Primary Ovarian Malignant Mixed Mullerian Tumour: Analysis of 17 Cases and Review of the Literature

Tounsi Nesrine 1, Chemlali Molka 1, Abdelwahed Nawel 1, Triki Amira 2, Doghri Rhaoudha 2, Ben Hassouona Jamel 1 and Rahel Khaled 1

1Department of Oncologic Surgery, Institute Salah Azaiz, Boulevard of Avril, Tunis, Tunisia
2Department of Pathology, Institute Salah Azaiz, Boulevard of Avril, Tunis, Tunisia

Introduction: Carcinosarcomas called also malignant mixed Mullerian tumors (MMMTs) are rare tumors with a poor prognosis and fast progression. Due to the rarity of MMMTs, only a few studies were published up to now.

Material and method: We report 17 cases of ovarian carcinosarcoma identified from 2000–2014 through tumor registry and pathology records from our institute (Salah Azaiz Tunisia). Fisher exact test was used to compare categorical variables. The Kaplan–Meier method was used to calculate survival. P values of <0.05 were considered statistically significant.

Result: All 17 patients underwent initial surgical treatment. Stage distribution was as follows: 3 stage I, 1 stage II, 11 stages III, and 2 stages IV. After surgery, 5 patients had no residual tumor with complete surgical staging. An improved survival was observed in patients treated with optimal cytoreductive surgery with no residual tumor (p=0.04). The majority of patients’ demonstrated homologous histology. No difference in survival was observed between the two groups (p=0.386). All patients but two underwent adjuvant chemotherapy. During the first year, 30% of patients died of the disease. OS for early stage (stages I and II) was better than OS for advanced stage (stages III and IV) (P=0.386).

Conclusion: We think that aggressive surgical treatment with optimal cytoreductive and no residual tumor may play an important role to achieve better results. However, other alternative systemic therapeutic approaches should be sought for patients with carcinosarcoma of the ovary.

Keyword: Ovarian carcinosarcoma; Malignant mixed; Mullerian tumor of ovary; Platinum-based chemotherapy

Introduction

Carcinosarcomas called also malignant mixed Mullerian tumors (MMMTs) are rare tumors with a poor prognosis [1-3]. These tumors can arise from different origins along the female genital tract and in the peritoneum; the most common site is the uterus, but they can also arise from the ovary, vagina, cervix and fallopian tubes [1,2]. It represents one of the most highly aggressive forms of ovarian cancer with fast progression and poor survival rate [3]. Due to the rarity of MMMTs, a few studies were published up to now. The purpose of this study was to identify all patients with diagnosis of ovarian carcinosarcoma treated at our institution in order to determine the response rates to chemotherapy, recurrence-free survival and overall survival (OS).

Material and Method

17 cases of ovarian carcinosarcoma were identified from 2000-2014 through tumor registry and pathology records from our institute (Salah Azaiz Tunisia). Clinical data including ages, sex, stage, surgery, chemotherapy treatment, and survival were collected from retrospective chart reviews. The surgical stage was assigned based on the International Federation of Gynecology and Obstetrics (FIGO). Statistical analysis was performed with Spss 15 software. Fisher exact test was used to compare categorical variables. The Kaplan-Meier method was used to calculate survival P values of <0.05 were considered statistically significant.

Results

The median age at diagnosis was 60 years (45-78). All 17 patients underwent initial surgical treatment (Clinical data of patients was show in Table 1). All patients were postmenopausal at diagnosis. The symptoms most commonly reported in our series were: 8 with a palpable pelvic mass at diagnosis, ascites in 8 patients and bowel sub- obstruction in 3 cases. At the time of diagnosis, CA-125 serum level was measured in 15 cases and was positive in 9 with a mean value 275. 6 IU/ml. No difference in survival was observed between patients who were CA-125 positive and those who were CA-125 negative (29 vs. 20 months; p=0.552). 14 women were evaluated by computer tomography scans of the thorax; abdomen and pelvis before surgery, showing the presence of peritoneal carcinomatosis in 5 cases. All other patients were evaluated by transvaginal ultrasound.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Stage</th>
<th>Surgical intervention</th>
<th>Residual disease after surgery</th>
<th>First treatment</th>
<th>Response to first chemo</th>
<th>Second treatment</th>
<th>Response to second chemo</th>
<th>Months of survival</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>IA</td>
<td>TAH, omentectomy, appendectomy, peritoneal biopsies, peritoneal washing + CLA</td>
<td>NVR</td>
<td>PEI*6</td>
<td>CR</td>
<td>N/A</td>
<td>N/A</td>
<td>110</td>
<td>NED, no evidence of disease</td>
</tr>
<tr>
<td>2</td>
<td>IIC</td>
<td>TAH+ omentectomy, appendectomy + douglassectomie + currage</td>
<td>NVR</td>
<td>PEI*03</td>
<td>CT stopped because of renal failure</td>
<td>NO</td>
<td>-</td>
<td>12</td>
<td>Died of ICD</td>
</tr>
<tr>
<td>3</td>
<td>IIIB</td>
<td>TAH, omentectomy, appendectomy, peritoneal biopsies, peritoneal washing &gt;1-cm (subdiaphragmatic)</td>
<td>PEI*06</td>
<td>PD</td>
<td>NO</td>
<td>-</td>
<td>12</td>
<td>DOD</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>IIIB</td>
<td>TAH+ resection grele + sigmoide</td>
<td>NVR</td>
<td>PEI*03</td>
<td>PD</td>
<td>CT Stoped because of renal failure</td>
<td>Metastaique Poumon</td>
<td>10</td>
<td>DOD</td>
</tr>
<tr>
<td>5</td>
<td>IA</td>
<td>TAH+ omentectomy, appendectomy + Currage</td>
<td>NVR</td>
<td>PEI*6</td>
<td>CR</td>
<td>N/A</td>
<td>N/A</td>
<td>45</td>
<td>Alive NED</td>
</tr>
<tr>
<td>6</td>
<td>IIIB</td>
<td>TAH+ colon sigmoide</td>
<td>&gt;1-cm</td>
<td>PEI*6</td>
<td>CR</td>
<td>Relapsed at 24 months (pelvic masse)</td>
<td>Surgery + PC 6</td>
<td>Progression</td>
<td>36</td>
</tr>
<tr>
<td>7</td>
<td>IV</td>
<td>biopsy</td>
<td>-</td>
<td>PEI*3 (neoadjuvant)</td>
<td>CT stopped because of renal failure</td>
<td>no</td>
<td>-</td>
<td>9</td>
<td>DOD</td>
</tr>
<tr>
<td>8</td>
<td>IV</td>
<td>biopsy</td>
<td>-</td>
<td>PEI*6 neoadjuvant</td>
<td>PD</td>
<td>NA</td>
<td>NA</td>
<td>11</td>
<td>DOD</td>
</tr>
<tr>
<td>9</td>
<td>IIIC</td>
<td>TAH, omentectomy, appendectomy, peritoneal biopsies, peritoneal washing &lt;1CM</td>
<td>PEI*6</td>
<td>PD</td>
<td>NA</td>
<td>NA</td>
<td>13</td>
<td>DOD</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>III</td>
<td>TAH + douglassectomie + omentectomy, appendectomy + currage</td>
<td>NVR</td>
<td>PEI*3</td>
<td>PD</td>
<td>NA</td>
<td>NA</td>
<td>16</td>
<td>DOD</td>
</tr>
<tr>
<td>11</td>
<td>IIIC</td>
<td>TAH+ omentectomy, appendectomy &gt;1-cm</td>
<td>NO</td>
<td>NA</td>
<td></td>
<td></td>
<td>&lt;1</td>
<td>Died (peritonit)</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>IIIC</td>
<td>TAH+ colon sigmoide</td>
<td>&lt;1CM</td>
<td>TAX-CBDCA*6</td>
<td>PD</td>
<td></td>
<td></td>
<td>17</td>
<td>DOD</td>
</tr>
<tr>
<td>13</td>
<td>IIIC</td>
<td>TAH, omentectomy, appendectomy, peritoneal biopsies, peritoneal washing &gt;1CM</td>
<td>PEI*6</td>
<td>CR</td>
<td></td>
<td>NED</td>
<td>8</td>
<td>NED</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>IIIC</td>
<td>TAH, omentectomy, appendectomy, peritoneal biopsies, peritoneal washing &gt;1CM</td>
<td>PEI*6</td>
<td>PD</td>
<td></td>
<td>Holoxan platine</td>
<td>PD</td>
<td>9</td>
<td>DOD</td>
</tr>
<tr>
<td>15</td>
<td>IIIC</td>
<td>TAH, omentectomy, appendectomy, &lt;1CM</td>
<td>PEI*6</td>
<td>CR</td>
<td>Relapsed at 120 months</td>
<td>Polymetastique (foie)</td>
<td>125</td>
<td>DOD</td>
<td></td>
</tr>
</tbody>
</table>
Table 1: Clinical data of patients with carcinosarcoma of the ovary.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment</th>
<th>Residual Tumor</th>
<th>Cytoreduction</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>TAH, omentectomy, appendectomy, peritoneal biopsies, peritoneal washing</td>
<td>NVR</td>
<td>TAX-CBDCA*6</td>
<td>CR</td>
</tr>
</tbody>
</table>

Abbreviations: NVR: No visible residual; PI, platinum/ifosfamide; CR, complete response; N/A, not applicable; NED, no evidence of disease; DOD = died of disease; PC, paclitaxel/carboplatin; PD = progressive disease; TAX-CBDCA: taxol and carboplatin; ICD=inter current disease.

Stage distribution was as follows: 3 stage I, 1 stage II, 11 stages III, and 2 stages IV. Fifteen patients were treated with a surgical approach that consisted of a total abdominal hysterectomy with bilateral adnexectomy, omentectomy, appendectomy and peritoneal washing. Frozen section was realized for all patients, confirming malignant mesenchymal tumor. Among these patients, 4 had bowel resection and one had partial cystectomy as result optimal cytoreduction was achieved. The remaining patient had only peritoneal biopsies. After surgery, 5 patients had no residual tumor with complete surgical staging. An improved survival was observed in patients treated with optimal cytoreductive surgery with no residual tumor compared to residual tumors (32 vs. 22 months; p=0.04). The histological report revealed that the majority of patients demonstrated homologous histology compared with patients with heterologous histology (13 patients vs. 5). No difference in survival was observed between the two groups (p=0.386) (Figure 1).

All patients but tow underwent adjuvant chemotherapy. One because she died a few days after surgery due to septic shock secondary to peritonitis and one due to advanced age. No néo-adjuvant chemotherapy was performed.

Figure 1: Kaplan-Meier survival analysis, comparing the life of patients. Between homologous group vs. heterologous groups.

Figure 2: Kaplan-Meier survival analysis, comparing the life of patients. Between early and advance stage.

The three patients had developed a pelvic mass, and they received second line of chemotherapy. Among the five women who achieved complete response to PEI chemotherapy, 2 had recurrence with distant metastases, one after 120 months and the second after 24 months (range: 5-15). Palliative treatment has been indicated. Concerning the two women who received 6 cycles of Taxol and Carboplatin, one had a complete response and the second had progressive disease. As for case
had progressive disease. During the follow-up. Whereas case 2 had disease recurrence eleven months later. During the first year, 30% of patients died of the disease. OS for early stage (stages I and II) was better than OS for advanced stage (stages III and IV) (39 months vs. 22 months) respectively but this was not statistically significant \( P=0.386 \).

**Discussion**

Carcinosarcoma of ovarian affects very often postmenopausal women [4]. As well; all 17 women in our study were postmenopausal at the time of diagnosis, with an average age of 60 years. Often, most patients presented with a palpable pelvic mass at diagnosis [4].

The clinical and radiological findings of ovarian carcinosarcoma and ovarian epithelial tumors were similar and it’s hard to distinguish between them, making their preoperative suspicion impossible [5]. Histologically, MMMT of the ovary were classified as heterologous or homologous subtype according to the presence or absence of a stromal component containing mesenchymal tissue not normally found in the ovary such as bone or cartilage [6]. Some studies reported that heterologous carcinosarcomas carried a worse prognosis, but recent evidence suggests that this histological feature does not significantly alter prognosis [7]. Sood et al. reported that patients with homologous sarcomatous elements had a significantly better survival compared to those with tumor containing heterologous elements [8]. In our series, the majority of patients demonstrated homologous histology (13 compared with 5 patients with heterologous histology). No difference in survival was observed between the two groups (\( P=0.386 \)). As well, the type of the sarcomatous element (heterologous vs. homologous) was not found to be a prognostic factor. In many studies, the majority of patients presented with advanced stage so feasibility of optimal cytoreductive surgery is not always possible [9-11]. That’s why; the advanced stage was correlated with worse prognostic [4]. Similarly in our study, the majority of patients had advanced stages (11 were stage IIIC and 2 stages IVB). It that aggressive surgical treatment with optimal cytoreductive and no residual tumor may play an important role to achieve a better result. As well, an improved survival was observed in patients treated with optimal cytoreductive surgery with no residual tumor compared to patients with residual tumors, and it was statistically significant. The optimal therapeutic management of patients with ovary carcinosarcomas remains unclear due to their rarity.

The role of cytoreductive surgery has not been prospectively evaluated. Only retrospective study support that complete cytoreduction (hysterectomy, bilateral salpingo-ophorectomy, omentectomy, pelvic and para-aortic lymph node dissection) with optimal debunking surgery, without residual disease should be the goal of surgical treatment because it can improve best outcome [12-14]. However, some studies report that even after optimal surgical cytoreduction, survival was not affected [11,15]. In our study, five patients from fifteen had no residual tumor with complete surgical staging. An improved survival was observed in patients treated with optimal cytoreductive surgery with no residual tumor compared to residual tumors (32 vs. 22 months; \( P=0.04 \)). Then, from fifteen patients who had adjuvant therapy, thirteen had (PEI) and only two patients were considered for PEI chemotherapy, for those with disease recurrence with distant metastases. Concerning the both women who received 6 cycles of Taxol and Carboplatin, one had a complete response and the second had progressive disease. During the first year, 30% of patients died of the disease. Currently, no clear consensus has been established to get a conclusion about the best adjuvant therapy for patients with OC [13]. As well, the optimal adjuvant chemotherapy of ovarian carcinosarcoma is debatable [10,16]. In fact, the benefit of the chemotherapy was evaluated on a few non-randomized prospective studies and some retrospective analysis. Some data have led to the conclusion that the chemo-sensitivity of OCs is less than serous epithelial ovarian cancer [13,17]. More particularly, no active agent shows to have a good result in patients with progressive disease after first-line chemotherapy [18]. In the literature, Paclitaxel/platinum-based chemotherapy has emerged as the first-line chemotherapy for the treatment of advanced epithelial ovarian carcinoma [19,20]. Compared to these older series, Platinum-based combination chemotherapy after optimal cytoreductive surgery would appear to have the best activity against primary malignant mixed mesodermal ovarian tumors with response rates ranging from 65% to 80% [21,22]. MMMT, known for its aggression and rapidly progressive tumor with a poor long-term prognosis [23]. Often patients presented with advanced stage and widespread metastases at the time of surgery [13,21]. They median overall survival ranges from 7 to 27 months [21].

**Conclusion**

Certain limitations apply to the current study. First, the study was retrospective by nature. Second we are limited by the number of patients. However, the vast majority of studies published in literature were about a case report. We believe that aggressive surgical treatment with optimal cytoreductive and no residual tumor may play an important role to achieve a better result. As well, an improved survival was observed in patients treated with optimal cytoreductive surgery with no residual tumor compared to patients with residual tumors, and it was statistically significant. Furthermore, other alternative systemic therapeutic approaches should be sought for patients with carcinosarcoma of the ovary.

**Acknowledgement**

None Financial or other competing interests.

**References**


