16]. The clinical response rate to platinum-based chemotherapy in the EOC group was 70-80% in high-grade serous ovarian cancer, 26.3% in advanced mucinous ovarian cancer, 23.1% in low-grade serous

ovarian cancer, and 20-55% in the OCCC group [17-21]. Opposite to other EOC types of OCCC, partial resistance to platinum-based chemotherapy and the absence of adequate alternative therapies other than platinum-based combinations complicate the treatment of the disease.

Zhao et al. reported the chemosensitivity rates in the OCCC group as 91.4% at stages I and II and 36.7% at stages III and IV [14]. Thang et al. achieved maximal cytoreduction in 90% of patients in their study including 130 OCCC patients. They administered adjuvant platinum-based chemotherapy to all followed-up patients (n=127), the rate of chemotherapy-refractory or resistant disease was 23% in the entire cohort and 64.5% in stage III-IV cases. They found that stage and chemotherapy resistance were independent prognostic factors in survival analysis [15].

OCCCs are considered high-risk EOCs because they behave more aggressively. Adjuvant chemotherapy is recommended, even with stage IA [22]. However, with the current information about chemotherapy resistance in OCCC, the benefit of this approach is controversial. Oseledchyk et al. evaluated a total of 1995 stage I OCCC patients and stated that platinum-based adjuvant chemotherapy did not improve OS [23]. In their study using SEER data, Bogani et al. [20] reported that chemotherapy was not beneficial at stages IA-B in OCCC although it improved overall survival data at stage IC.

Considering the high maximal cytoreduction and adjuvant treatment rates in our study, the high rate of disease failure (32.7%) and the progression of the disease observed in about %40 of patients in the advanced stages despite chemotherapy indicates both the aggressive behavior and non-responsiveness to chemotherapy of the OCCC.

Various results show that platinum-based chemotherapy may not be the most convenient treatment option for patients with OCCC. This led researchers to define alternative treatment combinations. However, NCCN (The National Comprehensive Cancer Network) guidelines still recommend the use of platinum-based chemotherapy in the treatment of OCCC [22]. In their randomized phase III study comparing the irinotecan + cisplatin combination with the paclitaxel + carboplatin combination in OCCC management, Sugiyama et al. were unable to detect survival advantage in the irinotecan + cisplatin group [24]. In addition, in the treatment of OCCC, new molecular targets such as epidermal growth factor receptor (EGFR), phosphatidylinositol 3'-kinase (PI3K) signaling pathway and, mitogen-activated protein kinase (MAPK) were identified and tested with no consensus on their effectiveness [25-27].

Considering the aggressiveness of OCCC, low response rates to first-line platinum-based adjuvant chemotherapy, and the fact that an effective chemotherapy regimen has not yet been found, it is clear that the most important step in the management of the disease is currently maximal surgical cytoreduction. Takona et al. [28] reported the median progression-free survival time in the OCCC group as 39 months in patients without residual tumor, 7 months in patients with residual tumors with <1 cm diameter, and 5 months in patients with residual tumors >1 cm in diameter. Patients without residual tumors had significantly better progression-free survival than those with a tumor smaller than 1 cm or a tumor diameter greater than 1 cm, whereas there was no significant prognostic difference between patients with a tumor diameter less than and greater than 1 cm. As reported above, this comparison could not be made due to the low rates of optimal and suboptimal cytoreduction. However, several studies state that residual tumor load in OCCC is an independent prognostic factor [13, 27, 28].

OCCC is generally diagnosed at a young age, frequently associated with endometriosis, detected in the early stages, and bilateral ovarian involvement is rare [4, 6, 7, 10, 29]. Our results are consistent with the previous findings. Studies detected endometriosis in 9-70% in OCCC patients [13, 30]. In our study, this rate was 17.5%.

The limitations of our study include the retrospective design and the small sample size. We demonstrated detailed clinical-pathological characteristics and adjuvant treatments of the patients. Most patients underwent complete staging and cytoreductive surgery, including systematic lymphadenectomy. Follow-up periods of the patients were long, and histopathological examinations were performed by experienced gynecological pathologists, all of which are the strengths of our study.

Conclusion

OCCC is a subtype of EOC with aggressive behavior, of which prognosis is determined by the stage of the disease. It partially responds to platinum-based adjuvant chemotherapy. Because effective adjuvant therapy has not yet been identified, the main goal in current OCCC management should be the absence of postoperative residual disease. Future studies on the current topic are therefore needed to better illuminate the molecular and genetic basis of OCCC and to define effective new chemotherapy combinations.

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