Liposarcoma of the extremities: a review of the cases seen and managed in a major tertiary hospital in Singapore

Ng Y C S, Tan M H

ABSTRACT

Introduction: Liposarcoma is one of the more common types of soft tissue sarcomas, presenting with a wide spectrum of clinical behaviour. However, there is little information on the outcome, management and survivability of patients with extremity liposarcoma in Singapore.

Methods: A retrospective review of all the patients with extremity liposarcoma, diagnosed between 1997 and 2007, was performed. Univariate and multivariate statistics were used on the data to evaluate the clinical presentations, treatment, outcome and survivability of patients seen.

Results: Over a ten-year period, 30 patients were seen for primary liposarcoma of the extremities. Three patients dropped out and 27 were managed and followed-up. Management included surgery and/or radiotherapy. Histological subtypes included 14 (51.9 percent) well-differentiated, five (18.5 percent) myxoid, four (14.8 percent) de-differentiated, and two (7.4 percent) each of round cell and pleomorphic variants. Four patients (14.8 percent) developed local or metastatic recurrent disease. The mean follow-up was 53 months, and the survival rate with primary disease at 53 months was 92.6 percent. The recurrence-free survival for primary disease at 53 months was 85.2 percent.

Conclusion: Liposarcoma of the extremities is relatively rare compared to other major soft tissue tumours. It is a highly pleomorphic disease, whose outcome is dependent on the histological subtype. Limb-sparing management includes wide resection of the tumour with/without radiation postoperatively.

Keywords: dedifferentiated liposarcoma, limb-sparing surgery, lipomatous tumour, liposarcoma, musculoskeletal tumour, soft tissue sarcoma

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INTRODUCTION

Liposarcoma is one of the more common types of soft tissue sarcomas and accounts for up to 30% of all such cases.[1] It can be defined as a malignant mesenchymal tumour consisting of lipoblasts. The well-differentiated subtype is the most common (> 50% of cases reported).[2] Based on molecular and cytogenetic studies, liposarcoma can be divided into three biological grades, encompassing five different sub-types. The low-grade group would include the well-differentiated subtype with a common 12q amplification. The intermediate-grade group would include the myxoid and round-cell subtypes. This group is characterised by a genetic reciprocal translocation of two genes, the TLS and CHOP genes, resulting in a chimeric t(12;16)(q13, p11) TLS-CHOP gene. The myxoid subtype is further classified into three groups based on round cell composition. The final high-grade group comprises the pleomorphic subtype, which is made up of complex karyotpes[3,4] as well as the de-differentiated subtype. The well-differentiated liposarcoma is the most common variant, and tend to arise in the limbs or retroperitoneum in the middle-aged or elderly population. The myxoid and round-cell subtypes account for the next largest groups (30%–40% of all liposarcomas), often presenting in a younger population. They have a higher risk of metastasis, and occur more often in the limbs. The de-differentiated and pleomorphic subtypes account for about only five percent of all liposarcoma cases. These tend to occur in the older age groups, presenting in the limbs or retroperitoneum. The pleomorphic variant carries an increased risk of both local and distant spread.[2,5,6]

Liposarcomas of the extremities are usually managed by limb-sparing surgery, with or without additional postoperative radiotherapy and/or chemotherapy. Adequate clinical and radiological assessments of the tumour have to be made prior to surgery in assessing the resectability of the tumour. Large tumours sometimes have radical margin involvement, which may necessitate further radical surgery

Department of Orthopaedic Surgery, Singapore General Hospital, Outram Road, Singapore 169608

Ng YCS, MBBS, MMed, MRCSE
Registrar

Tan MH, MBBS, FRCS
Senior Consultant

Correspondence to:
Dr Ng Yung Chuan Sean
Tel: (65) 6321 4047
Fax: (65) 6226 2684
Email: seanng31@gmail.com

to effect a cure completely. Neo-adjuvant therapy is seldom used. Due to the risk of local or systemic recurrence,[7] it might be of benefit to follow up the patient for as long as possible. In this series, we report the experience of the treatment of liposarcomas seen in our department over a period of ten years.

METHODS

All the patients were seen and managed by the senior author over a period of ten years from 1997 to 2007. Their records were retrieved and analysed for this study. 32 consecutive adult patients (19 men, 13 women) with a mean age of 50.9 (range 27–90) years, and with a liposarcoma of the extremity confirmed either by a Trucut biopsy or at final histology after surgery, were seen and managed. Trucut biopsies were only performed for patients with tumours that were clinically indistinct, and served to provide further evidence to confirm the diagnosis. Of the 32 patients, two were recurrent tumour cases and were excluded. The final data included only primary presentations.

Data on tumour presentation, course of management and treatment, and long-term outcome, were obtained from the patient's medical records. Recurrences after treatment were also studied. Every patient underwent a full history, thorough physical examination, routine blood tests, electrocardiogram and chest radiography. As radiographs and computed tomography (CT) were not particularly useful in identifying characteristics and margins of a soft tissue tumour, magnetic resonance (MR) imaging was done for all our patients. It was used to identify certain characteristics such as homogeneity, necrosis and bleeding; assess spread; and hence help to stage the tumour. CT of the chest and bone scintiscan were also done preoperatively to look for metastasis.

Summary statistics were obtained with established methods, including Kaplan-Meier analysis for survival and recurrence. Survival times and time to recurrence or death were measured from the date of definitive surgery, whether carried out primarily or for metastatic disease for palliation. Endpoints for analysis include local recurrence-free survival, distant recurrence (metastasis)-free survival, combined recurrence, recurrence-free (disease-free) survival, and overall survival. A p-value ≤ 0.05 was considered statistically significant.

RESULTS

The mean time to presentation of the 30 patients with primary tumours was 26.1 months, with a mean follow-up period of 53.2 months. Most patients noticed a mass, lump or swelling, not usually associated with pain. Locations of the tumours included a majority in the thigh (n = 22,

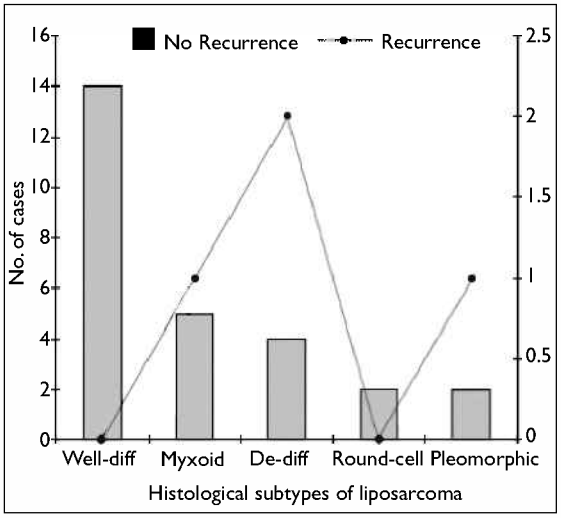

Fig. 1 Graph shows the recurrence frequency based on histology.

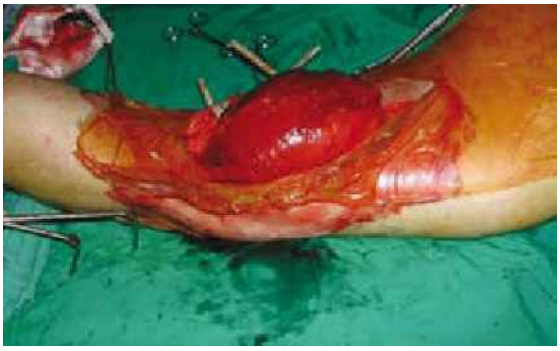

Fig. 2 Operative photograph shows a posterior thigh liposarcoma.

all primary), one in the shoulder, three in the forearm, one in the wrist, one in the knee and two in the soles. However, three patients with primary thigh tumours were excluded in the final numbers – two patients refused further treatment, and the last patient went overseas for further management. There were thus 27 patients at the final count.

Tumour size was assessed preoperatively using three-dimensional imaging with MR imaging, and the maximum dimension of the three planes (coronal, transverse and sagittal) was used. Tumour sizes in the 27 patients ranged from 7 to 22 cm in maximal linear dimension, with a mean of 13.8 cm. 11 (40.7%) of the patients also had Trucut biopsies done. Tumour grades included 17 (63.0%) low, seven (25.9%) intermediate, and three (11.1%) high subgroups in the final histology. Tumours were staged according to the Musculoskeletal Tumour Society staging system.[7] There were no patients in either Stage IA or IIIA. There were 15 (55.6%) patients with Stage IB, one (3.7%) with Stage IIA, and 11 (40.7%) with Stage IIB. The final histological subtypes included 14 (51.9%) well-differentiated, 5 (18.5%) myxoid, two

(7.4%) round-cell, four (14.8%) de-differentiated, and two (7.4%) pleomophic subtypes (Fig. 1).

The treatment strategy for all the liposarcomas seen was to aim for limb salvage. All patients underwent wide resection for their tumours. No amputations were performed. At final histology, only one (3.7%) patient had margin involvement of the resected specimen. He underwent further re-excision, and final histology returned negative for malignancy. All patients with low-grade disease did not receive adjuvant radiotherapy. Postoperative radiotherapy was given to patients who had less than adequate or compromised margins, and those who had tumours with subtypes known to be more biologically aggressive. 14 (51.9%) patients underwent postoperative radiotherapy. 12 had high-grade lesions (Stage IIA/B), one had an intermediate-grade myxoid liposarcoma, and one had margin involvement.

No patients underwent neoadjuvant chemotherapy. Chemotherapy was administered to three patients who had biologically more aggresive tumours (de-differentiated subtype). Four patients with primary disease developed either local recurrence and/or metastatic disease (Fig. 1). They were all Stage IIB tumours, and re-presented at a mean of 11.7 (5–18) months. No patient with well-differentiated liposarcoma developed any recurrence. Grouped according to original subtypes, two were de-differentiated liposarcomas, one was a pleomorphic and the last was a myxoid liposarcoma. One patient with de-differentiated tumour presented with lung and spinal cord (with cord compression) metastases, and received chemotherapy and surgery (decompression laminectomy and instrumentation); another had local recurrence of the tumour and was treated with wide resection. Subsequently, the patient developed right lung, liver and sigmoid colon metastases and was treated with chemotherapy. The pleomorphic subtype developed local recurrence and underwent a repeat wide resection of the tumour. The myxoid subtype developed a rib metastasis and underwent resection as well.

Patients were followed up for a mean of 53.2 (2–135) months. Two patients, who initially presented with primary disease, passed away at 54 and 65 months, respectively. The combined recurrence at 53 months was 14.8%. The local recurrence-free survival at 53 months was 92.6%, and the distant recurrence-free survival at 53 months was 92.6%. The recurrence-free survival for primary disease at 53 months was 85.2%. The overall survival at 53 months for primary disease at presentation was 92.6%. The median values of these parameters have not yet been reached. Analysis of the above values also showed no further association with age and gender of the patient, location of the primary tumour, and type of liposarcoma.

DISCUSSION

Among malignant tumours, liposarcoma of the extremities is uncommon. This was a retrospective study from a small subgroup of patients with liposarcoma, and excluded patients with liposarcoma from the more common retroperitoneal sites. In our series, patients with well-differentiated liposarcoma were treated with wide resection, and we had no recurrences or metastases in this group. This correlates well with some studies, which show very low metastatic rates. De-differentiation of a well-differentiated liposarcoma occurs when local foci of other cells are found, such as a malignant fibrous histiocytoma. This could represent clonal evolution, which has been shown to be capable of metatasis. In our series of patients, de-differentiated liposarcomas were the third most common subtype (n = 4), but had the highest numbers in recurrence (n = 2 out of four cases). One patient had metastatic disease, and another had both local recurrence and subsequent metastatic disease.

The myxoid liposarcoma group was the second most common subtype in our series. This group is a complex and distinct entity that exists in two forms. The first is a well-differentiated myxoid subtype similar to the well-differentiated liposarcoma; and the second form is characterised by a distinctive genetic reciprocal translocation of two genes, the translocation liposarcoma (TLS) and C/EBP-homologous protein (CHOP) genes, resulting in a fusion t(12;16)(q13, p11) TLS-CHOP gene. This latter form is further classified into three categories based on round cell composition. Metastatic potential is also very high, ranging from 20% to 70%. Our patients with myxoid liposarcoma, compared to other subtypes, were almost a decade younger (average age 45 vs. 52 years).[2,8,9] Most primary tumours presented in the thigh, although unusual sites such as the wrist, sole and popliteal fossa were also seen (Fig. 2). Metastasis to the extrapulmonary sites were a striking feature of this subtype. Examples included a patient who developed metastasis to the ribs at five months postoperatively and underwent subsequent resection; and a patient who presented with Stage III metastatic disease with a cubital fossa lesion. Myxoid liposarcoma have also been shown to have significant metastatic potential, and this was observed in our study population (one of five cases). There was also a relationship between tumour size and recurrence as seen in other studies, but our numbers were too small to show any statistical significance. Treatment results corroborated well with other studies, and wide resection with or without

radiotherapy might be the best choice for this group of patients.[10,11]

Round-cell liposarcoma is an intermediate-grade liposarcoma, and may be actually part of a continuum with myxoid liposarcoma. Cytogenic and molecular analyses have also found the same unique translocation t(12:16)(q13;p11), resulting in the fusion TLS-CHOP gene.[12] Some studies have shown a higher metastatic propensity for round-cell liposarcoma.[10] However, results of this subtype in our series were good. Two patients who were diagnosed with round-cell liposarcoma, underwent wide resection and adjuvant radiotherapy, and had no local or metastatic recurrence. There have been studies showing a response to chemotherapy for this group of tumours,[13] but none was given to our patients.

The subgroup of pleomorphic liposarcoma has been shown in studies to be a locally-aggressive and highly-metastasing tumour, with high local recurrence and metastatic rates, and high relapse and poor survival rates. We had two patients with this variant, and both were managed with wide resection and adjuvant radiotherapy. One patient developed local recurrence at 18 months and was treated with a further wide resection. The role of chemotherapy in the management of this variant is unclear, and none was given to our patients. Size of tumour correlates to clinical outcome. The patient with a relapse had a primary tumour of 19 cm and the other patient's tumour measured 9 cm, but our numbers are too small to have any significance, although they do seem to have similar characteristics and results compared to other series.[10,14,15] Both patients were still alive at the last follow-up. One patient with a huge 28-cm de-differentiated liposarcoma developed local recurrence at 11 months and had a further wide resection. He went on to develop multiple metastases to the lung, liver and sigmoid colon at 19 months, and received chemotherapy. He was alive at the last follow-up. This might serve to highlight some recent guidelines as published by the European Society of Medical Oncology, where the minimum clinical recommendations for diagnosis, treatment and follow-up for soft tissue sarcomas have been made.[16] For follow-up, it has been stated very clearly, that early detection of recurrence might influence the possibility of curative treatment. The patient should be followed up every three months with history taking and a physical examination. MR imaging of the site of resection of the primary tumour is proposed to be twice a year for the first 2–3 years, and then annually thereafter. A chest radiograph is also recommended every 3–4 months in the first 2–3 years for patients with high-grade tumours, then twice a year up to the fifth year, and annually thereafter.[16] The most important aim of a thorough follow-up is the early diagnosis of treatable, resectable and potentially curable localised or systemic recurrences. A secondary aim of follow-up is to detect treatment-related complications that might cause significant morbidity to the patient, such as lymphoedema, pain, or loss of neuromuscular function.

This study has its limitations. Patient numbers were small in our series and follow-up periods were not long, and hence may not truly reflect the natural history and progress of the different subtypes of liposarcoma. Management for all the cases was not standardised. Only 11 patients were offered a Trucut biopsy before surgery. This should instead be offered to all patients. As most liposarcomas are large and may not be homogeneous, Trucut biopsies may be unreliable in diagnosing subtypes accurately. Surgery should thus be offered to all patients, and final histology and subtyping be made after tumour excision.

The role of chemotherapy and radiotherapy in the management of liposarcoma is still controversial. Nonetheless, limb conservation surgery for liposarcomas with wide resection, with or without adjuvant radiotherapy, have shown good results in our series. Overall survival rates are more than 90% for primary disease at first presentation, and local and distant recurrence rates are low. The histological subtype, size and site of the original tumour, tumour grade and surgical stage of a liposarcoma also affect the prognosis, management and outcome of this disease. An increased survival rate might be possible if more emphasis is placed on the early detection, adequate treatment and follow-up of the disease.[17]

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