Management of patients with early-stage ovarian clear cell carcinoma: risk stratification and fertility conservation

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ABSTRACT
Objective We sought to describe clinicopathologic and treatment factors associated with oncologic outcomes in patients with early-stage ovarian clear cell carcinoma undergoing complete staging and in a sub-set of these patients undergoing fertility-conserving surgery.
Methods We retrospectively identified patients with ovarian clear cell carcinoma initially treated at our institution from January 1, 1996 to March 31, 2020. Survival was estimated using Kaplan–Meier curves and compared by log-rank test. Survival-associated variables were identified by Cox proportional hazards regression.
Results Of 182 patients, mismatch repair and p53 protein expression were assessed by immunohistochemistry on 82 and 66 samples, respectively. There were no significant differences in progression-free survival or overall survival between mismatch repair-deficient (n=6, including 4 patients with Lynch syndrome; 7.3%) and mismatch repair-proficient patients, whereas aberrant p53 expression (n=3; 4.5%) was associated with worse progression-free (p<0.001) and overall survival (p=0.01). Patients with stage IA/IC1 disease had a 95% 5-year overall survival rate (95% CI 88% to 98%); patients with stage IC2/IC3 disease had a similar 5-year overall survival rate (76%; 95% CI 54% to 88%) to that of patients with stage IA/IIB disease (82%; 95% CI 54% to 94%). There was no difference in 5-year overall survival in patients with stage IA/IC1 undergoing chemotherapy versus observation (94% vs 100%). Nine patients underwent fertility-sparing surgery and none experienced recurrence. Of five patients who pursued fertility, all had successful pregnancies.
Conclusions In patients with completely staged ovarian clear cell carcinoma, those with stage IA/IC1 disease have an excellent prognosis, regardless of chemotherapy. Aberrant p53 expression may portend worse outcomes. Additional investigation is warranted on the safety of fertility conservation in patients with stage IA/IC1 disease.

WHAT IS ALREADY KNOWN ON THIS TOPIC
In early-stage ovarian clear cell carcinoma, data are difficult to interpret as most research includes patients without comprehensive staging. International Federation of Gynecology and Obstetrics stage has been identified as an important predictor of outcomes, but there are few other prognostic indicators. Furthermore, it is unclear whether fertility conservation can safely be offered in select patients.

WHAT THIS STUDY ADDS
In patients with completely staged ovarian clear cell carcinoma, those with stage IA/IC1 disease have an excellent prognosis, regardless of chemotherapy. Approximately 7% of patients have mismatch repair-deficient disease, and although no difference in these patients’ outcomes is appreciated, the majority have Lynch syndrome. While aberrant p53 expression was found in 4.5% of cases, it may portend worse outcomes. Finally, fertility conservation may be considered in early-stage disease.

INTRODUCTION
Ovarian clear cell carcinoma is rare, representing 5–11% of ovarian carcinomas diagnosed in the USA. Ovarian clear cell carcinoma is histologically unique with distinct biology compared with other ovarian cancers; 57–81% and 19–22% of patients present with stage I or stage II disease, respectively. Ovarian clear cell carcinoma is diagnosed at a median age of 41 years, and the median age of presentation includes a median age of 41 years, and the median age of presentation includes a median age of 41 years.

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55 years, compared with 64 years for the more common serous type.\(^1\) It is less chemo-responsive than high-grade serous adenocarcinoma, and randomized trials of platinum-based therapies have demonstrated decreased progression-free survival in these patients versus non-clear cell histologies. Gynecologic Oncology Group trials 158, 172, and 182 reported 12-month progression-free survival of 44–65% in patients with optimally cytoreduced ovarian clear cell carcinoma compared with 71–73% in those with optimally cytoreduced non-ovarian clear cell carcinoma.\(^5\)\(^-\)\(^7\)

In early-stage disease, treatment patterns vary. European Society for Medical Oncology (ESMO) and National Cancer Care Network (NCCN) guidelines recommend pelvic and para-aortic lymphadenectomy in early stages, but this is inconsistently followed.\(^9\) In the MITO-9 study, lymphadenectomy was performed in only 54% of early-stage cases.\(^9\) Meanwhile, Surveillance, Epidemiology, and End Results (SEER) data suggest that 80% of stage I patients undergo lymphadenectomy.\(^10\) Patients with early-stage disease have an approximately 5% chance of nodal metastases (up to 38% with positive washings).\(^3\) Patients with undetected nodal metastases may be misclassified as stage I or II, with possible implications for post-operative treatment decisions and survival. Meanwhile, there are few known clinicopathologic features beyond stage that can help risk-stratify patients with clear cell carcinoma.

The surgical management of early-stage disease for women desiring fertility is unclear. ESMO states that fertility-sparing surgery can be offered for stage IA/IC1 low-grade serous, endometrioid, or mucinous ovarian carcinomas; however, ovarian clear cell carcinoma is not mentioned.\(^11\) Meanwhile, NCCN guidelines specify that fertility-sparing surgery is not recommended for these patients.\(^8\) Nevertheless, population-based studies suggest fertility conservation is still offered; in the MITO-9 trial, 7% of women with ovarian clear cell carcinoma underwent fertility conservation.\(^9\)

Given these uncertainties, we sought to assess outcomes in a large cohort of patients with early-stage ovarian clear cell carcinoma. While prior studies have included patients with presumed early-stage disease, we investigated patients with complete surgical staging, including lymph node assessment, and identified clinicopathologic and treatment factors that may be used to stratify risk, determined outcomes associated with post-operative chemotherapy, and described fertility conservation outcomes.

**METHODS**

**Case Selection**

We identified patients with a diagnosis of stage I and II ovarian clear cell carcinoma from January 1, 1996 to March 31, 2020 initially treated at Memorial Sloan Kettering Cancer Center who underwent complete surgical staging, including washings and lymph node biopsy. The inclusion time period was chosen as it corresponded to the formation of institutional databases that standardized patient data extraction. Exclusion criteria were lack of pathology review at our institution (n=25) and recurrent disease at time of initial evaluation at our institution (n=167). Patients who did not undergo staging (n=25) were excluded from survival analysis but were included in the report of outcomes associated with fertility conservation. All cases were diagnosed by a gynecologic pathologist and re-reviewed by another gynecologic pathologist to confirm diagnosis of ovarian clear cell carcinoma (Figure 1). The study was approved by our Institutional Review Board.

**Clinicopathologic Data**

Medical records were reviewed with a cut-off date of February 15, 2021. Stage was assigned following the International Federation of Gynecology and Obstetrics (FIGO) 2014 system. Tumor sections previously assessed for p53 and mismatch repair by immunohistochemistry underwent central pathology review to confirm classification (ie, p53 wild-type vs aberrant and mismatch repair immunohistochemical staining absent/deficient vs intact/retained). An additional 67 ovarian clear cell carcinomas not previously tested but for which tissue was available were assessed by immunohistochemistry for mismatch repair (n=37) and p53 (n=67) expression, as previously described.\(^12\) Aberrant p53 immunohistochemistry was defined as strong nuclear expression in >80% of tumor nuclei (overexpression), complete absence of expression in tumor cell nuclei with retained internal control (null), or unequivocal cytoplasmic expression.\(^12\) Mismatch repair deficiency was defined as loss of nuclear staining for any of the evaluated proteins (MLH1, PMS2, MSH2 and MSH6) in the presence of a positive internal control.\(^12\)

**Progression-Free and Overall Survival**

Clinicopathologic variables were evaluated for association with progression-free and overall survival, including age at diagnosis (< =50 or >50 years as a surrogate for menopausal status), race, adjuvant chemotherapy (yes or no), number of cycles of adjuvant therapy as determined by provider discretion in line with national guidelines, concurrent endometriosis, p53 immunohistochemical status, and mismatch repair deficiency by immunohistochemistry. Because patients with stage IA/IC1 disease were less likely to receive chemotherapy compared with patients with IC2–IIb disease (p=0.04), patients with IA–IC1 disease were combined into a lower-risk sub-group (n=120) and those with IC2, IC3, IIA, and IIB disease were combined into a higher-risk sub-group (n=62), consistent with prior studies.\(^10\)

**Statistical Analyses**

Survival analyses included progression-free survival (number of months between pathologic diagnosis and disease progression or last follow-up, whichever occurred first). There were no deaths before progression. Overall survival was defined as the number of months between pathologic diagnosis and death or last follow-up. Survival curves were estimated using the Kaplan–Meier method, and p values were generated using log-rank tests. For analyses
of primary treatment after surgery, landmark analysis, using 4 months as the landmark time, was applied to variables determined only after the date of diagnosis (eg, number of platinum cycles). p<0.05 was considered significant. All statistical analyses were performed using R version 4.1.1 (https://www.R-project.org/).

In accordance with the journal’s guidelines, we will provide our data for independent analysis by a selected team by the Editorial Team for the purposes of additional data analysis or for the reproducibility of this study in other centers if such is requested.

RESULTS
Study population
A total of 182 women were included in the study. Median patient age at diagnosis was 53 years (range 29–82), and 131 (72%) were white (Table 1). Forty-five percent (n=81) had stage IA disease, 21% IC1 (n=39), 9% IC2 (n=16), 14% IC3 (n=25), 5% IIA (n=9), and 7% (n=12) IIB disease; there were no IB cases. Surgeries were conducted by an open approach in 137 patients (75%) and by a minimally invasive approach (either robotic or laparoscopic) in 45 (25%). All patients underwent lymph node assessment with either sampling (n=80, 44%) or lymphadenectomy (n=102, 56%). Among patients who underwent lymph node sampling, the median number of pathologically assessed lymph nodes was eight (range 1–26) and, among those who underwent lymphadenectomy, the median number of pathologically assessed lymph nodes was 27 (range 14–75). Overall, 164 patients (90%) underwent omentectomy, 17 (9%) underwent lymph node biopsy, and one (<1%) did not undergo omental biopsy.

Factors Associated with Survival
Clinicopathologic characteristics were examined for association with progression-free and overall survival (Table 2 and Online supplemental table 1). On univariate analysis, p53-aberrant expression
Original research

and higher-risk stage were associated with worse progression-free survival (p<0.001 for both) and overall survival (p=0.01 and p<0.001, respectively). Although limited by sample size, all three patients with p53-aberrant tumors experienced recurrence at a median of 9.3 months, and two of the three patients died at 26.4 and 28.4 months after diagnosis. Notably, two of the three patients with p53-aberrant tumors presented with stage IA disease.

Although there were no significant differences in age, race, mismatch repair deficiency, or p53 status between patients with stage IA/IC1 and IC2–IIB disease, patients with higher-risk disease (stages IC2–IIB) received more cycles of post-operative chemotherapy (Online supplemental table 2). There was a significant association between disease stage and survival: patients with IA/IC1 disease had a 5-year overall survival rate of 94.9% (95% CI 88.2% to 97.8%); the 5-year overall survival rate for patients with IC2/IC3 disease was similar (75.8%; 95% CI 54.4% to 88.1%) to that of patients with IIA/IIB disease (82.1%; 95% CI 53.9% to 93.9%). After a median follow-up of 59.3 months (range 1.9–264.2), the 5-year progression-free survival rate was 88.2% (95% CI 80.5% to 93.0%) for the lower-risk (IA/IC1) group and 63.8% (95% CI 48.2% to 75.8%) for the higher-risk (IC2/IC3/IIA/IIB) group.

### Table 2 Progression-free survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>Progression (n)</th>
<th>5-year PFS rate (95% CI)</th>
<th>HR (95% CI)*</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 years</td>
<td>68</td>
<td>11</td>
<td>83.7% (71.6% to 91%)</td>
<td>1</td>
<td>0.214</td>
</tr>
<tr>
<td>≥50 years</td>
<td>114</td>
<td>26</td>
<td>78.3% (68.7% to 85.2%)</td>
<td>1.56 (0.77 to 3.17)</td>
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<tr>
<td>Race</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>White</td>
<td>131</td>
<td>27</td>
<td>80.4% (71.8% to 86.6%)</td>
<td>1</td>
<td>0.986</td>
</tr>
<tr>
<td>Non-white</td>
<td>34</td>
<td>6</td>
<td>83.2% (63.5% to 92.8%)</td>
<td>0.99 (0.41 to 2.42)</td>
<td></td>
</tr>
<tr>
<td>Stage (FIGO)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IA</td>
<td>81</td>
<td>7</td>
<td>90.7% (81.3% to 95.5%)</td>
<td>1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IC1</td>
<td>39</td>
<td>6</td>
<td>83% (65.9% to 92%)</td>
<td>1.87 (0.63 to 5.57)</td>
<td></td>
</tr>
<tr>
<td>IC2</td>
<td>16</td>
<td>5</td>
<td>67.7% (31% to 87.8%)</td>
<td>4.21 (1.34 to 13.30)</td>
<td></td>
</tr>
<tr>
<td>IC3</td>
<td>25</td>
<td>12</td>
<td>55.2% (29.7% to 74.7%)</td>
<td>7.16 (2.81 to 18.23)</td>
<td></td>
</tr>
<tr>
<td>IIA</td>
<td>9</td>
<td>4</td>
<td>53.3% (17.7% to 79.6%)</td>
<td>6.7 (1.96 to 22.94)</td>
<td></td>
</tr>
<tr>
<td>IIB</td>
<td>12</td>
<td>3</td>
<td>83.3% (48.2% to 95.6%)</td>
<td>3.5 (0.90 to 13.55)</td>
<td></td>
</tr>
<tr>
<td>Risk category</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk (IA/IC1)</td>
<td>120</td>
<td>13</td>
<td>88.2% (80.5% to 93%)</td>
<td>1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High risk (IC2/IC3/IA/IIB)</td>
<td>62</td>
<td>24</td>
<td>63.8% (48.2% to 75.8%)</td>
<td>4.37 (2.22 to 8.60)</td>
<td></td>
</tr>
<tr>
<td>Concordant endometriosis</td>
<td></td>
<td></td>
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<tr>
<td>Absent</td>
<td>60</td>
<td>10</td>
<td>80.9% (67% to 89.4%)</td>
<td>1</td>
<td>0.257</td>
</tr>
<tr>
<td>Present</td>
<td>122</td>
<td>27</td>
<td>80.2% (71.3% to 86.5%)</td>
<td>1.52 (0.73 to 3.14)</td>
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<tr>
<td>p53 IHC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aberrant</td>
<td>3</td>
<td>3</td>
<td>Not reached</td>
<td>1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Wild-type</td>
<td>63</td>
<td>13</td>
<td>84.2% (71.6% to 91.5%)</td>
<td>0.06 (0.02 to 0.25)</td>
<td></td>
</tr>
<tr>
<td>MMR IHC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retained</td>
<td>76</td>
<td>18</td>
<td>78.8% (66.5% to 87%)</td>
<td>1</td>
<td>0.815</td>
</tr>
<tr>
<td>Deficient</td>
<td>6</td>
<td>1</td>
<td>83.3% (27.3% to 97.5%)</td>
<td>0.75 (0.10 to 5.68)</td>
<td></td>
</tr>
<tr>
<td>Post-operative chemotherapy‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>15</td>
<td>2</td>
<td>92.9% (59.1% to 99%)</td>
<td>1</td>
<td>0.687</td>
</tr>
<tr>
<td>Received</td>
<td>165</td>
<td>34</td>
<td>79.8% (72.2% to 85.5%)</td>
<td>1.40 (0.34 to 5.86)</td>
<td></td>
</tr>
<tr>
<td>Platinum cycles‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>15</td>
<td>2</td>
<td>92.9% (59.1% to 99%)</td>
<td>1</td>
<td>0.687</td>
</tr>
<tr>
<td>1–3</td>
<td>19</td>
<td>0</td>
<td>100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;3</td>
<td>146</td>
<td>34</td>
<td>77.4% (69.2% to 83.7%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*If a variable contains certain levels event=0, then there is no HR or p value provided.
†P value obtained by applying permutation log-rank test with 5000 permutation times if events count n <3.
‡'Post-operative chemotherapy' and 'Platinum cycles' related variables are analyzed using landmark analysis with landmark time set to be 4 months.
FIGO, Federation of Gynecology and Obstetrics; IHC, immunohistochemistry; MMR, mismatch repair; PFS, progression-free survival.
to 75.8%) for the higher-risk (IC2–IIB) group (p<0.001; Figure 3A). The 5-year overall survival rate was 94.9% (95% CI 88.2% to 97.8%) for the lower-risk (IA/IC1) group and 77.9% (95% CI 62.0% to 87.8%) for the higher-risk (IC2–IIB) group (p<0.001; Figure 3B).

Among 120 patients with stage IA/IC1 disease, 118 were included in landmark analysis for treatment outcomes. Post-operatively, 13 patients (11.0%) underwent observation and 105 (89.0%) received chemotherapy. Of the patients receiving chemotherapy, 15 (14%) received 1–3 cycles and 90 (86%) received >3 cycles. All patients received a platinum doublet. When comparing patients with IA/IC1 disease who received chemotherapy versus those who did not, there was no difference in 5-year progression-free survival (89% vs 92%; p=0.90) or 5-year overall survival rates (94% vs 100%; p=NS).

Among 62 patients with IC2–IIB disease included in the landmark analysis, two (3.2%) declined additional chemotherapy. One patient had IC3 disease and is alive with disease after 73.0 months of follow-up. Among patients with IC2–IIB disease, four received 1–3 cycles and 56 received >3 cycles. None of the four patients with IC2–IIB disease who received 1–3 cycles experienced recurrence after a median follow-up of 21.6 months (range 13.3–55.8), while 23 of the 56 patients with IC2–IIB disease who received >3 cycles recurred (5-year progression-free survival rate 61%; 95% CI 45% to 74%).

Fertility Conservation
Nine patients underwent fertility-sparing surgery, eight of whom had complete staging including omentectomy. Seven patients underwent unilateral salpingo-oophorectomy with peritoneal biopsies and pelvic and para-aortic lymph node sampling and omentectomy, one patient underwent bilateral salpingo-oophorectomy with peritoneal biopsies and pelvic and para-aortic lymph node sampling and omentectomy with uterine preservation, and one patient underwent unilateral salpingo-oophorectomy without additional staging surgery such as lymph node assessment or omentectomy (this patient was excluded from survival analysis given her lack of surgical staging; however, her disease has not recurred after nearly 15 years of follow-up). Six patients had minimally invasive staging surgeries. Of surgically staged patients, two had stage IA, four had IC1, and two had IC2 disease. After surgery, seven of the nine patients received six cycles of carboplatin/paclitaxel, one received three cycles of carboplatin/paclitaxel, and one underwent observation.

None of the patients who underwent fertility-sparing surgery experienced recurrence after a median follow-up time of 95.4 months. Five patients pursued fertility, three with assisted reproductive technology including one patient who received donor egg in vitro fertilization after bilateral salpingo-oophorectomy. Of these five patients, all have had one or more successful pregnancies. Median time from completion of chemotherapy to conception was 29.8 months (range −0.3–39.5). Three of the nine patients had completion hysterectomy and none had residual disease on pathology.

DISCUSSION
Summary of Main Results
We assembled a completely surgically staged cohort to investigate the following important questions in the management of early-stage ovarian clear cell carcinoma: What clinicopathologic factors can be used to risk-stratify patients? What is the association between chemotherapy and outcomes in patients with fully staged IA–IIB disease? Is fertility conservation safe in carefully selected patients?

We found approximately 7% of patients had mismatch repair-deficient tumors, many of whom also had Lynch syndrome. While sample sizes were limited, we found patients with p53-aberrant disease may have worse outcomes. Meanwhile, we observed no difference in progression-free or overall survival associated with receipt of chemotherapy in 120 patients with stage IA/IC1 disease. Finally, we report that none of the nine patients undergoing fertility conservation recurred after a median follow-up of 95.4 months.

Results in the Context of Published Literature
Because of the known association between Lynch syndrome and ovarian clear cell carcinoma, we investigated the association of mismatch repair immunohistochemistry with survival outcomes.14 15 There was no survival difference between patients with mismatch repair-deficient compared with mismatch repair-proficient tumors. Among tumors from 82 patients evaluated by mismatch repair immunohistochemistry, six (7.3%) were mismatch...
repair-deficient and four of five patients with germ line testing had Lynch syndrome. This study adds to a growing body of literature showing mismatch repair deficiency is associated with ovarian clear cell carcinoma.\textsuperscript{16,17} This has implications for Lynch-associated cancer screening, cascade testing, and possibly candidacy for immunotherapy for patients with this tumor type. We also observed poor progression-free and overall survival in patients with p53-aberrant tumors despite early-stage disease, although the sample of p53-aberrant ovarian clear cell carcinomas was small.

To better understand the association between chemotherapy and survival in early-stage disease, we separated patients into low-risk (IA/IC1) and high-risk (IC2–IIb) groups. There were no significant differences in progression-free or overall survival associated with chemotherapy receipt in patients in the low-risk group, consistent with the literature. A retrospective study of 6107 patients with stage IA–IC1 disease (86% of whom underwent lymphadenectomy) found no survival benefit to adjuvant chemotherapy in this subgroup.\textsuperscript{18} Additional retrospective studies have also reported little benefit to chemotherapy in early-stage disease.\textsuperscript{19–21} Our findings from this study of 120 patients with low-risk disease also suggest that chemotherapy can be deferred in patients with fully staged IA–IC1 disease. The recommendation for observation in IC1 disease was integrated into ESMO and NCCN guidelines for patients with stage IA–IC1 ovarian clear cell carcinoma in 2022.\textsuperscript{8,11} Until 2022, however, the NCCN recommended intra-venous chemotherapy for all patients with greater than stage IA disease.\textsuperscript{8}

We also sought to report on outcomes of patients desiring fertility conservation. The ESMO 2019 ovarian cancer guidelines do not provide recommendations for fertility-sparing surgery specific to ovarian clear cell carcinoma, and NCCN guidelines specifically recommend against fertility conservation in this setting.\textsuperscript{8,11} Our findings support emerging evidence that fertility-sparing surgery may be considered in select patients. We report on nine patients who underwent fertility conservation, none of whom experienced recurrent disease after a median follow-up of 95.4 months. The literature is limited with regard to fertility conservation in this patient population: a National Cancer Database analysis of 33 women with stage IA and 24 women with stage IC ovarian clear cell carcinoma found no difference in survival between patients undergoing fertility-sparing surgery versus radical cytoreduction, although lymphadenectomy was deferred in nearly half of the cases.\textsuperscript{22} A systematic review of 132 patients with stage IA/IC disease undergoing fertility-sparing surgery reported a 15% relapse rate; however, the analysis did not account for whether patients were fully staged.\textsuperscript{22} Meanwhile, the MITO-9 study of 240 patients with ovarian clear cell carcinoma reported 7.1% of patients underwent fertility-sparing surgery, but it did not report on what proportion recurred.\textsuperscript{9}

**Strengths and Weaknesses**

Many of the limitations of this study are inherent to investigations of rare tumor types. Small sample sizes limit the strength of conclusions regarding association of survival outcomes with certain variables, including p53 status, mismatch repair deficiency, and fertility conservation. We sought to mitigate this by performing additional p53 and mismatch repair immunohistochemistry on available samples, but population sizes remained small. Nevertheless, we hope the data reported here add to a growing body of literature that can inform the care of women with this rare disease. While we attempted to limit referral and selection bias in the study design by including only patients seen at our institution from time of diagnosis who underwent surgical staging, it is possible additional variables were unaccounted for, which may have biased certain therapeutic decisions such as the use of chemotherapy or decision to offer fertility conservation. Finally, this study spanned nearly three decades, during which time many aspects of ovarian cancer management have changed, including advancements in radiographic imaging and increased use of minimally invasive surgery.

**Implications for Practice and Future Research**

Despite the above limitations, data reported here may facilitate continued refined ovarian cancer management guidelines as well as future systematic reviews and meta-analyses. The data suggest that mismatch repair deficiency can be observed in ovarian clear cell carcinomas, which may have implications for both treatment and cascade testing in patients who are germline mismatch repair-deficient. Additionally, larger studies are required to assess whether p53 immunohistochemistry could be used to identify early-stage patients at higher risk of recurrence who should undergo more intensive surveillance. As such, we suggest mismatch repair and p53 immunohistochemical assessment of all ovarian clear cell carcinomas. Furthermore, our successful conservation of fertility in nine patients suggests that national guidelines should consider including fertility conservation as an option in carefully selected women with early-stage ovarian clear cell carcinoma.

**CONCLUSIONS**

The rarity of ovarian clear cell carcinoma along with its frequent diagnosis in younger patients desiring fertility can complicate management. Providers are often forced to navigate limited data when triaging appropriately staged patients to chemotherapy or fertility conservation. We report a single-institution experience in a population of fully staged patients and introduce evidence suggesting mismatch repair and p53 immunohistochemistry may be warranted in the workup of early-stage disease. We reinforce prior evidence that chemotherapy provides little benefit to patients with stages IA/IC1 ovarian clear cell carcinoma. Finally, we report on the outcomes of nine patients who safely underwent fertility-sparing surgery. Moving forward, multi-institutional studies that leverage larger patient populations may be necessary to provide additional insight into these questions.

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