Primary ovarian malignant mixed mesodermal tumor: report of four cases

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Summary

Malignant mixed mesodermal tumors (MMMTs) are highly aggressive and usually diagnosed at advanced stages. MMMT originates from either the ovary or the uterus. Because this disease is relatively rare, an optimal treatment modality has not yet been established. The authors report four cases of ovarian MMMT (one heterologous MMMT and three homologous MMMTs) during 1990-2011. The patients underwent operation immediately after histopathologically confirmation and were treated with platinum-based combination chemotherapy. The extent of operation, the outcomes of radiation therapy, and the proper chemotherapeutic regimen are still controversial. The authors report herein four cases of ovarian MMMTs along with a brief literature review.

Key words: Ovarian MMMTs; Carcinoma; Sarcoma.

Introduction

Malignant mixed mesodermal tumors (MMMTs, also termed carcinosarcomas, sarcomatoid carcinomas, or malignant mixed Müllerian tumors) are relatively rare in the female genital tract and are most commonly found in the uterus [1]. Ovarian MMMTs account for only one percent of all ovarian tumors [2].

Histologically, MMMTs are epithelial tumors that are comprised of both carcinomatous and sarcomatous components. It is subclassified as heterologous or homologous according to the absence or presence of stromal components containing mesenchymal tissue which are not normally found at the primary tumor site [1]. Heterologous elements most frequently include rhabdomyosarcoma, followed by chondrosarcoma, osteosarcoma, and liposarcoma [3].

MMMTs are highly aggressive and rapidly progressive with poor long-term prognoses when compared to epithelial ovarian cancers. The median survival ranges from six to 12 months and more than 70% of the patients died of the disease within one year [2]. Most patients present with widespread metastases at the time of surgery, making optimal tumor debulking difficult [4]. Treatments of the advanced disease include complete surgical staging and debulking along with postoperative adjuvant chemotherapy, which may have unproven benefits in patients with ovarian MMMTs [5, 6]. Prognostic variables analyzed previously included stage, histologic type, treatment method, and surgical approach. The authors report herein four cases of ovarian MMMTs along with a brief literature review.

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Case Report

Case 1

A 65-year-old woman who experienced one month of dyspnea, abdominal distension, and weight loss presented at the present hospital. No fever, vaginal bleeding, or abdominal pain was noted. By pelvic examination, a large, hard, and unmovable mass was palpated in the left lower quadrant. Transvaginal sonography showed a large mixed echoic left ovarian mass. Computed tomography (CT) revealed a 16×20×25-cm multilobulated hypodense mass with multifocal enhancing irregular soft tissue components (Figure 1A). A right inguinal lymph node, approximately 2.3 cm in size, and multiple pelvic/para-aortic enlarged lymph node were noted. Small amounts of ascites and large amounts of bilateral pleural effusions were noted. Positron emission tomography (PET) exhibited a large lobulated mass in the lower abdomen and pelvic cavity with central photopenia as well as multiple lymphadenopathies in the pelvic, para-aortic, and right inguinal lesions. The serum CA 125 level was 986 U/ml and other tumor markers were within the normal range. Endoscopic studies yielded normal results, but a colonoscopic study could not be undertaken because the mass crushed her rectum. Thoracentesis was performed and pleural effusion contained many neutrophils, macrophages, and mesothelial cells, which showed no evidence of malignancies. During the laparotomy, the authors found a 20-cm multilobulated left ovarian tumor that densely adhered to the uterus, sigmoid colon, rectum, peritoneum, cul-de-sac, and omentum. Diffuse carcinomatosis was noted and multiple seeding nodules were noted beneath the diaphragm. The patient underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, total omentectomy, both pelvic, para-aortic and right inguinal lymph node dissection, peritonectomy, and multiple biopsy. Histopathological examination demonstrated an ovarian MMMT at Stage IIIc. Following the surgery, the patient was placed on an adjuvant combination chemotherapy regimen consisting of cisplatin and ifosfamide. Chemotherapy was administered as follows: cisplatin (20 mg/m$^{2)}$ and ifosfamide (1.5 mg/m^2). She is currently being treated with chemotherapy and remains in a stable status.

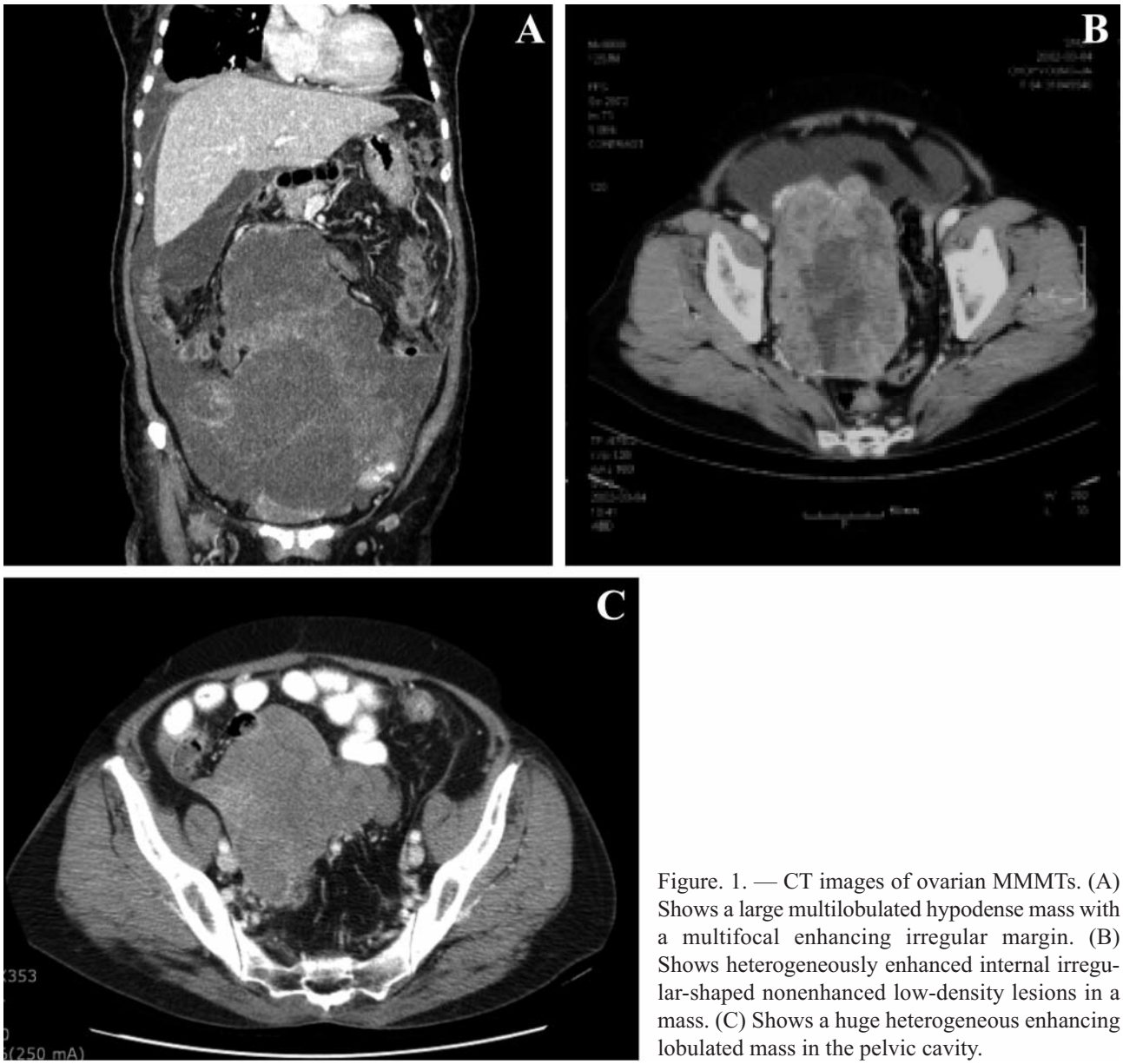

Figure. 1. — CT images of ovarian MMMTs. (A) Shows a large multilobulated hypodense mass with a multifocal enhancing irregular margin. (B) Shows heterogeneously enhanced internal irregular-shaped nonenhanced low-density lesions in a mass. (C) Shows a huge heterogeneous enhancing lobulated mass in the pelvic cavity.

Case 2

A 48-year-old woman who experienced low abdominal pain and had a palpable mass visited the present hospital. CT showed a 12 ×10×11-cm solid mass in her left ovary (Figure 1B). During the laparotomy, a large mass in the left ovary was partially ruptured.

In the right ovary, there was a two-cm endometrial cyst that adhered to the pelvic peritoneum. An enlarged lymph node was noted five cm over the aortic bifurcation site. The patient underwent total hysterectomy with bilateral salpingo-oophorectomy, omentectomy, and para-aortic lymph node dissection. Histopathologic examination demonstrated MMMT of the left ovary and left tube at Stage Ib. Following the surgery, the patient received six cycles of adjuvant combination chemotherapy consisting of cisplatin (75 mg/m^2) and paclitaxel (135 mg/m^2). She underwent a second-look operation and her pathologic results were negative. She is still healthy during a follow-up period of two years.

Case 3

A 64-year-old woman who experienced low abdominal pain for one month visited the present hospital. CT showed large amounts of ascites and a 7×4.5×3.5-cm mass in the right ovary (Figure 1C). Laparotomy revealed about three litres of bloody ascites and a solid mass in the right ovary. Cancerous masses had infiltrated the uterus and posterior cul-de-sac. An omental cake was also noted. Enlarged lymph nodes were noted in bilateral external iliac areas, but the other internal organs did not show any abnormal findings. She underwent right adnexectomy, omentectomy, and both iliac node biopsy. Histopathologic examination demonstrated a MMMT, including heterologous component, chondrosarcoma, involving the omentum and both external iliac nodes. Following the surgery, she received six cycles of combination chemotherapy, cisplatin (20 mg/m^2), ifosfamide (1.28 mg/m^2), and etoposide (75 mg/m^2). CT taken at 12 months

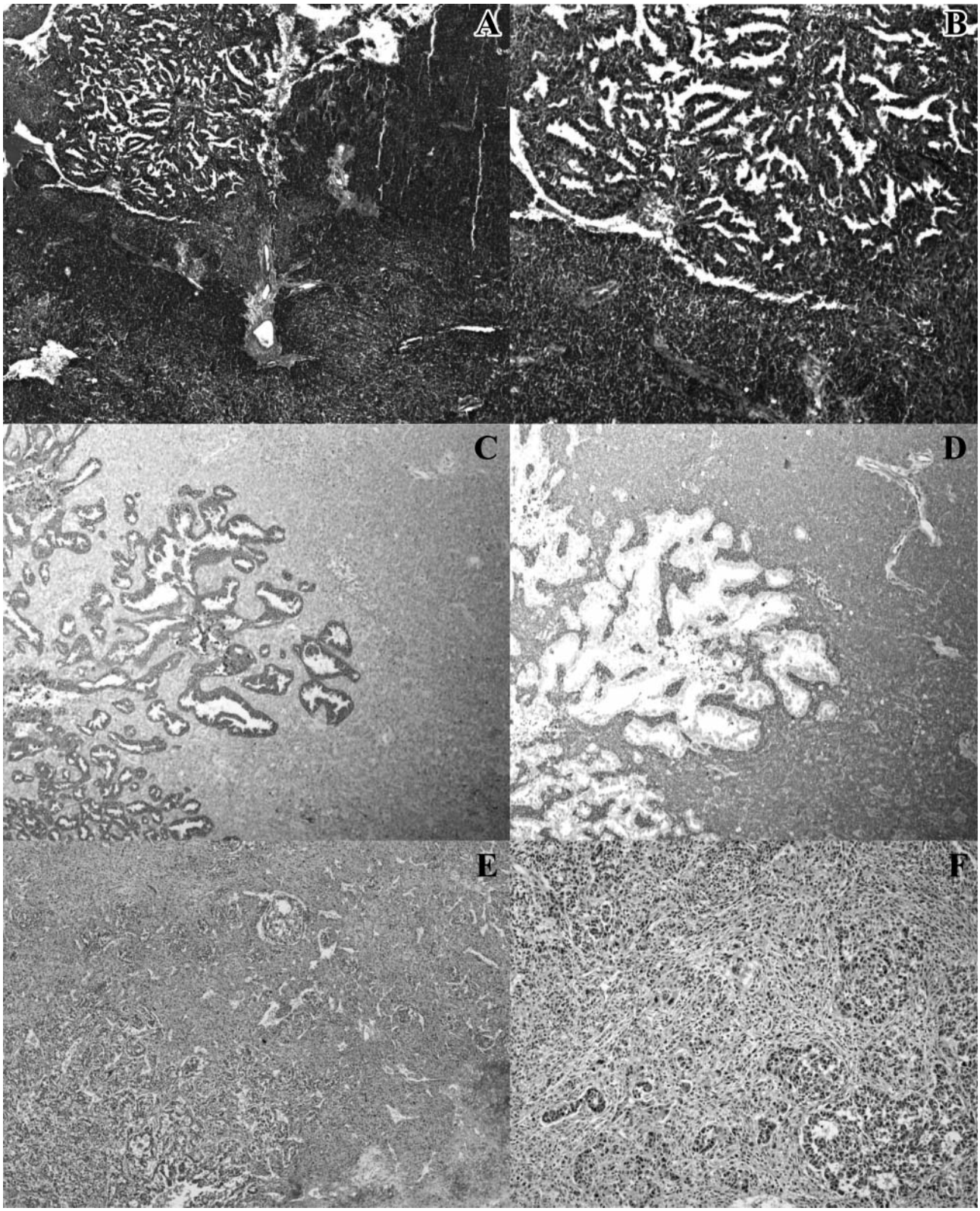

Figure 2. — The pathologic finding of the ovarian MMMT. (A) Low power showing adenocarcinoma with an underlying sarcomatous area; H&E, x40. (B) x100. (C) Malignant glandular epithelium is immunohistochemically positive for pancytokeratin (CK MNF116) (x100). (D) malignant stromal component is immunohistochemically positive for vimentin (CK MNF116) (x100). (E) The tumor was composed of adenocarcinoma and homologous high grade sarcoma; H&E, x40. (F) Low power showing well-formed glands amid pleomorphic spindle cells; H&E, x100.

showed multiple recurrences in the liver and lung. She received a seventh cycle of the same regimen; she experienced pancytopenia. She died of sepsis during the chemotherapy.

Case 4

A 66-year-old woman presented with a low abdominal palpable mass. CT showed large amounts of ascites and a large mass in the right ovary. Laparotomy revealed a 17.5×15×4.5-cm solid mass in the right ovary with brownish ascites. The left adnexa showed no abnormal lesions but adhered to the peritoneum, while the right ovarian mass adhered to the posterior cul-de-sac. There were no abnormal findings in the other internal organs. She underwent a right adnexectomy and omentectomy. Histopathologic examination revealed a MMMT containing endometrioid carcinoma and sarcoma. After the operation, she received six cycles of combination chemotherapy of cisplatin (20 mg/m^2) and ifosfamide (1.5 mg/m^2). Twelve months later, she was checked with CT. A CT taken 12 months after chemotherapy revealed that there was a solid mass in the pelvic cavity. She underwent the secondary debulking operation. At operation, the mass was found to adhere to the small bowel and thus the authors resected the mass along with the small bowel. The pathologic report revealed that the mass was a MMMT involving the small bowel serosa. After the secondary operation, the disease progressed and the patient died of the disease.

Discussion

Primary ovarian MMMTs are very rare, accounting for approximately one percent of all ovarian malignancies [7]. This disease is most prevalent in old women, with the median age being 67.5 years [8]. As with epithelial ovarian cancer, the most common clinical symptom is abdominal distension [8]; in the present series, all patients complained of abdominal distension and discomfort. Patients are usually at an advanced stage of disease by the time of diagnosis; approximately 70% of patients present at Stage III or IV disease and die of the tumor shortly after diagnosis [9, 10]. Widespread metastases are common at the time of surgery, which makes optimal surgical debulking more difficult. Of the present cases, only one underwent an optimal surgery. It is generally known that, in ovarian carcinoma, bulk residual tumors are associated with worse prognoses but this has not been statistically proven with ovarian MMMTs [11]. Sood *et al.* compared overall survival between the optimal surgery and suboptimal surgery groups in 47 cases for 17 years and found that in the optimal surgery group (residual mass < two cm), median survival was 25 months, while it was eight months in the suboptimal group. Harris *et al.*[11] compared survival between the optimal surgery and suboptimal surgery groups and found that there was no significant difference between the two groups, while the time to tumor recurrence was longer than in the optimal surgery group, . Table 1 shows the survival difference between the optimal and suboptimal groups: five studies showed that survival was prolonged in the optimal group, while two studies showed that there was no significant difference between the two groups. Surgery alone is seldom curative even in patients with optimally resectable disease [12]. As with other epithelial ovarian cancer cases, adjuvant radiation therapy was not effective in MMMT cases; furthermore, this therapy increased the incidence of side effects.

Table 1. — *Mean survival between optimal and suboptimal group.*

	Optimal Surgery	Suboptimal Surgery
Sood *et al*. [7]	25 months	8 months
Rutledge *et al.* [8].	25 months	16 months
Duska *et al*. [2]	No difference between both groups	
Brown *et al*. [1]	14.8 months	3.1 months
*Harris *et al*. [11]	No difference between two groups	
Silasi *et al*. [5]	46 months	27 months
Muntz *et al*. [13]	24 months	10 months

*In the optimal group, the time to recurrence was longer

Until the mid-1990s, whole abdominal radiation therapy was performed; however, it was unsuccessful in controlling MMMTs and had many side effects. Even now the value of radiation therapy (with or without chemotherapy) is disputed [13].

Many authors agreed that combination chemotherapy is better than single agent chemotherapy. However, there are different opinions regarding the proper regimen. Until the 1980s, a combination therapy of vincristine, actinomycin D, and cytoxan (VAC) integrated with whole pelvic/abdominal radiation was used. The response rates were 31%-42% [10, 14]. Morrow *et al.* [10] showed an objective response rate of 10% in patients who received doxorubicin adjuvant chemotherapy. After the mid-1980s, Moore *et al.*[12, 14] reported on cisplatin-based chemotherapy, and thereafter it has been used in combination with cisplatin or carboplatin. Sood *et al.* [7] found that an objective response rates were 12% in patients with non-platinum-based adjuvant treatment and 80% in patients with platinum-based adjuvant treatment. Table 2 shows comparisons between groups which received platinum-based chemotherapy. Survival ranged from 8.2 to 53 months. In the present cases, the authors used cisplatin-based chemotherapy. The side effects of the platinum-based chemotherapy regimen, especially ifosfamide, are significant. In the present series, one patient developed pancytopenia and sepsis, after which she had to be treated at the intensive care unit. The combination of paclitaxel/carboplatin has been found by the Gynecologic Oncology Group(GOG) to have effects comparable to cisplatin/paclitaxel but less toxicity [4]. Duska *et al.* [2] reported that 57% of the 28 patients with MMMTs, showed a complete response to the combination of paclitaxel and carboplatin and that their mean survival was 27.1 months. However, Sit *et al.* [4] reported a mean survival of 19 months when the same regimen was used.

As mentioned above, MMMTs are comprised of carcinomatous and sarcomatous components. MMMT can be subclassified as heterologous or homologous according to the absence or presence of a stromal component contain-

Table 2. — *Previous studies using platinum- based chemotherapy in ovarian MMMTs.*

	Patients evaluated	Chemotherapy regimen	Progression-free survival	Survival
Rutledge *et al*. [8]	20	Carboplatin (AUC:6) + taxol (175 mg/m2)	12 months	21 months (55% alive at 2 years)
Mok *et al*. [12]	10	Cisplatin (75 mg/m2) + ifosfamide (1.2 mg/m2)		46 months
Thigpen *et al*. [16]	132	Cisplatin (50 mg/m2)	5.2 months	11.7 months
Brown *et al*. [1]	65	Platinum-based chemotherapy	6.4 months	8.2 months
Harris *et al.* [11]	40	Platinum-based chemotherapy		8.7 months
Duska *et al.* [2]	28	Carboplatin (AUC 5-7.5) + taxol (175 mg/m2)	9 months	27.1 months
Sit *et al.* [4]	13	Carboplatin (AUC 5) + taxol (175 mg/m2) Cisplatin (50mg/m2) + ifosfamide (5mg/m2)	10 months	Carboplatin + taxol: 19 months Cisplatin + ifosfamide: 23 months
Silasi *et al.* [5]	22	Cisplatin (40 mg/m2) + ifosfamide (1.2 g/m2)	Cisplatin + ifosfamide: 13 months	Cisplatin-ifosfamide: 53 months
		Carbopaltin (AUC 5) + taxol (175 mg/m2)	Carboplatin + taxol: 6 months	Carboplatin-taxol: 38 months

ing mesenchymal tissue which is not normally found at the primary tumor sites.

Survival differences between patients with homologous and heterologous components are still controversial [12, 15]. Mok *et al.* [12] demonstrated that the presence of a heterologous component has no significant impact on survival. In contrast, Sood *et al*. [5] and other investigators showed that the presence of a heterologous component is related to poor prognoses.

Ovarian MMMTs are a rare malignancy with poor prognoses. Because of their rarity, an optimal treatment modality has not yet been established. For advanced-stage ovarian MMMTs, many authors recommend optimal cytoreduction and adjuvant chemotherapy-including platinum as part of the regimen. The present authors reported four cases of ovarian MMMTs with a brief literature review.

Acknowledgement

Written informed consent was obtained from the patients for publication of this case report. The study was approved by our institutional review board (KC13ZISE0200).

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