SURVIVAL ANALYSIS ON ADULT EXTREMITY SOFT TISSUE SARCOMA: A SINGLE INSTITUTION STUDY OF 10 YEARS DURATION

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Soft tissue sarcoma is one of the commonest orthopaedic related malignancy. Approximately 80% of sarcoma arises from soft tissue and 20 % from bone[8 3]. However, from the general point of view, soft tissue sarcoma is one of the rarest malignancies with incidence reported was less than 1%. Its classification is based on the direction of the differentiation of the soft tissue either collagen (fibrous tissue), fat or cartilage for instance.

Several demographic factors and a few other possible prognostic factors have been demonstrated previously that may influence the patients' survival. This study involved 128 patients for 10 years duration (1st January 2001- 31st January 2010) from one of the tertiary center for orthopaedic oncology in the country. Besides demographic studies, the prognostic clinical characteristics were assessed for differences in overall survival by using Kaplan Meier method as well as Cox proportional hazard regression.

From this study, it was found the overall median survival time was 10 years with 5- year overall survival of 58%. No demographic results were statistically significant in affecting the overall survival (age, sex, sites of tumor, and subtypes, p-value >0.05). Treatments of soft tissue sarcoma for example limb salvage or amputation surgery, pre- and post- operative chemotherapy and radiotherapy, as well as outcome of the tumor which was second malignancy were all not statistically significant as well (p- value >0.05).

Pulmonary and distant (non-pulmonary) metastasis, and local recurrence were the prognostic factors that significantly affect the overall survival (p <0.001). Nevertheless, after a multivariate analysis, only pulmonary (CI:3.08, p <0.001) and distant (non-pulmonary) (CI:2.30, p <0.004) metastasis were significantly associated with survival.

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2.1 ABSTRAK

Sarcoma tisu lembut merupakan antara kanser paling kerap dikesan dalam bidang ortopedik onkologi. Ia terdiri daripada 80% dan selebihnya 20% daripada kanser tulang. Secara umumnya, kanser tisu lembut sebenarnya merupakan antara satu daripada kanser yang sukar didapati berbanding dengan jenis lain. Kanser ini boleh dikelaskan mengikut jenis tisu asal ia bermutasi seperti kolagen, lemak mahupun tulang rawan misalnya.

Beberapa data demografik serta faktor yang boleh memberi impak kepada nilai hidup pesakit kanser telah dikaji sebelum ini. Kajian kali ini melibatkan 128 pesakit dalam tempoh 10 tahun (1 Januari 2001 hingga 31 Disember 2010) satu daripada pusat rawatan tertiari utama ortopedik onkologi negara. Selain daripada faktor demografik, pelbagai faktor lain yang mungkin memberikan kesan turut dinilai di mana beberapa ujian seperti “Kaplan Meier” serta “Cox proportional hazard regression”.

Hasil daripada kajian ini menunjukkan tempoh “median survival time” selama 10 tahun dengan kadar “5- year survival” sebanyak 58%. Turut didapati tiada aspek demografik (umur, jantina, sub- jenis tumor, lokasi) adalah tidak signifikan dengan nilai $p > 0.05$. Aspek rawatan sarkoma tisu lembut juga turut dinilai dan didapati rawatan pembedahan, kemoterapi, radioterapi, serta komplikasi kanser seperti barah seterusnya turut tidak signifikan dengan nilai $p > 0.05$.

Namun begitu, aspek komplikasi kanser yang lain iaitu kanser yang berulang, kanser yg merebak ke paru-paru serta organ lain didapati memberi kesan kepada kehidupan pesakit, dibuktikan dengan nilai $p < 0.001$. Tetapi, apabila ujian "Cox proportional hazard regression" dijalankan, hanya kanser yang merebak ke paru- paru (CI:3.08, $p < 0.001$) serta organ lain (CI:2.30, $p < 0.004$) yang memberikan kesan negatif kepada nilai hidup pesakit.

2.2 ABSTRACT

Soft tissue sarcoma is one of the commonest orthopaedic related malignancy. Approximately 80% of sarcoma arises from soft tissue and 20 % from bone[8] [3]. However, from the general point of view, soft tissue sarcoma is one of the rarest malignancies with incidence reported was less than 1%. Its classification is based on the direction of the differentiation of the soft tissue either collagen (fibrous tissue), fat or cartilage for instance.

Several demographic factors and a few other possible prognostic factors have been demonstrated previously that may influence the patients' survival. This study involved 128 patients for 10 years duration (1st January 2001- 31st January 2010) from one of the tertiary center for orthopaedic oncology in the country. Besides demographic studies, the prognostic clinical characteristics were assessed for differences in overall survival by using Kaplan Meier method as well as Cox proportional hazard regression.

From this study, it was found the overall median survival time was 10 years with 5- year overall survival of 58%. No demographic results were statistically significant in affecting the overall survival (age, sex, sites of tumor, and subtypes, p-value >0.05). Treatments of soft tissue sarcoma for example limb salvage or amputation surgery, pre- and post- operative chemotherapy and radiotherapy, as well as outcome of the tumor which was second malignancy were all not statistically significant as well (p- value >0.05).

Pulmonary and distant (non-pulmonary) metastasis, and local recurrence were the prognostic factors that significantly affect the overall survival ($p < 0.001$). Nevertheless, after a multivariate analysis, only pulmonary (CI:3.08, $p < 0.001$) and distant (non-pulmonary) (CI:2.30, $p < 0.004$) metastasis were significantly associated with survival.

3.0 INTRODUCTION

3.1 BACKGROUND AND STUDY LITERATURE

Soft tissue sarcoma is a rare malignancy, with only less than 1% from all adult malignancies[1]. Nonetheless, it comprises 60-70% of the most common orthopaedic related soft tissue malignancy before bone related tumours [2]. It is classified depending on the direction of the differentiation of the soft tissue either collagen (fibrous tissue), fat or cartilage for instance.

Based from the Malaysia Cancer Registry in year 2007, extremities soft tissue sarcoma is the least common malignancy and included in the "others" category due to its small fraction [3]. Nevertheless, the treatment for soft tissue sarcoma is not only unique but it caters to different histology, grade and type of the sarcoma. Over the years the treatment evolves from limb amputation to limb salvage surgery with adjuvant treatments such as radiotherapy and chemotherapy given either pre- operative or post- operatively.

There have been many studies produced that show effectiveness and the appropriateness of the treatment or therapy recommended to help prolonged patients' survival. However, in our local setting we had yet to see sufficient data on the prevalence, incidence and the prognosis in relation to the current treatment. Therefore, this study is intended to analyze the survival of patients referred to 'Hospital Universiti Sains Malaysia' (HUSM) for management of the extremities soft tissue sarcoma.

3.2 PROBLEM STATEMENT

Soft tissue sarcoma is not one of the commonest malignancy, with incidence less than 5/100 000 population[3,4] . Despite that, its management involves multi- disciplines which is mandatory (surgeons, radiologists, pathologists, oncologists)[5] . This is to ensure the survival and to improve the quality of life of the patients.

A malignant soft tissue swelling should be suspected when there is a presence of deep swelling with its size more than 5cm in diameter[6] . After adequate clinical assessment, imaging like radiographs and MRI are needed before proceeding with tissue diagnosis via biopsy[7,8] . Once a tissue diagnosis of soft tissue sarcoma is obtained, definite management will be decided. Before patients undergo surgery, it has to be decided which type of surgery would provide the best function to the patients, in which options are either wide resection and reconstruction, limb amputation or even joint disarticulation. Adjunct therapies post operatively may need to be given depending on the formal histopathological diagnosis as well as per discussion with the oncologist.

There are a few options available such as brachytherapy, post- operative radiotherapy or chemotherapy. There has been conflict with post- operative chemotherapy, despite it may assist in prolonging disease- free survival, there was no proven benefit seen in improving overall survival. In a certain condition such as highly malignant, large or borderline resectable tumors, a pre-operative radiotherapy or chemotherapy might be considered.

In keeping with the current management for the soft tissue sarcoma, a lot of studies has shown improvement in survival of the patients. With promising numbers internationally, I would like to see how the trend like in Malaysia is. To date there is yet a study to discuss on the survival and outcome of the soft tissue sarcoma. Hopefully with this study it would help to visualize the response of the current treatment in Malaysia's population. We can also observe the prevalence and incidence of this disease in local setting. Besides, with HUSM as one of the oncology center, this will help in establishment of the database of the soft tissue sarcoma when subsequent data needs to be collected.

4.0 LITERATURE REVIEW

4.1 EPIDEMIOLOGY

Soft tissue sarcoma (STS) is one of the rarest mesenchymal malignancies. They are heterogenous with more than 50 types currently reported[5 1]. A multidisciplinary approach is mandatory to minimize recurrence, to maximize survival and preserve functionality and quality of life [4 3]. Approximately 80% of sarcoma arises from soft tissue and 20 % from bone[24] . It accounts for 1% of adult tumor and 15% of pediatrics age group tumor [25] .

From the European study, the incidence of soft tissue sarcoma reported was less than 5/ 100 000/ year[9] . In the United States, around 8700 new soft tissue sarcomas were diagnosed yearly while 1500 cases were reported annually in the UK[26] . On the other hand, in Asia pacific region, 18000 new cases of sarcoma of bone and soft tissue were reported which accounted around 14400 soft tissue sarcoma cases expected each year[24] . From Malaysia National Cancer Registry 2007-2011, out of 103 507 cases of malignancy reported, only 434 of them (0.004%) was of soft tissue sarcoma[5 5] .

4.1.1 AGE AND GENDER PREDISPOSITION

In soft tissue sarcoma, there is no obvious gender predisposition. There is however slight male predominance in liposarcoma[30,5].

In adult soft tissue sarcoma, it is more prominent with increasing age with median age onset at 56-58 years old[30,35]. Based on World Health Organization (WHO), the onset of the disease is more common in the 6th decade of life[14,25]. On a contrary, myxoid type liposarcoma has an earlier age of onset with peak incidence between 4th to 5th decade of life. Synovial sarcoma also shows earlier age of onset, typically below 40 years of age. Otherwise other types of liposarcoma, and other sarcomas for instance pleomorphic sarcomas, fibrosarcoma and leiomyosarcoma, majority of the occurrence are within the mentioned age groups.

4.1.2 SITE

Soft tissue sarcoma can arise from any sites of body, however the highest incidence were noted from lower extremities. Lower limb is the most involved site with 46%, followed by trunk 19%, upper limb 13%, retroperitoneum 12%, head and neck 9% and other regions 1%[44]. Thigh region is the most affected area of the lower limb which usually located in deep soft tissue[63]. Some of the soft tissue sarcomas are anatomical dependent; pleomorphic sarcoma and liposarcoma

are commonly found in extremities while leiomyosarcoma and also liposarcoma are also commonly found in retroperitoneum and intra- abdominal cavity[44].

Pleomorphic sarcoma being the most common soft tissue sarcoma has more affinity to deep seated skeletal muscles in the extremities. It rarely occurs in retroperitoneum or intra-abdominally. This is not so different from fibrosarcoma, as it also arises from fascia and aponeurosis of deep structures, similarly it takes after deep locations. Likewise, for synovial sarcoma, it correspondingly occurs in deep tissues, as it originates from area at close proximity with joints[44].

As for liposarcoma, as mentioned earlier, is commonly found in the lower extremities, with pelvis and thigh region being the most predominant sites. These findings support with what had been reported worldwide[25,53,51]. In most literature, the retroperitoneum and lower extremities are reported to have high incidence of large liposarcoma.

4.1.3 TUMOR SIZE

Soft tissue sarcomas are often detected late, with common presentation of large mass that has been growing for lengthy period, and painless. Sometimes patients present with compressive effect due to the large mass occupying the compartment and impinges on the nearby structures. Especially when the mass originates from pelvic or intra- abdominal cavity, the tumor grows to a very significant size without causing any significant signs and symptoms. Similar symptoms and

trend can also be seen when the mass emerges from deeper soft tissue structures, it precludes positive finding during palpation during early part of the disease.

4.2 SUBTYPES OF SOFT TISSUE SARCOMA

The soft tissue sarcomas are classified from its histological features. They are distinguished from their cellular type, and aided by other histogenetic studies to obtain the accurate diagnosis such as histochemistry, immunohistochemistry, and electron microscopy. The identification is more challenging in malignant soft tissue due to lack of cell differentiation. Another way of classifying is by grading the histology into benign, low grade or high grade malignancy. The diagnosis will be further supported by other modalities such as clinical behavior, radio- imaging, and many more.

Histogenesis	**Benign**	**Malignant**
Fibrous	Fibromatosis	Fibrosarcoma
Fibrohistiocytic	Benign fibrous histiocytoma	Pleomorphic sarcoma
Adipose	Lipoma	Liposarcoma
Smooth muscle	Leiomyoma	Leiomyosarcoma
Vascular	Hemangioma	Angiosarcoma
Striated muscle	Rhabdomyoma	Rhabdomyosarcoma
Synovial	Synovioma	Synovial sarcoma

Nervous	Schwannoma Neurofibromatosis	MPNST PNET
Osseous		Extraskeletal Ewing sarcoma Extraskeletal osteosarcoma
Cartilaginous		Extraskeletal chondrosarcoma
Lymphatics	Lymphangioma	Lymphangiosarcoma Malignant hemangiopericytoma
Uncertain		Alveolar sarcoma Epithelioid sarcoma

Table 1: Soft tissue tumor classification

4.2.1 PLEOMORPHIC SARCOMA

Pleomorphic sarcoma is the most common tumor in adults. As mentioned earlier, it is found commonly between 5th to 6th decade of life, and commonly occurs in lower extremities. It has an affinity to deep skeletal muscle. This tumor usually consists of mucoid lobules with high content myxoid ground substance and 5% would associates with haemorrhagic content. Therefore, often false diagnosis of hematoma was made instead due to this presentation. There are many variants depending on the predominant cell type such as fibroxanthoma, malignant fibroxanthoma or inflammatory fibrous histiocytoma. Histologically they consist of fibroblasts, histiocyte- like cells and primitive mesenchymal cells arranged in storiform manner. Some also has atypical and bizarre

giant cells with abnormal mitotic figure, which can be less commonly seen. Some tumor cells observed had rich myxoid matrix and usually indicates a more favourable prognosis than other subtypes.

4.2.2 LIPOSARCOMA

This type of sarcoma is the second most common after pleomorphic sarcoma. It also largely affects lower extremities with estimated 40% of the incidence followed by retroperitoneum. The same age group also affected by this type of sarcoma. The tumor is typically well circumscribed and multilobulated.

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Its histological grade correlates well with the malignant potential. Well differentiated type provides the best prognosis, and consists of mature fat lobules, very few lipoblasts with fibrocollagenous tissues. The other type is myxoid, which comprises of mucinoid surface and round cell. It is the most common histological type in liposarcoma. The high grade liposarcomas are of pleomorphic and dedifferentiated type. They are associated with extensive haemorrhage and necrosis. The dedifferentiated type generally transforms from a multiple recurrence of well-differentiated type. Pleomorphic liposarcoma on the other hand, contains multivacuoles, lipoblasts as well as atypical stromal cells, with abnormal mitotic figures. These features are characteristic for the other high grade sarcomas as well, but presence of lipoblasts differentiates liposarcoma from the other subtypes.

4.2.3 FIBROSARCOMA

This type of soft tissue sarcoma originates from the fascial and aponeurosis of deep soft tissue. It had a wide range of age group affected, from 30 till 80 years of age. This tumor is made up of fibroblasts, and they produce collagen fibers which in turn appear as bifringent wavy fibres. This feature is quite common in differentiated fibrosarcoma. These fibers are uniformly arranged spindle cells with intersecting fascicles which form herringbone pattern. They have minimal atypical cells and mitotic figures, thus it is challenging to distinguish between low grade fibrosarcoma with fibromatosis. On a contrary with poorly differentiated fibrosarcoma, it shows minimal fascicular arrangement and associated with more nuclear atypia, pleomorphism with high mitotic rate[4 4] . Because of these features, the diagnosis of fibrosarcoma can overlap with pleomorphic sarcoma.

4.2.4 SYNOVIAL SARCOMA

Despite being named synovial sarcoma, it is a misnomer as it occurs from region near the joint and not from within the joint itself. It usually affects younger age group around 30- 40 years old with male predominance. Synovial sarcoma is a high grade tumor with common incidence of pulmonary metastasis as well as regional lymph nodes metastasis. Most of the patients have poor prognosis of 50% in 5 years and as low as 25% in 10 years of overall survival.[4 4]

The tumor is characterized by mineralization or calcification that can be identified from radio- imaging modalities. Rarely it has contiguity with synovium- line space. It is also presents with ill- defined mass with infiltration and gel- like consistency. Histopathologically there is biphasic or even monophasic cells with evidence of spindle and epithelial cells and further confirmed with multiple immunohistochemistry staining. The neoplasm also contains dense stromal hyalinization with focal calcification. The presence of calcification actually signifies a more favourable prognosis than its other subtypes[44].

4.2.5 LEIOMYOSARCOMA

This is the sarcoma resulted from mutation from involuntary smooth muscle. It comprises of less than 7% of all soft tissue sarcoma of the extremity. It is more commonly affected the uterus and abdominal cavity. Incidence is found higher in the middle age group especially at 5^{th} to 7^{th} decade of life. Patients usually present with painful mass when it is deep seated. Histopathologically the tumor consists of spindle cells with abundant, fibrillary, 'cigar- shaped' and atypical nuclei. Secondary changes like focal haemorrhage can also be seen. Other areas also show fibrocollagenous adipose, muscle and tendinous tissue with focal areas of infiltration by the malignant tumor cells. Special staining will aid in confirming this type of sarcoma[44].

4.2.6 RHABDOMYOSARCOMA

This type of soft tissue sarcoma is less common as well. It originates from striated or skeletal muscle. Rhabdomyosarcoma is more common among paediatric age group than in adults. It is a highly malignant tumor that often results with poor prognosis in survival. This tumor occurs mainly at head and neck as well as genitourinary region. Incidence of extremity rhabdomyosarcoma is less than a third. Advancing age, large tumor size more than 5cm and location at the extremity are associated with worse prognosis and survival.

There are a few types of rhabdomyosarcoma which are classified according to the predominant cells histopathologically. There are alveolar, pleomorphic, embryonal and anaplastic subtype. The alveolar subtype is highly predominant in the extremities. Microscopically rhabdomyoblasts and smooth muscles can be observed. Small round cells with hyperchromatic nuclei or even polygonal-shaped tumor cells with abundant eosinophilic cytoplasm and contained diagnostic cross striations are observed as well[44].

4.3 STAGING

4.3.1 LOCAL STAGING

4.3.1.1 PLAIN FILM RADIOGRAPHY

The role of plain radiograph in diagnosing soft tissue tumor is limited as compared to primary bone tumor. The well recognized drawback is lack of contrast resolution but this limitation should not be underestimated as it can still provide information on presence of matrix calcification, periosteal reaction and cortical destruction in soft tissue tumors. Furthermore, it is an easy, cheap and universally available tool [16] .

4.3.1.2 CT SCAN

CT scan has a little value in diagnosing primary soft tissue tumors as compared to bone tumors.

4.3.1.3 MRI

Magnetic resonance imaging has become the preferred modalities for primary soft tissue tumor evaluation as it provides superior soft tissue contrast resolution. Besides, it also provides true multiplanar images in axial, sagittal and coronal and devoid of artifacts which commonly appears in CT scan[13,58]. In addition, it can produce accurate diagnosis by delineating the soft tissue extent of the tumor[71].

The intensity of signal varies from low (black) to high (white), depending on chemical composition of the soft tissues and the modalities of execution. T1 and T2 weighted image has a different signal intensity depending on the used times. Intravenous administration of gadolinum enhances hypervacular lesion and results in high signal intensity in T1 weighted images. STIR (Short T1 inversion recovery) supresses fat signal so gadolinum enhanced signal intensity are contrasted against black bone marrow or soft tissue fat.

Different subtypes of soft tissue sarcoma manifests differently in MRI. In malignant fibrous lesions like pleomorphic sarcoma and fibrosarcoma, they show low signal on T1 and high signal on T2- weighted images. The subtypes of liposarcoma manifest differently in MR images. Few studies have been done to evaluate the different subtypes of liposarcoma in MRI. Well differentiated type has the appearance of high SI (signal intensity) lesion on T1 weighted image corresponding to fat with fine septae within it, and faint enhancement of lesion post gadolinum suggestive of little vascularity. As for myxoid type, T1 weighted image shows homogenous mass isointense with muscle and homogenous high signal intensity with linear septae in T2 weighted images. Post contrast usually shows heterogenous non-enhancing areas which corresponds with accumulated mucinous material with no capillary network. Pleomorphic and dedifferentiated liposarcoma, as well as other sarcoma for instance synovial sarcoma are aggressive and high grade. Haemorrhage and necrosis are usually present with high degree of cellular pleomorphism. On T1 and T2 weighted image shows heterogenous mass containing low and high SI, indicates area of haemorrhage and necrosis with marked heterogenous enhancement post gadolinum which shows rich vascularity of this lesion [3,21,17] .

In conclusion, MR images play a vital role in diagnosis soft tissue tumor. However, the baseline imaging should still start with plain radiography and proceed with other imaging algorithms if needed. Biopsy is mandatory if malignancy is suspected as histology remains the gold standard for diagnosis [16] .

4.3.1.4 COMPARING CT AND MRI AS LOCAL STAGING

It has been well established that the MR imaging was more superior to CT scan. MRI can depict tumor boundaries and delineate interface between tumor and surrounding soft tissue, generally fat and muscle[5] . MRI also demonstrates the anatomical relationship with neurovascular structures better as compared to CT. This is important as a part for pre- operative planning. Besides, the extent of involvement of bone marrow abnormality, if present, can be visualize clearly[1].

Furthermore, the advantage of multiplanar images (coronal, sagittal and axial) from MRI adds on the superiority in visualizing the tumor from CT scan. It provides a clearer 3- dimensional image as compared to CT.

However, CT is superior to MRI in showing mineralized tissue such as bone and calcium deposition[16] . Sundaram M and colleagues, 1990 concludes that even though the rim of sclerotic bone is not seen in MRI, it can be pictured well in CT. However, it adds to no additional information to what that already available in plain x- rays[6 8] .

Panicek et al in 1999 concludes that CT and MR imaging are equally accurate in local staging of primary soft tissue and bone tumors[5 7] .

In general, MR is superior to CT in studying the soft tissues, bone marrow and spine, while CT scan is better to study calcified tissues as well as the best imaging modalities for pulmonary metastasis.

4.3.2 DISTANT STAGING

4.3.2.1 CT SCAN

Soft tissue sarcomas spread via hematogenously, particularly to the lung. Nicholas et al, 2005 reported high grade soft tissue sarcoma such as pleomorphic sarcoma, fibrosarcoma, synovial sarcoma, pleomorphic and dedifferentiated type of liposarcoma has a high tendency for pulmonary metastasis. Nevertheless, there are other subtype such as myxoid subtype which favors extra pulmonary metastasis and synovial sarcoma which also commonly has lymphatic spread[52]. Michelle AG et al, stated high number of pulmonary metastasis in high grade subtypes with tumor size more than 5cm but statistically not significant[27].

CT is the best modality to detect pulmonary nodules. It has the accuracy of 99.6% in detecting pulmonary spread and its sensitivity is greater than plain radiography and traditional tomography. Therefore, CT should be done as initial evaluation for patient suspected to have