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Malignant Mixed Mullerian Tumours of the Uterus – A Ten-Year Experience

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ABSTRACT

Objectives: To review the clinico-pathological features of malignant mixed Mullerian tumours of the uterine corpus, their prognosis and treatment outcome.

Methods: A retrospective study of malignant mixed Mullerian tumours of the uterus seen at KK Women's & Children's Hospital from January 1989 to December 1998.

Results and Conclusion: Twenty-six patients with mean age of 56.5 years were analysed. Twenty (76.9%) were menopausal. None had previous pelvic irradiation. Vaginal bleeding and uterine enlargement were the commonest presenting symptom and sign. Diagnostic dilatation and curettage obtained the diagnosis in 15 patients. Majority of patients had surgery with adjuvant chemotherapy, while adjuvant radiotherapy was offered only recently. Positive peritoneal washings were significantly associated with advanced disease. There were seven patients with stage I, four with stage II, nine with stage III and four with stage IV disease. There were 17 homologous and nine heterologous tumours. Presence of heterologous stromal components did not influence the stage of the disease. Increasing depth of myometrial invasion was associated with poorer survival. Prognosis of patients with stage III and IV disease were poor, with none surviving to two years. All the patients with stage I disease were still alive at the end of the study period. In conclusion, malignant mixed Mullerian tumours of the uterine corpus are aggressive tumours associated with poor prognosis.

Keywords: malignant mixed Mullerian tumours

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INTRODUCTION

Malignant Mixed Mullerian Tumours (MMMTs) or carcinosarcomas are composed of malignant epithelial (carcinomatous) and mesodermal (sarcomatous) components. They can occur in any of the female reproductive organs but most commonly in the uterine corpus due to the embryological development of the uterus. They account for 2-5% of all malignant neoplasm of the uterine corpus[1-4]. The national figure for Singapore is about 3.0% over the last 10 years and our hospital figure for the period of study is 5.4%. MMMTs are very aggressive tumours with extremely poor prognosis[1,2,5-10]. Five-year survival rates are about 30-40% in stage I disease[11] and considerably less in advanced stages[1-3,12-14].

MMMTs are sub-divided into homologous and heterologous tumours. In homologous tumours, both the carcinomatous and sarcomatous elements present are normal components of the Mullerian system. In heterologous tumours, sarcomatous elements that have no benign counterpart in the uterus, such as skeletal muscle, bone and cartilage, are present[15]. Homologous and heterologous MMMTs occur with approximately equal frequency[16].

MMMTs of the uterus arise in the endometrium and the epithelial component usually predominates. Endometroid adenocarcinoma is the most common epithelial component but other variations such as clear cell, mucinous and papillary-serous also occur. The mesodermal component is most commonly undifferentiated sarcoma in homologous tumours and rhabdomyosarcoma in heterologous tumours.

This paper is a review of the clinico-pathological features; the prognosis and treatment outcome of the cases of malignant mixed Mullerian tumours of the uterine corpus seen at our institution.

METHODS

Patients with MMMT of the uterus seen at KK Women's & Children's Hospital (previously known as Kandang Kerbau Hospital) over a 10-year period, from January 1989 to December 1998, were identified from the Singapore Cancer Registry and the hospital tumour registry. There were 26 cases and their clinical records were reviewed to obtain historical, operative and pathological data. Staging was according to the International Federation of Gynaecology and

Obstetrics (FIGO) staging system for cancer of the uterine corpus.

Results were expressed as mean (range). Statistical analysis was done using Chi-square test. Survival analysis was performed using Kaplan-Meier survival analysis method.

RESULTS

The majority (92.3%) of our patients were more than 40 years old, with a mean age of 56.5 (17-71) years. There were 23 (88.5%) Chinese and three Malays in our group of patients. Twenty (76.9%) were menopausal at the time of presentation, of which 13 were diagnosed within 10 years after menopause. The median interval from menopause to diagnosis was nine years with a range of one to 30 years. None had previous pelvic irradiation.

Four (15.4%) were nulliparous. Five (19.2%) were obese with a body-mass index of more than 25. Four (15.4%) patients had hypertension. None had diabetes mellitus.

Vaginal bleeding was the commonest presenting symptom, occurring in 22 patients (84.6%); followed by lower abdominal pain in 6 (23.1%); loss of weight in 6 (23.1%) and abdominal mass in 4 (15.4%). Nineteen patients (73.2%) had uterine enlargement and 11 (42.3%) had a palpable abdominal mass.

Diagnostic dilatation and curettage obtained the diagnosis in 15 patients. Pipelle endometrial sampling made the diagnosis in a patient who was unfit for anaesthesia. The remaining patients had a hysterectomy without prior dilatation and curettage as indicated by their symptoms and uterine enlargement. The diagnosis was obtained only after histological examination of the hysterectomy specimen.

Staging by laparotomy was performed in 22 patients. In the other four patients, one was unfit for anaesthesia and was not staged surgically. A second patient had polypectomy performed for an endometrial polyp. Histology of the polyp showed MMMT of the uterus. Subsequent dilatation and curettage confirmed that the tumour was limited to the polyp. This patient was staged as 1A and did not have any further surgery. A third patient had an exophytic tumour extruding from the cervical os and was thought to have cervical cancer. Cancer staging of the cervix was performed and was staged as 3A. Histology returned as MMMT of the uterus. The plan was for debulking surgery after completion of neoadjuvant chemo-radiotherapy. The patient completed radiotherapy but subsequently defaulted chemotherapy and she passed away soon after. The last patient chose to have her operation performed at another hospital and no data was unavailable.

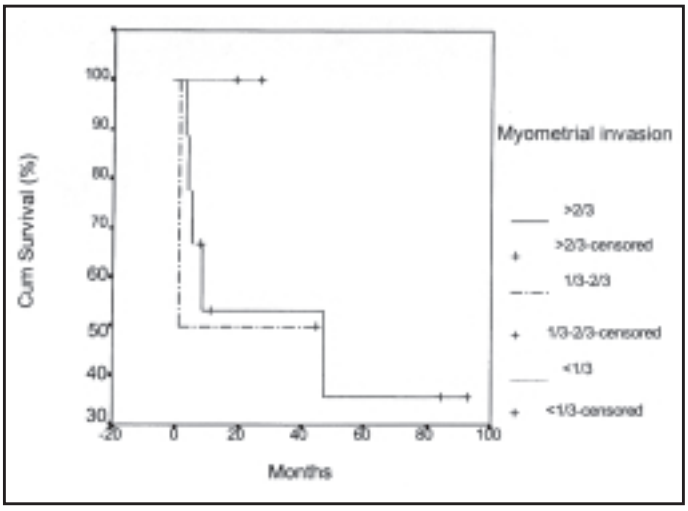

Fig.1 Kaplan-Meier survival analysis by myometrial invasion.

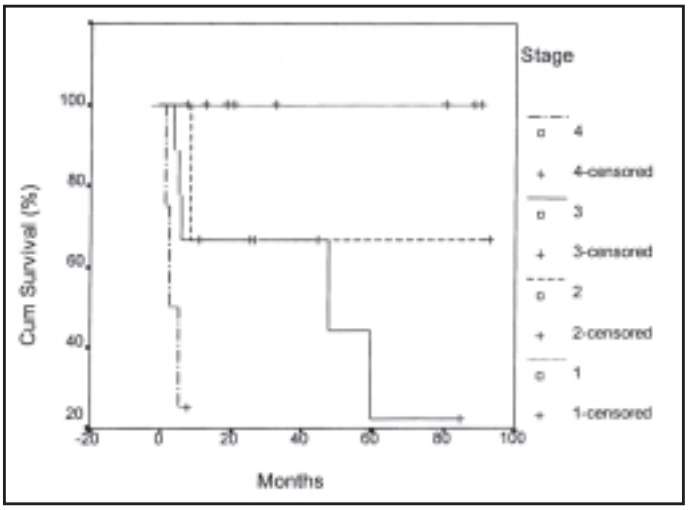

Fig.2 Kaplan-Meier survival analysis by stage.

At laparotomy, hysterectomy with bilateral salpingo-oophorectomy was performed. Peritoneal fluid for cytology was obtained in 17 of the 22 cases. Seven of the eight positives occurred in patients with stage III or IV disease. This was statistically significant at p=0.038. Omentectomy was performed in 13 patients; pelvic lymphadenectomy or node sampling was performed in 16 patients and para-aortic lymphadenectomy or node sampling in six. There were seven patients (29.2%) with stage I; 4 (16.7%) with stage II; 9 (37.5%) with stage III and 4 (16.7%) with stage IV disease.

Tumour size ranged from 1.0-30.0 cm on gross pathology. The majority of patients (81.8%) had a moderately enlarged uterus eight to 12 week size. Two patients had uterus more than 12-week size (9.1%) and two others less than eight-week size (9.1%).

Thirteen patients had myometrial invasion. Two of the 13 (15.4%) had less than one-third myometrial invasion, another 2 (15.4%) had invasion to the middle third of the myometrium. Nine (69.2%) had greater than two thirds invasion including 6 (46.2%)

Table I. Histopathology: Epithelial components.

	n*
Endometroid adenocarcinoma	19
Squamous carcinoma	12
Anaplastic carcinoma	6
Serous carcinoma	5
Clear cell carcinoma	2
Mucinous carcinoma	0

* Some tumours had more than one type of epithelial component.

patients who had full thickness myometrial invasion. Increasing depth of myometrial invasion was associated with poorer survival as shown by Kaplan-Meier survival curve (Fig. 1).

Histopathological reports of the tumours were obtained from hysterectomy specimens, or from dilatation and curettage, Pipelle endometrial sampling and polypectomy where a hysterectomy was not performed. Seventeen (65.4%) of these were homologous tumours and 9 (34.6%) were heterologous tumours. Of the homologous tumours, there were 16 undifferentiated sarcomas and one leiomyosarcoma. Of the heterologous tumours, there were seven chondrosarcomas, four rhabdomyosarcomas and one osteosarcoma (some heterologous tumours have more than one stromal component). Presence of heterologous stromal components did not influence the stage of the disease (p=0.916). However, our numbers were too small to compare survival between specific types of stromal components. Details of the epithelial components are shown in Table I.

Fourteen patients (53.8%) had metastases at the time of diagnosis. The sites of metastases included other pelvic organs (7), other intra-abdominal organs (7), lymph nodes (4) and distant metastases to the liver, lung and spine (2). Some patients had metastases in more than one location.

Twelve patients received adjuvant chemotherapy. There was a trend towards improved survival but our numbers were too small to achieve any statistical significance. Two patients with stage I tumour received adjuvant radiotherapy. One of these patients was supposed to receive combination chemo-radiotherapy but she refused chemotherapy. Neoadjuvant radiotherapy was given to the patient who was thought to have cervical cancer, this patient died before surgery. Combination chemo-radiotherapy was given in three patients. This type of adjuvant therapy was offered only in the last one year of the series, hence the small number. The patient who was unfit for anaesthesia received radiotherapy as her only form of treatment.

The survival rate for each stage is as shown in Fig. 2. Stage III and stage IV disease showed poor prognosis with all patients dying within two years. All the patients with stage I disease were still alive at the end of the study period. The longest survival for a stage I patient was $8^1/_2$ years (range 1 to $8^1/_2$ years) at the end of the study period.

At the conclusion of the study, 10 (38.5%) patients had died. There were no patients lost to follow-up except for the one that was operated at another hospital.

DISCUSSION

The majority of our patients were menopausal at the time of presentation and most of them presented in their 5th to 7th decade of life. There was one patient who presented at a much younger age of 17 years. This is consistent with reports in the literature[1,3-5,17-20]. The reported median interval from menopause to presentation at 15 to 17 years[3,18,21] is more than our figure of nine years. Nulliparity has been reported to occur in from none to 32% of patients[1-3,11,18] Macasaet and Williamson[3,18], have reported obesity in 20% to 31%. Previous pelvic irradiation is a recognised predisposing factor for MMMT in about 15% (up to 29%)[1,3,11,18,19,22-24]. However, in our series, none had previous pelvic irradiation.

Our finding of vaginal bleeding and uterine enlargement as the commonest symptom and sign respectively is consistent with reported literature[15]. Many authors have reported that a definitive histological diagnosis from curettings can be made only in 50-70% of cases[17,25,26] the small amount of tissue obtained, the frequent necrosis and inflammation of the tumour surface being limiting factors. Also, uterine curettings can be misleading in that only one type of tissue may be obtained, i.e. either the epithelial or stromal component only, and the true biphasic nature of the tumour becomes apparent only when the entire specimen is available for study[16,27]. However, in our series, endometrial curettings made the diagnosis in all the patients who had a dilatation and curettage performed. Pipelle endometrial sampling also correctly diagnosed one patient who was unfit for anaesthesia.

MMMTs are among the most malignant neoplasms known to occur in the uterus[28]. Piver & Lurain[27] reviewed 19 studies including 610 patients, the average five-year survival for all stages was 21%. Seventy to 90% of tumour-related deaths occurred within 18 months of diagnosis[2,6,9]. The relatively large proportion of cases (30-60%) in advanced stages at time of diagnosis reflect the aggressive nature of the tumour[27,29]. Most authorities agree that the most important prognostic factor is the extent of the tumour at the time of diagnosis and treatment, the prognosis being very poor when the tumour has

extended beyond the uterus[2,7,16,18,25,30-34]. DiSaia et al[35] (1973), studied 94 patients with MMMT and found that their patients with stage I disease had a 53% two-year survival, whereas survival decreased to 8.5% in stage II and stage III when the disease had extended to cervix, vagina or parametrium and there were no survivors in those with disease outside the pelvis (stage IV). In our series, 50% of cases were in the advanced stage (FIGO stage III and stage IV) at time of diagnosis and all these patients died within two years of diagnosis. All our stage I patients were still alive at end of study.

The other important prognostic factor is the depth of myometrial invasion[8,11-13,16,19,27,32,33,36-38]. In our series, increasing depth of myometrial invasion was associated with poorer survival. The patient whose tumour was restricted to a polyp did not require a hysterectomy and she still did not show any sign of tumour recurrence by the end of the study. The clinical stage of the disease and the incidence of lymphatic metastases seem directly related to the depth of myometrial invasion[22,37].

Some authors have found that patients with tumours containing heterologous components do worse than those whose tumours contained homologous components. However, other authors did not find statistically significant differences in survival between homologous and heterologous tumours[15]. Our study did not show any differences in survival between the two groups. It is controversial whether MMMTs containing cartilage as the only heterologous component have a better prognosis than those with other heterologous components[1,2,6,37]. As our study contains a small number of patients with heterologous components, we were unable to compare survival in sub-groups with specific types of heterologous tissues.

Positive peritoneal washings are associated with a poor prognosis[11,39,40], reflecting the advanced stage of the disease. This was shown in our study and was statistically significant.

FIGO staging of MMMTs of the uterus is the same as for endometrial carcinoma. Tumour spread occurs by direct extension to the cervix and vagina followed by other pelvic organs including the bladder and rectum. Lymphatic spread to local and regional lymph nodes appears to occur at an early stage of the disease. Gallup et al[20] reported nodal involvement in 35% of FIGO stage I and stage II patients. Other studies have shown that about a third of patients have lymph node metastases at the time of diagnosis[22,32]. Haematogenous spread is also common[1,11,14,18,19], usually to lung, liver and bone. More than half of our patients had metastases at the time of diagnosis; the majority of metastases occurring in other pelvic organs and intra-abdominal organs.

Due to the aggressive nature of MMMTs and its poor prognosis, various therapeutic modalities have been employed in its treatment. Surgery in the form of abdominal hysterectomy and bilateral salpingo-oophorectomy remains the principal treatment[1,41-44]. Adjuvant chemotherapy has been shown to be beneficial[45,46]. Adjuvant radiotherapy was noted to improve disease controllability in the pelvis[7,31,38]. The role of combined adjuvant radiotherapy and chemotherapy still remains to be defined. Kohorn et al[24] have reported an 80% survival of three to five years in five patients treated by a combination of surgery, radiotherapy and chemotherapy, though other larger studies[1,47] have reported no beneficial effect on survival by radiotherapy. In our series, adjuvant chemotherapy showed a trend towards improved survival but did not achieve statistical significance because of insufficient numbers. Combined adjuvant chemotherapy and radiotherapy was only offered in the last two years of the series. Although early results seem promising, its long-term benefits await further evaluation. Radiotherapy alone was used for one patient who was a poor surgical risk. The optimal treatment for this rare but aggressive tumour remains to be established.

CONCLUSION

Malignant mixed Mullerian tumours of the uterine corpus are uncommon but not rare. They present with vaginal bleeding and uterine enlargement like the majority of uterine cancers. They are highly aggressive tumours associated with poor prognosis.

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