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Ovarian clear cell carcinoma, outcomes by stage: The MSK experience

Catherine A. Shu [a], Qin Zhou [b], Anjali R. Jotwani [a], Alexia Iasonos [b], Mario M. Leitao Jr. [c,d], Jason A. Konner [a,d], Carol A. Aghajanian [a,d,*]

[a] Gynecologic Medical Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA
[b] Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY, USA
[c] Gynecology Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA
[d] Weill Cornell Medical College, New York, NY, USA

HIGHLIGHTS

- Clear cell ovarian carcinoma frequently presents at an early stage.
- Women with stage IA disease have an excellent prognosis.
- Survival for IC disease varies based on surgical rupture vs. surface involvement.

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ABSTRACT

Objective. Ovarian clear cell carcinomas (OCCCs) are rare, and uncertainty exists as to the optimal treatment paradigm and validity of the FIGO staging system, especially in early-stage disease.

Methods. We performed a retrospective cohort study of all OCCC patients diagnosed and treated at Memorial Sloan Kettering Cancer Center between January 1996 and December 2013. Progression-free survival (PFS) and overall survival (OS) were calculated by stage and race, and comparisons were made using the log-rank test. Statistical significance was set at $p < 0.05$. Type and duration of treatment were also recorded.

Results. There were 177 evaluable patients. The majority of patients were stage I at diagnosis (110/177, 62.2%). Of these, 60/110 (54.6%) were stage IA, 31/110 (28.2%) were stage IC on the basis of rupture-only, and 19/110 (17.3%) were stage IC on the basis of surface involvement and/or positive cytology of ascites or washings. Patients with stage IA and IC based on rupture-only had similar PFS/OS outcomes. Patients with stage IC based on surface involvement and/or positive cytology had a statistically significant decrement in PFS/OS. Stage was an important indicator of PFS/OS, while race was not.

Conclusions. OCCC often presents in early stage. Women with stage IA OCCC have excellent prognosis, and future studies should explore whether they benefit from adjuvant chemotherapy. Women with IC OCCC need further staging clarification, as surgical rupture alone affords better prognosis than surface involvement and/or positive cytology. Women with advanced OCCC have poor survival and are often chemotherapy resistant/refractory. New treatment paradigms are needed.

1. Introduction

The histologic subtypes of ovarian cancer include high grade serous, clear cell, endometrioid, mucinous, and low grade serous. Each subtype is a distinct disease with a different biology [1]. Ovarian clear cell carcinoma (OCCC) is rare, accounting for approximately 5–10% of all ovarian carcinomas in North America, and a higher percentage in East Asia [2,3]. It typically occurs at a younger age, is diagnosed at an earlier stage, and often is associated with endometriosis [3–5]. Because it is often discovered at an early stage, the overall prognosis is good, as women with stage I disease have an excellent outcome [6]; however, women with advanced OCCC tend to have a much worse prognosis than those with high grade serous carcinomas (HGSC) of equivalent stage [7,8].

The difference in prognosis has been attributed primarily to the chemoresistant nature of OCCC. Although the standard treatment remains debulking surgery followed by chemotherapy with paclitaxel and carboplatin, controversy exists as to the role of chemotherapy for stage IA disease, the most effective chemotherapy regimen, the number of cycles, and the role of radiation therapy. Several trials have attempted to address these questions.

The Gynecologic Oncology Group (GOG) conducted a randomized phase III trial of three versus six cycles of adjuvant paclitaxel and

* Corresponding author at: Memorial Sloan Kettering Cancer Center, 300 East 66th Street, Room 1303, New York, NY 10065 USA.
E-mail address: aghajanc@mskcc.org (C.A. Aghajanian).

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carboplatin in early-stage epithelial ovarian cancer (EOC) [9]. While there was no statistically significant difference in recurrence rate between the two groups, an exploratory analysis broken down by histology showed a significant risk reduction for receiving six cycles in the serous subtype [10]. On the other hand, this difference was not observed for OCCC, raising the question of the efficacy and optimal number of cycles of upfront chemotherapy.

The Japanese Gynecologic Oncology Group (JGOG) performed a randomized phase III trial (JGOG3017) of paclitaxel/carboplatin versus irinotecan/cisplatin as first-line chemotherapy in patients with stage IC-IV OCCC. No differences in 2-year progression-free (PFS) or overall survival (OS) were seen [11]. Of note, 66.4% of patients enrolled on this study had stage I disease and, accordingly, the event rate was low.

A retrospective Canadian study examined women with stage I and II OCCC treated with paclitaxel and carboplatin for three cycles, followed by abdominopelvic irradiation or observation [6]. They found that the addition of radiotherapy did not offer any benefit for patients with stage IA and IC (rupture-only). However, for stage IC patients with surface involvement or positive cytology and stage II patients, the addition of radiotherapy improved disease-free survival by 20% at 5 years.

Given the fundamental questions remaining in OCCC, more information about this rare subtype is needed. We conducted a retrospective systematic review of all OCCC cases diagnosed and treated at Memorial Sloan Kettering Cancer Center (MSK) over an 18-year period.

2. Methods

Institutional Review Board/Privacy Board permission was obtained for this study. Patients were identified through the institutional database. The medical records of all women treated for ovarian or pelvic clear cell carcinoma at MSK between January 1996 and December 2013 were reviewed. Data collected included demographic information; clinical, surgical, chemotherapy, and radiotherapy information; and dates and nature of follow-up. All patients were restaged using the FIGO 2014 staging system, and women with stage IC disease were further broken down into intraoperative rupture vs. surface involvement and/or positive cytology and/or ascites (hereafter referred to as surface involvement). Women with both surgical rupture and surface involvement were counted in the surface involvement subgroup. Racial information was captured through both the patient registration system and the Cancer Database, a tumor registry run by MSK.

Only primary patients treated at MSK were included. For inclusion, a gynecologic pathologist at MSK must have confirmed the histologic diagnosis of ovarian or pelvic clear cell carcinoma. Initial debulking surgery may have been at MSK or elsewhere, as long as women had their upfront chemotherapy at MSK within three months of diagnosis. Women who presented to MSK at time of recurrence were excluded. Women with a concurrent advanced malignancy were also excluded, as were women with only pathology review or lack of sufficient follow-up.

2.1. Statistical analysis

The associations between the type/response of chemotherapy treatment and stage were tested using the Fisher-Exact test. The endpoints selected for analysis included PFS and OS. PFS was defined as the time from histologic diagnosis to the date of progression or recurrence, death, or last follow-up. OS was defined as the time from histologic diagnosis to the date of death or last follow-up. Comparisons were performed using the Log-Rank test.

Response to chemotherapy was broken down into refractory (progression within 1 month of chemotherapy), resistant (progression between 1 and 6 months of chemotherapy), and sensitive (progression after 6 months of chemotherapy).

3. Results

3.1. Patient and disease demographics

There were 227 women with a diagnosis of OCCC at MSK between January 1996 and December 2013 (Table 1). Thirty-nine patients presented at time of disease recurrence; 3 patients had no follow-up; 2 patients had pathological review only; 5 patients had a concurrent advanced stage malignancy; and 1 patient had mixed mucinous/clear cell histology, leaving 177 women for this analysis.

The median age at diagnosis was 53 (range, 30–82). As expected, early-stage disease predominated: 110 (62.2%) patients had stage I disease, 17 (9.6%) had stage II disease, 39 (22.0%) had stage III disease, and 11 (6.2%) had stage IV disease. Among the stage I patients, 60 (54.6%) had stage IA disease, and 50 (45.4%) had stage IC disease. Within the IC patients, 31 (62.0%) patients were staged as IC due to rupture-only, while 19 (38.0%) patients had surface involvement or positive cytology.

The majority (84.7%) of women were white, 14 (7.9%) were East Asian, 8 (4.5%) were Indian, and 5 (2.8%) were black. Race was self-reported.

3.2. Upfront chemotherapy treatment

Of the 176 women with available chemotherapy data, 170 (96.6%) underwent upfront chemotherapy, mostly with a platinum-agent and taxane, and 157 (89.2%) underwent more than 3 cycles of chemotherapy (Table 2A). There was no statistically significant difference between the stage and the number of cycles of chemotherapy received, although 11 (100.0%) women with stage IV disease underwent more than 3 cycles. When broken down by stage IA vs. IC, 51/60 (85.0%) of women with stage IA disease underwent more than 3 cycles, as compared to 46/49 (93.9%) of women with stage IC disease (Table 2B). Of the 157 women with more than 6 months of post-chemotherapy follow-up, 17 (10.8%) had refractory disease, 16 (10.2%) had resistant disease, and 124 (79.0%) met the criteria for sensitive disease. The true rate of platinum resistance is better represented by measuring the rate in advanced disease patients: 22/44 (50.0%) women with stage III/IV disease had chemotherapy-refractory or resistant disease, compared to 11/113 (9.7%) women with stage I/II disease ($p < 0.001$), largely reflecting the high cure rate in early-stage disease.

The overall 3-year PFS rate was 62.7% (95% CI: 54.7–69.7%), and 67 (37.9%) women progressed or died (Fig. 1A). Median PFS was 9.7 months for stage IV, 13.8 months for stage III, and the median was not reached for stages I–II (Fig. 2A). The median follow-up time for the non-progressed survivors was 47.9 months (range, 3.7–200.5 months).

Table 1
Patient demographics.

Variable	All	%
All	177	
Age at diagnosis		
Median (mean)	53 (52.4)	
Range	30–82	
Race		
White	150	84.7
East Asian	14	7.9
Indian	8	4.5
Black/other	5	2.8
FIGO 2014 stage		
I	110	62.2
II	17	9.6
III	39	22.0
IV	11	6.2
Within the 110 stage I pts		
IA	60	54.6
IC with rupture only	31	28.2
IC with surface involvement, positive washings, or ascites	19	17.3