

The Outcome of Pleomorphic Sarcoma at University Malaya Medical Center - A Fifteen-Year Review

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SUMMARY

Pleomorphic sarcoma is the most common sarcoma. Reports of outcome as well as evaluation of prognostic factors in the literature show great variation. We looked at our experience in treating this tumour at University Malaya Medical Center. This is a review of patients diagnosed with Pleomorphic Sarcoma from January 1990 to December 2005 at University Malaya Medical Center. Outcome measures studied are the overall survival, disease free survival and local recurrence of disease. Prognostic factors for survival and local recurrence which were studied are the tumour size, depth, stage, type of surgery, adjuvant therapy, and surgical margin. There were fifty four patients available for analysis of demographics. The mean age at presentation was 52.3 ± 16.7 years. There were thirty male patients (56%) and twenty four female patients (44%) in the study population. The patients were predominantly Malay (44.4%) and Chinese (42.6%). There were two Indian patients (3.7%) and five patients from other races (9.3%). Thirty patients had disease affecting the extremities while six patients had disease affecting the trunk. Patients with tumour affecting the trunk had 100% mortality. In patients with tumour affecting the extremity, 46.7% presented with Stage 3 disease. The overall median survival was 39 months. The overall survival rate at 3 years was 53.3% and the 5 years was 30.0%. The disease free survival rate at five years was 27.6%. However, if patients who presented with metastasis were excluded, the 5 year survival rate was 60% while the disease free survival was 53.3%. Recurrence rate was 33.3%. Factors affecting survival was stage, size and location of tumour. No factors were found to correlate with higher local recurrence rate. In conclusion, Pleomorphic Sarcoma is a heterogenous disease with variable outcome. In our centre, late presentation with advanced disease significantly affects the overall outcome of this condition. Tumour size and location are important prognostic factors. Inherent tumour behavior and aggressiveness probably outweigh current treatment modalities as the most important prognostic factor in the management of Pleomorphic Sarcoma.

KEY WORDS:

Pleomorphic Sarcoma, Outcome, Prognostic factors

INTRODUCTION

Ever since its first description in 1964, the histopathologic entity of Pleomorphic sarcoma or previously known as Malignant Fibrous Histiocytoma (MFH), has been surrounded with controversies¹. Variations in diagnostic criteria as well

as the presence of different subtypes add to its confusion. However, through the years, it has emerged as the most common soft tissue sarcoma as reported in most published literature^{2,3,4}. Earlier reports of the outcome of this disease revealed poor prognosis with about 30 percent survival rate at 5 years⁵. However, more recent reports have reported an improvement in the survival rate for these patients^{6,7}. A multitude of prognostic factors have also been shown to affect outcome but there is a lack of consistency with different reports stating different prognostic factors. Apart from the tumour behaviour, patient factors such as the time of presentation have been shown to affect the overall survival. So far, no literature has been published with regards to the outcome of this tumour and factors affecting its prognosis in this region. Therefore, we wish to report on the long-term outcome of patients presenting with Pleomorphic Sarcoma and its possible prognostic factor in patients managed in the University Malaya Medical Center.

MATERIALS AND METHODS

This is a review of patients diagnosed with Malignant Fibrous Histiocytoma or Pleomorphic Sarcoma from January 1990 to December 2005 in University Malaya Medical Center. The particulars of the patients were obtained from the histopathological database of the Department of Pathology. During the period of the study, fifty-four patients were diagnosed with either Malignant Fibrous Histiocytoma or Pleomorphic Sarcoma. However, only thirty six patients had complete admission records, histopathological examination reports and valid contact numbers to ascertain the final outcome of the disease. In this pool of thirty-six patients, thirty had involvement of the extremities and six patients had involvement of the trunk and thorax. These two groups of patients were analysed separately.

The outcome measures analysed include the disease free survival as well as local recurrence of the disease. Disease free survival was defined as patients who were still alive without clinical evidence of local recurrence or metastatic disease at the time of review (1st December 2007). Local recurrence of the disease was defined as reappearance of the tumour at the primary surgical site after complete excision of the tumour. This recurrence was proven by histopathological examination.

The prognostic factors studied were:

1. Tumour size: Obtained from macroscopic examination of the tumour and is defined as the maximal linear dimension of the tumour.

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2. Tumour depth: Tumours are deemed superficial when they are located superficial to the deep fascia and deep seated if they are located deep to the deep fascia.
3. Stage of disease: Patients are staged using Computed Tomography of the chest (CT Chest), Magnetic Resonance Imaging (MRI) where available, Bone Scintigraphy where available and are classified according to Enneking's classification⁸.
4. Metastasis at presentation is defined as presence of distant spread discovered within three months of presentation.
5. Administration of Adjuvant therapy: In addition to the surgery, the effect of chemotherapy and radiotherapy was analysed.
6. Type of surgical intervention: Either limb sparing surgery with wide resection of the tumour or ablative surgery by amputation was performed in this group of patients⁹.
7. Margins: As determined by pathologist through microscopic examination. Either all the margins of the tumour are clear of tumour or there is contamination with tumour.

The statistical analysis of the data was carried out with SPSS version 13.0. Survivorship of patients was illustrated using Kaplan Meier survivorship study as well as survival at three years and five years. The significance of the prognostic factors was analysed using Chi- Square test with significance set at 95% confidence limit.

RESULTS

There were fifty four patients available for analysis of demographics. However, subsequent analysis of outcome and prognostic factors will only include thirty six patients with complete records.

The mean age at presentation was 52.3 ± 16.7 years. There were thirty male patients (56%) and twenty four female patients (44%). The patients were predominantly Malay (44.4%) and Chinese (42.6%). There were only two Indian patients (3.7%) and five patients from other ethnic groups (9.3%).

The analysis was done separately for the two groups. The first group included patients who had disease involving the trunk and thorax. There were six patients in this group. They had 100% mortality rate with a median survival of 4.5 months. The locations of the tumour were the lung in one patient, the pelvis in three patients and the retroperitoneal space in two patients, as shown in Table I. Four (66.7%) of these cases were inoperable tumours due to the location and size of the tumour.

The second group of patients had tumours involving the extremities. In this group, the patients presented at a mean duration of 9.8 ± 11.7 months after appearance of the swelling. At the time of excision, the mean tumour size was 12.7 ± 6.3cm in its maximal dimension. Ninety percent of the tumours were purely soft tissue tumour and there were three cases (10%) that involved the bone. Eighty percent were located deep to the deep fascia while twenty percent were superficial. In terms of tumour histology, Chart 1 shows the distribution of the various subtypes. The commonest form encountered was the pleomorphic type, followed by the myxoid type.

In terms of stage of disease at presentation, 46.7% of patients presented with Stage 3 disease (with metastasis). The tumour was limited to one compartment in 16.7% of cases and had extended to more than one compartment in 36.7% of cases. All the tumours were reported as high grade tumour (Grade 3).

Surgically, nineteen patients underwent wide resection (63.3%) and eleven patients (36.7%) underwent amputation above the level of the disease. There was one patient with bone MFH that underwent wide resection and endoprosthetic replacement. The surgical margins were clear in 76.7% of cases. 43.3% of these patients received adjuvant chemotherapy while 13.3% of patients had adjuvant radiotherapy. The others did not receive any form of adjuvant treatment. The adjuvant chemotherapy given was Doxorubicin and Ifosfamide.

The overall median survival was thirty-nine months. The three years survival rate was 53.3% while at 5 years, the survival was 30.0%. The disease free survival rate at five years was 27.6%. However, if patients who presented with metastasis were excluded, the five years survival rate was 60% while the disease free survival rose to 53.3%. Chart 2 shows the Kaplan Meier survivorship for this group of thirty patients.

We found that only two of the factors analysed were statistically significant; (a) metastasis at presentation and (b) tumour size. The median survival for patients without metastasis was seventy seven months while those with metastasis had a median survival of thirteen months. As mentioned earlier, 46.7% of patients had metastasis at presentation. In the group that presented without metastatic disease, five eventually developed metastasis. The median duration for appearance of metastatic disease was thirty three months. Chart 3 depicts the difference in survival between those who had metastasis and those who did not have metastatic disease at presentation.

Our study showed that tumour size significantly affected the outcome. The difference in survivorship of tumours less than ten centimeters compared to tumours ten centimeters or more is depicted in Chart 4. Smaller tumour size at presentation gave a better outcome. Other factors such as deep-seated tumours, extra-compartmental disease, recurrence, positive surgical margin, type of surgical procedure and administration of adjuvant therapy did not affect survival significantly in our study.

Recurrence occurred at a rate of 33.3%. Statistical analysis did not reveal any significant factors which affected the recurrence rate. The factors that we analysed were surgical margin, tumour depth, compartment status, the surgical procedure done, tumour size and postoperative radiotherapy.

Table I: Site of axial tumour

Site of Tumour	Frequency
Lung	1
Pelvis	3
Retroperitoneal	2

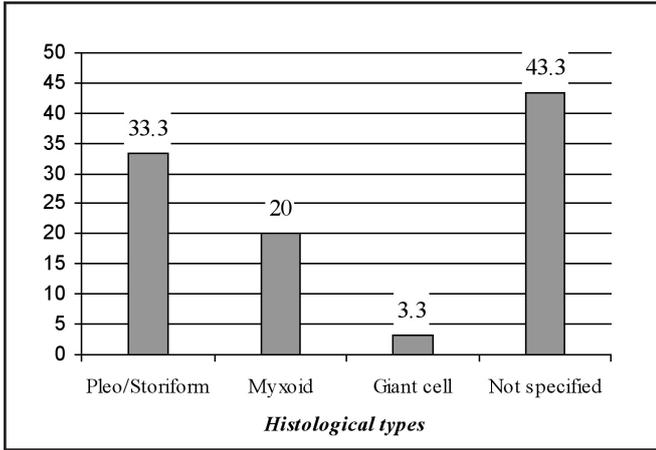


Fig. 1: Histological subtypes of Malignant Fibrous Histiocytoma

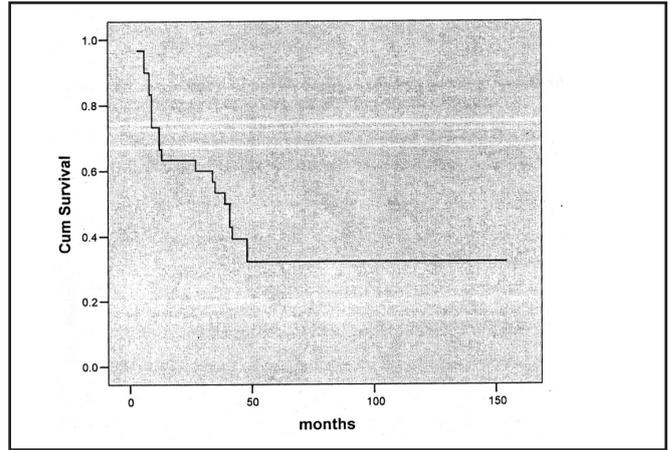


Fig. 2: Survivorship curve for patients with Malignant Fibrous Histiocytoma affecting the appendicular skeleton

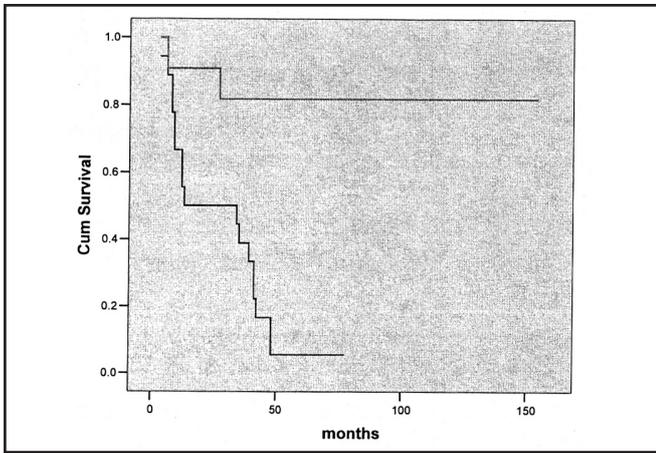


Fig. 3: Comparison of survivorship between patients with metastasis and those without

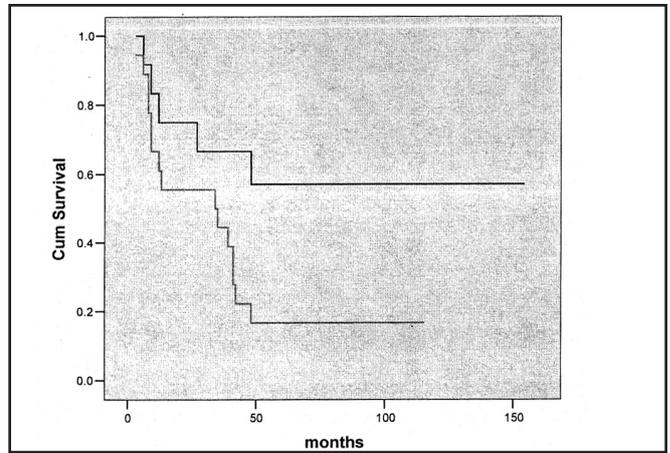


Fig. 4: Comparison of survivorship between tumour less than 10cm and tumours 10cm or more

DISCUSSION

Since the description of Malignant Fibrous Histiocytoma as an entity in 1964, it was soon realized that some of the previous diagnosis of Pleomorphic Liposarcoma or Fibrosarcoma could actually have been Malignant Fibrous Histiocytoma¹. The discovery of this tumour was soon followed by various subtyping and this created greater uncertainty as to tumour behaviour and prognosis¹⁰.

However, Pleomorphic Sarcoma (MFH) soon emerged as the commonest soft tissue sarcoma in most published literature with this tumour comprising thirty to forty eight percent of all soft tissue sarcomas^{2,3,4,11}. Gutierrez in a large review of 8249 soft tissue sarcoma reported that Malignant Fibrous Histiocytoma constituted 31.5% of all soft tissue sarcoma¹². This tumour has also been reported to involve not only the soft tissue of limbs but also the bone and lungs^{13,14}.

Most published literatures on outcome as well as prognostic factors showed this tumour to be a heterogenous entity with variable survival rates as well as prognostic factors. Belal in a retrospective review of 109 cases of Pleomorphic Sarcoma

quoted a relapse free survival rate of 39% at five years and 36% at ten years¹⁵. This is comparable to the figures quoted by Bertoni in his publication in 1985 whereby the five year survival rate was 36%⁵. This is in contrast with other reports which quoted survival rates of up to 70%^{6,7,16,17}. Most of these studies excluded patients who had metastasis at presentation. In our series, we defined metastasis at presentation as patients who demonstrated distant spread within three months of presentation. This is because the surgical excision often preceded computed tomography of the chest and bone scan. Hence, the staging could have been delayed. Secondly almost half the patients in our series presented at a very late stage and therefore, would not give a true reflection as to the overall prognosis of this tumour if treated early. When these patients were analysed, the disease free survival was only 27.6%. If patients with metastasis at presentation were excluded, the overall survival rate rose to sixty percent while the disease free survival was 53.3%. The vast difference in outcome is most likely a reflection of the inherent nature of this tumour. Its response to systemic chemotherapy is not as established as seen in the treatment of Osteosarcoma and Ewing's sarcoma.

Analysis of prognostic factor in our series showed that apart from the presence of metastatic disease, tumour size and location was the only other significant factors in affecting survival. Tumours affecting the pelvis, retroperitoneal space and lung have uniformly poor outcome in our study. However, tumour size is the most consistent prognostic factor affecting survival with various publications reporting similar findings^{5, 7, 17}. Zagars in a review of 271 patients with Pleomorphic Sarcoma reported that the factors which affected metastatic recurrence were tumour size more than 10cm as well as myxoid type histological subtype¹⁸. Other prognostic factors which have been reported to be important in survival were tumour grade, tumour depth, a more proximal location of the tumour and surgical margin^{5, 7, 16, 17, 18}.

The significance of local recurrence in the overall outcome of soft tissue tumours has been debated. Ueda T in 1997 reported the significance of local recurrence as a prognostic factor. He reported that local recurrence after definitive surgery was an important factor but local recurrence at presentation was not¹⁹. However, Gustafsson et al reported that patients who had local recurrence without metastatic disease were considered to have good prognosis with a five year metastasis free survival rate of 73%⁴. In our study, cross tabulation between the occurrence of recurrence and outcome was not statistically significant. This probably shows that the prognosis of Pleomorphic sarcoma is determined by the presence of systemic disease as with most tumours.

In our study, no significant factors were found to affect the rate of recurrence. One particularly surprising finding was that even positive surgical margin did not influence the recurrence rate. This is in contrast with most publications which quoted this as one of the more consistent factors in determining the occurrence of local recurrence^{5, 7, 11}. Tanabe concluded that possible factors which might contribute to this were more liberal definition of positive margins, inclusion of tumours with low grade behaviour, and a shorter follow up duration²⁰. In our study, probably the most important factor was the survival of patients was too short to detect recurrence as we had included patients who have metastatic disease at presentation. If these patients were excluded, our sample might also be too small to generate any significant conclusion regarding the effect of positive surgical margin on local recurrence. Other important prognostic factors for local recurrence which have been described are depth of tumour and postoperative radiotherapy.

In conclusion, Pleomorphic sarcoma is a heterogenous disease with variable outcome. In our set up, late presentation significantly affects the overall outcome of this

disease due to advanced disease at presentation. Tumour size and location are important prognostic factors. Inherent tumour behaviour and aggressiveness probably outweigh current treatment modalities as the more important prognostic factors in the management of Pleomorphic Sarcoma.

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