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Original Article

Clinical Characteristics of Clear Cell Ovarian Cancer: A Retrospective Multicenter Experience of 308 Patients in South Korea

Hee Yeon Lee, MD, PhD[1], Ji Hyung Hong, MD, PhD[2], Jae Ho Byun, MD, PhD[3], Hee-Jun Kim, MD, PhD[4], Sun Kyung Baek, MD, PhD[5], Jin Young Kim, MD, PhD[6], Ki Hyang Kim, MD, PhD[7], Jina Yun, MD[8], Jung A Kim, MD[9], Kwonoh Park, MD[10], Hyo Jin Lee, MD, PhD[11], Jung Lim Lee, MD[12], Young-Woong Won, MD, PhD[13], Il Hwan Kim, MD[14], Woo Kyun Bae, MD, PhD[15], Kyong Hwa Park, MD, PhD[16], Der-Sheng Sun, MD, PhD[17], Suee Lee, MD, PhD[18], Min-Young Lee, MD[19], Guk Jin Lee, MD, PhD[20], Sook Hee Hong, MD, PhD[21], Yun Hwa Jung, MD[22], Ho Jung An, MD, PhD[23]

Running title: Clear Cell Ovarian Cancer in Korea

Correspondence: Jae Ho Byun, MD, PhD

Department of Internal Medicine, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea, 56 Dongsu-Ro, Incheon 21431, Korea

Tel: 82-32-280-6078 Fax: 82-32-280-6100 E-mail: jhbyun37@catholic.ac.kr

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[1]Department of Internal Medicine, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, [2]Department of Internal Medicine, Eunpyeong St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, [3]Department of Internal Medicine, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, [4]Department of Internal Medicine, Chung-Ang University College of Medicine, Seoul, [5]Department of Internal Medicine, Kyung Hee University School of Medicine, Seoul, [6]Department of Hematooncology, Dongsan Hospital, Keimyung University School of Medicine, Daegu, [7]Department of Internal Medicine, Busan Paik Hospital, Inje University College of Medicine, Busan, [8]Department of Internal Medicine, Soonchunhyang University College of Medicine, Bucheon, [9]Department of Internal Medicine, Kyung Hee University Gangdong Hospital, Seoul, [10]Department of Internal Medicine, Pusan National University Yangsan Hospital, Yangsan, [11]Department of Internal Medicine, Chungnam National University College of Medicine, Daejeon, [12]Department of Hemato-oncology, Daegu Fatima Hospital, Daegu, [13]Department of Internal Medicine, Hanyang University College of Medicine, Seoul, [14]Department of Internal Medicine, Haeundea Paik Hospital, Inje University College of Medicine, Busan, [15]Department of Hematology-Oncology, Chonnam National University Hwasun Hospital, Chonnam National University College of Medicine, Hwasun, [16]Department of Internal Medicine, Korea University College of Medicine, Seoul, [17]Department of Internal Medicine, Uijeongbu St Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, [18]Department of Internal Medicine, Dong-A University Hospital, Busan, [19]Department of Internal Medicine, Soonchunhyang University Hospital, Soonchunhyang University College of Medicine, Seoul, [20]Department of Internal Medicine, Bucheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, [21]Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, [22]Sun General Hospital, Daejeon, [23]Department of Internal Medicine, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

Abstract

Purpose

To evaluate clinical characteristics and treatment pattern of ovarian clear cell carcinoma (OCCC) in Korea and the role of adjuvant chemotherapy in early stage

Materials and Methods

Medical records of 308 cases of from 21 institutions were reviewed and data including age, performance status, endometriosis, thromboembolism, stage, CA-125, treatment, recurrence, and death were collected.

Results

Regarding stage of OCCC, it was stage I in 194 (63.6%), stage II in 34 (11.1%), stage III in 66 (21.6%), and stage IV in 11 (3.6%) patients. All patients underwent surgery. Optimal surgery (residual disease ≤1cm) was achieved in 89.3%. Majority (80.5%) of patients received postoperative chemotherapy. The most common regimen was taxane-platinum combination (96%). Median relapse-free survival (RFS) was 138.5 months for stage I, 33.4 for stage II, 19.3 for stage III, and 9.7 for stage IV. Median overall survival (OS) were not reached, 112.4, 48.7, and 18.3 months for stage I, II, III, and IV, respectively. Early stage (stage I), endometriosis, and optimal debulking were identified as favorable prognostic factors for RFS. Early stage and optimal debulking were also favorable prognostic factors for OS. Majority of patients with early stage received adjuvant chemotherapy. However, additional survival benefit was not found in terms of recurrence.

Conclusion

Majority of patients had early stage and received postoperative chemotherapy regardless of stage. Early stage and optimal debulking were identified as favorable prognostic factors. In stage IA or IB, adding adjuvant chemotherapy did not show difference in survival. Further study focusing on OCCC is required.

Korean Cancer Association

Keywords

Carcinoma, Ovarian Epithelial, Adenocarcinoma, Clear cell, Korea, Chemotherapy, Adjuvant

Introduction

Globally ovarian cancer is the 7th leading cause of cancer-related death among women. In Korea, it is the 10th common female cancer. Its incidence is continuously increasing by 1.6% of annual percentage change [1]. Epithelial ovarian cancer is a heterogeneous group with eight histologic subtypes according to WHO classification. Although these subtypes have different biology, they have been treated in the same way since clinical trials have mostly included serous carcinoma, the most common histologic subtype.

Ovarian Clear cell carcinoma (OCCC) accounts for 3-10% of epithelial carcinoma. Significant geographic difference has been noted in the prevalence of OCCC [2]. The prevalence is higher in Japanese and Asian populations than in western countries [2]. A recent Japanese study has reported that OCCC is increased significantly, accounting for up to 30% of epithelial ovarian cancer [3]. Several social-environmental factors, related to ovulation and menstruation, have been suggested as the reasons for the increasing incidence of OCCC [3]. According to Korean Central Cancer Registry, the proportion of OCCC was 11.6% [1]. Compared to high grade serous carcinoma (HGSC), OCCC usually presents at younger age and lower stage. OCCC is known to be associated with endometriosis and putative precursor lesion [2,4]. It has a high frequency of thromboembolic complication [2,4]. Early stage OCCC confined to ovary has favorable prognosis. However, OCCC in advanced stage has poor prognosis due to its inherent chemoresistance. Notwithstanding its chemoresistance and good prognosis in early stage, adjuvant chemotherapy in early stage OCCC is commonly used and conflicting data have been reported [5,6]. In terms of genetic profile, PIK3CA and ARID1A mutations at high frequency have been noted, while BRCA mutation and TP53 mutation at low frequency are commonly found in HGSC [7-11]. Hence, treatment for OCCC that is different

from HGSC is needed.

Thus, the objective of this study was to evaluate clinical characteristics and treatment pattern of OCCC in Korea. Additionally, the role of adjuvant chemotherapy in early stage OCCC was assessed.

Materials and Methods

1. Patients and Treatments

This was a retrospective study of 308 cases of clear cell ovarian carcinoma from 21 institutions in South Korea between January 1995 and December 2015. All patients underwent surgery and had histologically confirmed pure clear cell ovarian carcinoma. Medical records were reviewed. Data including age, Eastern cooperative oncology group (ECOG) performance status, presence of endometriosis and history of thromboembolism (TE), stage of OCCC, initial level of CA-125, treatment (surgery, chemotherapy), recurrence, and death were collected. Presence of endometriosis was checked according to pathologic report from surgery. Surgical staging was done according to International Federation of Gynecology and Obstetrics (FIGO) guidelines for ovarian cancer (8th edition, 2017). Optimal surgery was defined as residual disease ≤1 cm. The Institutional Review Board of each institution approved this study. Informed consent was waived due to its retrospective nature.

2. Statistical analyses

Recurrence-free survival (RFS) and overall survival (OS) were determined from the date of pathologic diagnosis to the date of recurrence or death using the Kaplan-Meier method.

Survival rate was derived from life table. To evaluate prognostic factors for RFS and OS, univariate and multivariate Cox regression analyses were done. Univariate analyses were performed with factors including age, performance status, stage, histologic grade, endometriosis, thromboembolism, optimal debulking and postoperative chemotherapy. Multivariate analyses were done with factors of p-value <0.1 at univariate analyses. All statistical analyses were performed using Statistical Package for Social Sciences (SPSS/PC+ 18.0, Chicago, IL), and a p-value of less than 0.05 was considered statistically significant.

Results

1. Patient characteristics and treatment

Three hundred and eight patients were included in this study. Baseline characteristics of these patients are summarized in Table 1. Their median age at diagnosis was 51 years (range, 25-81 years). The majority (78.6%) of patients had ECOG performance status of grade 0 or 1. Regarding the stage of disease (n=303), it was stage I in 194 (63.7%), stage II in 34 (11.1%), stage III in 66 (21.6%), and stage IV in 11 (3.6%). Median CA-125 level was 72.3 IU/ml (range, 1.9-8930) in all patients. It was 45.7 IU/ml in stage I, 98.9 IU/ml in stage II, 192.1 IU/ml in stage III, and 694.8 IU/ml in stage IV. About one-third (34.9%) of patients had co-existing endometriosis and 19 (6.2%) patients had history of TE. Histologic tumor grading was done for 141 patients and grade 3 in 81 (45.9%) patients.

Table 2 shows treatment pattern for OCCC. Eight (2.6%) patients received neoadjuvant chemotherapy (Table 2). All patients underwent surgery. Two-hundred and seventy-seven (89.9%) patients underwent total hysterectomy including previous hysterectomy, both salpingo-

oophrectomy, omentectomy, and pelvic lymph node dissection. The others underwent unilateral salpingo-oophorectomy with or without hysterectomy. They were all young aged (under 40) and had stage I disease. Optimal surgery was achieved in 275 (89.3 %) patients. Postoperative chemotherapy was administered in 248 (80.5%) patients. The most commonly used regimen was taxane-platinum combination (96%). The median number for administered cycles of chemotherapy was 6 (range, 1-12).

2. Survival outcomes

Median follow-up duration was 31.2 months (range, 0.5–195.4 months). Recurrence occurred in 119 (40.2%) patients. Twelve (3.9%) cases had missing information for recurrence or progression and 72 (23.4%) cases had missing information for survival. Median RFS for stage I, II, III, and IV were 138.5 months (95% CI, 87.8-189.2 months), 33.4 months (95% CI, 0-97.1 months), 19.3 months (95% CI, 4.5-10.5 months), and 9.7 months (95% CI, 7.9-11.4 months), respectively (log rank $p < 0.001$, Fig. 1A). Median OS was not reached in stage I, 112.4 months (95% CI, 59.5-165.3 months) in stage II, 48.7 months (95% CI 18.8-78.7 months) in stage III, and 18.3 months (95% CI 2.5-34.1 months) in stage IV (log rank $p < 0.001$, Fig. 1B). One-year recurrence (or progression)-free survival rates for stage I, II, III, and IV were 90%, 83%, 63%, and 30% in stage I, II, III, and IV, respectively. Three-year recurrence-free survival rates for stage I, II, III, and IV were 80%, 47%, 34%, and 30%, respectively. Overall survival rates at 1-year was 99%, 95%, 80%, and 70%, respectively. These rates at 3-year were 96%, 85%, 54%, and 40% for stage I, II, III, and IV, respectively.

3. Prognostic factors

In univariate analyses, early stage (I), endometriosis, optimal debulking (residual

disease ≤1 cm), and adding postoperative chemotherapy were favorable prognostic factors for RFS. Early stage, optimal debulking, and adding postoperative chemotherapy were also significant prognostic factors for OS. In multivariate analyses, early stage, endometriosis, and optimal debulking remained as favorable prognostic factors for RFS. Early stage, and optimal debulking predicted longer OS (Table 3).

4. Adjuvant chemotherapy in early stage OCCC

Role of adjuvant chemotherapy in patients with early stage OCCC was evaluated. Ninety-four (30.5%) patients had stage IA or IB disease, and 77 (81.9%) patients received adjuvant chemotherapy. Adjuvant chemotherapy was administered in 69 (81.2%) patients with stage IA (n = 95), and 8 (88.9%) with stage IB (n = 9). Median RFS was 95.2 months in patients with adjuvant chemotherapy. It was not reached in patients without adjuvant chemotherapy (p = 0.57). Median OS was not reached.

Discussion

The aim of the present study was to assess clinical features and prognosis of Korean OCCC and study the role of adjuvant chemotherapy in early stage OCCC. Similar to global epidemiology of OCCC, majority of Korean OCCC patients presented at younger age (median 51 years) and early stage. About three-quarter of patients had stage I or II disease. According to the Surveillance, Epidemiology, and End Results (SEER) data, the incidence of OCCC in epithelial ovarian cancer was different according to ethnicity, 4.8% in whites, 3.1% in blacks, and 11.1% in Asians [12]. Machida et al. [3] have reported recent trends of epithelial ovarian

cancer in Japan. They found the significant increase of OCCC in recent years, and an incidence of about 30% for epithelial ovarian cancer. Moreover, patients aged between 30 and 50 showed similar incidence of OCCC with serous carcinoma [3]. Several factors are responsible for the increase of OCCC, including earlier menarche, lower use of oral contraceptives (OC) compared to western countries, and low pregnancy rate. Those could increase the number of ovulations in lifetime which in turn raise the risk of endometriosis, the known precursor of OCCC. Compared to Caucasians or African Americans, Asian women seem to have higher prevalence of endometriosis, although medical utilization may account partly for the difference [13]. In Korea, OCCC accounts for 11.6% of epithelial ovarian cancer, not as high as that in Japan. However, its incidence has been increased continuously at an annual percentage change of 1.6%. According to Kim et al [14], the incidence of OCCC in Korea has increased significantly since 1999. Current Korean trends and status in terms of pregnancy, menarche, and the use of OC are similar to those in Japan. Thus continuous increase of OCCC in Korea is expected.

The association of endometriosis and OCCC has been studied widely. Endometriosis is accepted as a precursor lesion of OCCC. Son et al. [15] recommended active surveillance with at least 1-year interval in asymptomatic patients with endometriosis. In terms of prognosis, conflicting data have been reported. OCCC with endometriosis has been reported to be associated with early stage and good prognosis [16,17]. Meanwhile no difference in prognosis of OCCC according the presence of endometriosis has been reported [18,19]. In the present study, about one third of patients had endometriosis. These patients showed longer median RFS (median, not reached vs. 67.5 months; log rank p = 0.029) and OS (not reached; log rank p = 0.054), although the difference in OS was not statistically significant. OCCC patients are known to be at high risk of venous TE (15-42%). Negative impact of TE on prognosis has been reported [20,21]. The incidence of venous TE has been reported to be more than two times more

compared to that of serous carcinoma, with those with advanced stage having higher risk [20]. Thus in recurrent OCCC patients, life-long anticoagulation is recommended [20]. In the current study 6.2% patients had TE. No prognostic role of TE was revealed. Due to the retrospective nature of this study, its incidence might have been underestimated.

Oliver et al. [22] reported that OCCC in early stage has better prognosis than serous carcinoma. However it has significant poorer prognosis in advanced stage. Progression-free survival rate and survival rate in early stage (I, II) OCCC at 5-year were 75% and 80%, respectively, compared to 63% and 78% in serous carcinoma [22]. In the present study, relapse-free survival rate and overall survival rate at 5-year for stage I and II were 68% and 91%, respectively, showing good prognosis of early stage OCCC.

International collaborative ovarian neoplasm trial 1 (ICON 1) has evaluated adjuvant chemotherapy in early stage epithelial cancer [23]. Ten-year follow-up results confirmed the benefit of adjuvant chemotherapy [23]. OCCC is classified as high risk of recurrence. Thus adjuvant chemotherapy is recommended regardless of stage or surgical result (optimal or suboptimal) [23,24]. In ICON 1trial, OCCC accounted for 12% of enrolled patients, and more than 80% of patients had serous, mucinous or endometrioid histology [25]. Using SEER data, Oseledchyk et al. [6] have assessed adjuvant chemotherapy in stage I OCCC. Their study included 1995 patients with stage I OCCC and found that adjuvant chemotherapy was not associated with improved OS. In the present study, over 80% of patients received postoperative chemotherapy. The proportion was similar for all stages. In stage IA or IB patients, adjuvant chemotherapy was not related to longer RFS. Considering the fact that minority of patients with OCCC were included in ICON 1 trial and that OCCC has distinct biology including intrinsic chemoresistance, genetic profile, and good prognosis in early stage, the role of adjuvant chemotherapy in early stage OCCC should be reconsidered.

Due to the nature of this retrospective study from multicenter, there were missing data. In addition, the completeness of optimal surgical staging including inspection and palpation of all peritoneal surfaces; biopsies of any suspect lesions for metastases; peritoneal washing; infracolic omentectomy; (blind) biopsies of right hemidiaphragm, of right and left paracolic gutter, of pelvic sidewalls, of ovarian fossa, of bladder peritoneum, and of cul-de-sac; sampling of iliac and periaortic lymph nodes is unclear.

In conclusion, this study showed clinical features, treatment patterns and prognosis of OCCC in Korea. Majority of patients had early stage and received postoperative chemotherapy regardless of stage. Early stage (stage I), and optimal debulking (residual disease <1cm) were identified as favorable prognostic factors for RFS and OS. Patients with endometriosis showed better prognosis. In patients with stage IA and IB, adding adjuvant chemotherapy did not show difference in survival. Considering the distinct biology of OCCC and its continuous increasing incidence, particularly in Asian, further study focusing on OCCC is required.

Conflicts of Interest

Conflict of interest relevant to this article was not reported

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Table 1. Patient characteristics

Characteristics	n = 308
Age (years)	51 (range, 25-81)
ECOG Performance status	
0	75 (24.4)
1	167 (54.2)
2	53 (17.2)
3	1 (0.3)
NA	12
Stage	
Ia	85 (27.6)
Ib	9 (2.9)
Ic	100 (32.5)
IIa	5 (1.6)
IIb	10 (3.2)
IIc	19 (6.2)
IIIa	15 (4.9)
IIIb	11 (3.6)
IIIc	40 (13)
IV	11 (3.6)
CA-125 (IU/ml)	72.34 (range, 1.9-8930)
Stage I	45.7
Stage II	98.9
Stage III	192.1
Stage IV	634.8
Endometriosis	107 (34.9)
Thromboembolism	19 (6.2)
Tumor grade	
1	10 (3.3)
2	50 (19.5)
3	81 (45.9)
NA	166

ECOG, Eastern Cooperative Oncology Group; NA, not available
Values are presented as number (%)

Table 2. Summary of treatments

Treatment	N = 308
Neoadjuvant chemotherapy	8 (2.6)
Paclitaxel Carboplatin	5 (55.6)
Paclitaxel Cisplatin	3 (33.3)
Other	1 (11.1)
Debulking operation	308 (100)
Optimal	275 (89.3)
Suboptimal	33 (10.7)
Postoperative chemotherapy	248 (80.5)
Paclitaxel Carboplatin	177 (73.1)
Paclitaxel Cisplatin	25 (10.3)
Docetaxel Carboplatin	28 (11.6)
Docetaxel Cisplatin	2 (0.8)
Other	10 (4.1)

Table 3. Prognostic factors for recurrence free survival

	RFS				OS			
	Univariate		Multivariate		Univariate		Multivariate	
	HR	p value	HR (95% CI)	p value	HR	p value	HR (95% CI)	p value
Age (≥ 50 vs. < 50 years)	0.06	0.806			1.21	0.272		
ECOG PS (2, 3 vs. 0, 1)	1.41	0.236			2.78	0.096		
Stage (II, III, IV vs. I)	22.89	***<0.001***	2.2 (1.42-3.43)	***<0.001***	20	***<0.001***	3.57 (1.6-7.96)	***<0.001***
Histologic grade (2, 3 vs. 1)	2.01	0.156			1.7	0.199		
Endometriosis (no vs. yes)	4.76	***0.029***	1.65 (1.09-2.51)	0.019	1.97	0.059		
Thromboembolism (yes vs. no)	0.8	0.503			0.91	0.867		
Optimal debulking (no vs. yes)	76.46	***<0.001***	13.44 (6.35-28.46)	***<0.001***	51.4	***<0.001***	6.04 (1.86-12.75)	***<0.001***
Postoperative chemotherapy (no vs. yes)	15.68	***<0.001***			19.1	***<0.001***		

RFS, relapse free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval;000 ECOG, Eastern Cooperative Oncology Group; PS, performance status

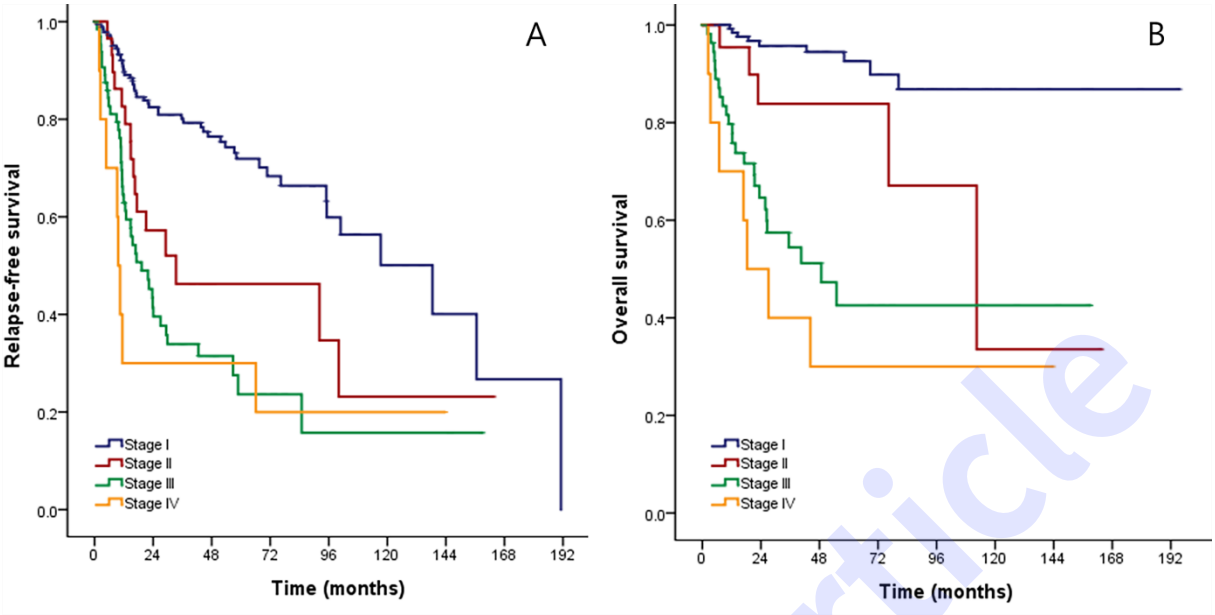

Fig. 1. Kaplan-Meier curves of relapse-free survival (A) and overall survival (B).