Evaluation of Outcomes of Mucinous Ovarian Cancer Treated at a Tertiary Care Cancer Hospital in Pakistan

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Abstract

Objective To evaluate the clinicopathological features and survival outcomes of mucinous ovarian cancer (MOC) patients in an Asian population.

Study Design Descriptive observational study.

Place and Duration of Study Shaukat Khanum Memorial Cancer Hospital, Lahore, Pakistan, from January 2001 to December 2016.

Methods Data of MOC were evaluated for demographics, tumor stage, clinical characteristics, tumor markers, treatment modalities, and outcomes from electronic Hospital Information System.

Results Nine-hundred patients with primary ovarian cancer were reviewed, out of which 94 patients (10.4%) had MOC. The median age was 36 ± 12.4 years. The most common presentation was abdominal distension 51 (54.3%), while the rest presented with abdominal pain and irregular menstruation. Using FIGO (The International Federation of Gynecology and Obstetrics) staging, 72 (76.6%) had stage I, 3 (3.2%) stage II, stage III in 12 (12.8%), and 7 (7.4%) had stage IV disease. The majority of patients 75 (79.8%) had early-stage (stage I/II), while 19 (20.2%) presented with advanced-stage (III & IV). The median follow-up duration was 52 months (range 1–199 months). Among patients with early-stage (I&II), 3- and 5-year progression-free survival (PFS) was 95%, while for advanced stage (III&IV), PFS was 16% and 8%, respectively. The overall survival (OS) in early-stage I&II was 97%, while for advanced stages III & IV, the OS was 26%.

Conclusion MOC is a challenging and rare subtype of ovarian cancer requiring special attention and recognition. Most patients treated at our center presented with early stages and had excellent outcomes, while advanced-stage disease had dismal results.

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Keywords ► mucinous ovarian cancer ► rare subtype

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Introduction

Epithelial ovarian cancers (EOC) are the second-most common gynecologic malignancy. The main subtypes are serous, mucinous, endometrioid, and clear cell carcinomas. These types show significant differences in clinical, genetic, and molecular behaviors. Mucinous ovarian cancer (MOC) is a rare subtype of malignant ovarian cancer. It accounts for 3 to 10% of all epithelial ovarian cancers. MOC has a different natural history, biology, behavior, and molecular profile, with different chemotherapy responses compared with other histological subtypes. It can primarily be of ovarian origin or metastatic from the gastrointestinal (GI) tract. Previously, there was a dilemma in finding the exact pathology because of limited diagnostic techniques and knowledge about the disease. With recent advancements in pathology, gene expression profiling, identification of subtypes and various modalities available for exploring the GI tract, it has become possible to find the precise origin of mucinous tumors. The unilateral nature and increase in size indicates that it is of ovarian origin. Diagnosis is often made in the early stages as it usually presents with huge abdominal masses. MOC is mostly diagnosed in patients at a younger age than patients with other types of epithelial ovarian cancers and the only clinical risk factor associated is tobacco smoking.

Aaround 65 to 80% of MOCs are stage I or II, according to the FIGO staging system. MOC treatment is the same as other histological subtypes, i.e., upfront debulking surgery where possible, followed by platinum-based chemotherapy when indicated. Twenty-six percent of MOC are diagnosed in younger females who are less than 44 years of age, and fertility-sparing surgery (FSS) with curative intent is offered to eligible patients. Early-stage disease carries a better prognosis than the advanced stage because of less chemotherapy sensitivity of MOC. The median survivals of stage III and IV MOC disease are only up to 15 to 33 months compared with 50 months for advanced stage serous and endometrioid subtypes of EOC. This study highlights the incidence, tumor characteristics, management, and outcomes of MOC treated at our institute. We hypothesized that our results would be different from western data, considering resource limitation with mainly non-availability of molecular profiling/targeted agents.

Materials and Methods

Between January 2001 and December 2016, all patients who presented to Shaukat Khanum Memorial Cancer Hospital & Research Center (SKMCH&RC), Lahore, Pakistan, with Stage I to IV MOC were included in the study. Patient's data were extracted from the electronic hospital information system after getting approval from the Institutional Review Board (IRB). The need for patient-informed consent was waived off by IRB because of the retrospective nature of the study. All the patients had initial diagnostic surgery performed outside SKMCH&RC by gynecologists, upon confirmation of malignancy they were referred to our center. Here, the pathologies were reviewed by SKMCH&RC pathology laboratory, and then they were accepted into our hospital. Mixed histologies were excluded. The majority of our patients underwent upper and lower GI endoscopies. All our patients were adequately staged. Computed tomography (CT) scans were used for radiological staging. All cases were discussed in multi-disciplinary team (MDT) meeting for treatment planning after the completion of diagnostic work up as per the hospital policy. Those patients who were planned for surgery in MDT, their surgeries were performed by a gynecology surgeon. Patients with stage IA had fertility sparing surgery in which unilateral salpingo-oophorectomy, pelvic washings, omentectomy, peritoneal biopsies, pelvic and para-aortic lymphadenectomy, and appendectomy if there was suspicion of appendix being involved were performed. While all others who underwent surgery had radical surgery performed as per the ovarian protocol. The most common chemotherapy regimen used was carboplatin/paclitaxel; however, in a few patients, capecitabine and oxaliplatin were also used. It was as per treating the oncologist's choice. Standard doses of chemotherapy were used. All patients were followed up by CT scans and tumor markers CA-125 and CEA. The demographics, age, tumor characteristics, tumor markers, details of interventions, and outcomes were recorded in the data analysis software.

Statistical Analysis

Statistical Package of Social Sciences (SPSS) software (version 20.0; Chicago, IL, USA) was used for statistical analysis of the data. Mean ± standard deviation was used for continuous variables, while frequencies and percentages were reported for categorical variables. Progression-free survival (PFS) was defined as the time between the date of diagnosis and the date of progression, death or last follow-up. The overall survival (OS) was the interval between diagnosis and death from any cause or last follow-up. The Kaplan–Meier method was used to estimate survival as a function of time, and survival differences were analyzed using the log-rank test.

Results

Ninety-four patients with a histologically confirmed diagnosis of MOC were identified. There was no history of smoking in any of our patients. Patient and tumor characteristics are outlined in Table 1. The largest tumor size recorded was 40 cm. Most of the patients, 42 (44.7%), had right-sided tumors. The most common metastatic site seen was omentum in 10 (10.6%) patients. The majority of the patients, 51 (54.3%), presented with abdominal distension. Of most of our patients, 72 (76.6%) had stage I at diagnosis. Eighty-six patients (91.4%) had ECOG PS 0–1. Investigations and treatment modalities are outlined in Table 2. Diagnostic upper and lower GI endoscopies were done in 74 (78.7%) patients. FSS was done in 27 (28.7%) patients. The most commonly used first-line chemotherapy in our patients was carboplatin and paclitaxel. Neoadjuvant chemotherapy was given in 14 (14.9%), 40 (42.6%) had adjuvant chemotherapy, while 40
(42.6%) had no chemotherapy as the majority of patients had stage I disease (Table 2).

Overall, in 74 (78.7%) patients, the disease was in remission, 9 (9.6%) had relapsed, and 11 (11.7%) had progressive disease. Out of 94 patients, 78 (83%) were alive, while 16 (17%) had died.

Among patients having stage I disease, 4 (5.6%) patients relapsed, in stage II no relapses were seen, while 10 (83.3%) patients had relapse or progression in stage III, 7 (100%) patients with stage IV had disease progression.

The 3- and 5-years PFS for early-stage (I&II) was 95%, while for advanced stage (III&IV), 3-year PFS was 16%, and 5-year PFS was 8%. The median PFS for early-stage (I&II) was 59 months while for advanced stage (III&IV) was 3 months. The 3- and 5-year OS for early-stage (I&II) was 97% and for advanced stages (III&IV) 26%. The median OS for early stage (I&II) was 59 months while for advanced stage (III&IV) was 16 months (Table 3).

The 3- and 5-year PFS and OS in months and percentages for individual stages I, II, III, IV are shown in Table 4.

The survival graphs are shown in Fig. 1A–D.

Among patients undergoing FSS, radical completion surgery, and only suboptimal surgeries done for diagnostic purposes outside hospital is mentioned in Table 5.

**Discussion**

Ovarian cancer is the fifth commonest cancer in Pakistani women.\(^4\)

The mucinous histology is rare. In our study, in 16 years, only 94 cases of 900 EOC were found, comprising 10.4% of the total cases. As a result of this, conducting randomized controlled trials of sufficient statistical power and exploring potential therapeutic targets is difficult.

We previously reported a 13.4% frequency of MOC among 544 EOC patients from our center.\(^5\) To the best of our knowledge, this is the first study of primary mucinous ovarian cancer as a separate entity, from Pakistan.

The exact incidence of MOC is controversial, as there is no reliable method to distinguish between primary MOC and mucinous adenocarcinoma metastatic to the ovary. The incidence ranges from 3 to 11.9% in different studies.\(^1,11\) Different algorithms incorporating size, laterality, immunohistochemical markers, morphological characteristics such as expansile and infiltrative growth patterns, and inspection of digestive organs have been used to differentiate between primary and metastatic MOC of the ovary.\(^7,11,16\)
The diagnosis of primary MOC requires careful pathological and diagnostic assessment. About 80% of the mucinous carcinomas of the ovary are metastatic from another site. Hence comes the role of diagnostic upper and lower GI endoscopies. In an earlier study done at our center, 17.6% of patients who were initially suspected to have primary

**Table 3** Survival outcomes in early and advanced stage diseases

<table>
<thead>
<tr>
<th>Stage group</th>
<th>3 years PFS (%)</th>
<th>5 years PFS (%)</th>
<th>3 years OS (%)</th>
<th>5 years OS (%)</th>
<th>PFS months</th>
<th>OS months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early (I and II)</td>
<td>95</td>
<td>95</td>
<td>97</td>
<td>97</td>
<td>59</td>
<td>59</td>
</tr>
<tr>
<td>Advanced (III and IV)</td>
<td>16</td>
<td>8</td>
<td>26</td>
<td>26</td>
<td>3</td>
<td>16</td>
</tr>
</tbody>
</table>

Abbreviations: 3 years, 3 years; 5 years, 5 years; OS, overall survival; PFS, progression free survival.

**Table 4** Stage-wise survival outcomes

<table>
<thead>
<tr>
<th>Stage</th>
<th>3 years PFS (%)</th>
<th>5 years PFS (%)</th>
<th>3 years OS (%)</th>
<th>5 years OS (%)</th>
<th>PFS months</th>
<th>OS months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>95</td>
<td>95</td>
<td>97</td>
<td>97</td>
<td>55 (1–199)</td>
<td>57 (1–199)</td>
</tr>
<tr>
<td>Stage II</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>81 (81–99)</td>
<td>81 (81–99)</td>
</tr>
<tr>
<td>Stage III</td>
<td>25</td>
<td>12</td>
<td>28</td>
<td>28</td>
<td>4 (1–78)</td>
<td>15 (3–78)</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Could Not reach</td>
<td>Could Not reach</td>
<td>19</td>
<td>Could Not reach</td>
<td>3 (1–19)</td>
<td>19 (8–42)</td>
</tr>
</tbody>
</table>

Abbreviations: 3 years, 3 years; 5 years, 5 years; OS, overall survival; PFS, progression free survival.

**Fig. 1** (A) Stage-wise progression-free survival (PFS). (B) Stage-wise overall survival (OS). (C) Progression-free survival with regards to surgery. (D) Overall survival with regard to surgery.

The diagnosis of primary MOC requires careful pathological and diagnostic assessment. About 80% of the mucinous carcinomas of the ovary are metastatic from another site.
Mucinous ovarian cancer (MOC) is a disease in constant evolution. Early-stage MOC is associated with excellent outcomes with 5-year survival rates approaching 90%, whereas the advanced stage disease is associated with inferior prognosis. Data from seven prospective studies involving stage III–IV patients showed a median OS of 14.6 months. The reason for a good prognosis in the early stages is the low propensity of nodal and peritoneal metastasis. In contrast, poor prognosis in advanced-stage disease may be attributed to low chemotherapy sensitivity of this disease. Our study showed a median OS of 57.5 months for stage I disease (range 1–199 months), while 81 months for stage II disease probably because of lesser number of patients with stage II disease, and second, all patients in stage II received chemotherapy. For stage III, the median OS was 15 months, and for stage IV disease, the median OS was 19 months. Paitasides et al found OS of 33.6 and 23.4 months, respectively, for stage III and IV disease. Morrice et al reported the median OS of 33 and 12 months for stage III and IV MOC, respectively. For stage III and IV disease, PFS was 4 and 3 months, respectively, in our study. In a retrospective study, the PFS reported was 13 months for stage III and 6.9 months for stage IV. In another study, the median PFS for stage III and IV MOC was 5.7 months. These differences are not statistically significant. The 5-year OS reported for stages I&II combined are 86%, while for advanced stage III&IV are 28%. Our study showed 5-year OS for early stage I&II of 97%, while for advanced stage III&IV the OS was 26%.

In recent years, molecular testing has enhanced the understanding of the biology of primary mucinous ovarian cancer, which may have an impact on the treatment and outcomes of MOC. The MOC is associated with defects in KRAS, BRAF, HER2, EGFR, ALK, MSI, PTEN, PI3KCA, and Src alterations. Genetic alterations are shifting the paradigm of MOC toward targeted therapies. Unfortunately, the molecular testing was missing in our patients, probably because the study included the patients diagnosed until 2016 and second because of cost constraints.

There were some limitations of our study, including small sample size from a single institution and retrospective analysis. Twenty-six percent patients had diagnostic surgery done outside surgery, where there may lack proper surgical oncology skills. MOC was diagnosed on surgical specimens or referred blocks sent to our pathology laboratory, with incomplete information in some cases. In several cases, the exact size of the tumor and sometimes even laterality was not mentioned. Similarly, in several cases pathological grade and subtypes (expansile and infiltrative) were also not available.

On the contrary, this study has probably the largest patient number and previously no such research has taken place in Pakistan, which explicitly sees clinicopathological characteristics and outcomes of MOC.

**Conclusion**

Mucinous ovarian cancer is a disease in constant evolution. Results of our study show that the OS is higher for patients presenting with early stage disease as compared with those

<table>
<thead>
<tr>
<th>Table 5 Survival outcomes with regard to surgery performed</th>
<th>PFS</th>
<th>OS %</th>
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<tbody>
<tr>
<td>FSS</td>
<td>89%</td>
<td>95</td>
</tr>
<tr>
<td>Radical cytoreductive surgery</td>
<td>89%</td>
<td>92</td>
</tr>
<tr>
<td>Only diagnostic surgery</td>
<td>39%</td>
<td>47</td>
</tr>
</tbody>
</table>

Abbreviations: FSS, fertility-sparing surgery; OS, overall survival; PFS, progression free survival.
with non-mucinous histologic subtypes of ovarian cancer. However, for women with stage III/IV, mucinous ovarian cancer prognosis is poor with significantly lower survival rates. These results correspond with published western literature. Because of limited resources leading to lack of use of targeted therapy, these results seem encouraging and outcomes could have been better with availability of targeted therapy such as bevacizumab.

**Funding**
None.

**Conflict of Interest**
None declared.

**References**