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ORIGINAL STUDY

Malignant proximal fibular tumours : A case series of 17 patients

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The aim of this study was to establish whether the proximity of significant neurovascular structures around the surgical excision results in higher rates of recurrence and poorer survival outcomes. A retrospective study of all patients treated at a regional bone tumour unit for proximal fibula Ewing's tumours and osteosarcomas was conducted, and in total 17 patients were identified. The recurrence rate of all cases was 29.4% and the overall 5 year survival was 70.5%. The recurrence rate just for osteosarcoma was 50%, which compared poorly to published recurrence rates throughout the appendicular skeleton. The 5-year survival for proximal fibula osteosarcoma of 50% was also worse than generalised survivorship data reported in non-metastatic osteosarcoma. This series demonstrates that malignant proximal fibula tumours are a difficult entity to manage and recurrence rates and patient survival are poor for osteosarcoma.

Keywords : bone tumour ; proximal fibula ; osteosarcoma ; Ewing sarcoma.

INTRODUCTION

The superior tibiofibular articulation is an arthrodial joint which exists in the tightly enclosed fourth compartment of the knee joint. The proximity of this compartment to the trifurcation of the popliteal vessel and the common peroneal nerve makes the management of extraosseous tumours of the proximal fibula challenging in bone tumour surgery.

The incidence of primary bone tumours in the fibula is 2.5% (*4*). At the proximal fibula, the commonest malignant tumour types are osteosarcoma and Ewing's sarcoma (*9*). Achieving clear histological margins for malignant tumours is a key goal in their management and generally two types of en bloc resection are undertaken, both described by Malawer (*9*) in 1984. Type 1 or marginal resection describes excision of the proximal fibula with 2-3 cm of diaphysis and muscle cuff in all directions. The common peroneal nerve is preserved. Type 2 or wide extra-compartmental resection involves resection with 6 cm of normal diaphysis, the anterior and lateral muscle compartments, the peroneal nerve, the anterior tibial artery and the tibiofibular joint extra-articularly. Erler *et al* described two additional approaches in 2004, both of which were based on

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Malawer's Type 1 approach, however one technique involved resection of the deep peroneal nerve and a second involved preservation of the proximal tibiofibular joint (*5*). There is no evidence to support the application of one technique over another ; however factors deciding the type of excision include tumour size, grade and proximity to major neurovascular structures.

The management of all localised Ewing's sarcomas and osteosarcomas should be conducted within a multidisciplinary team (MDT) at a specialist centre. The current management for osteosarcoma involves multi-agent pre-operative chemotherapy followed by surgical resection and then post operative chemotherapy (*14*). Ewing's sarcoma is also managed by adjuvant chemotherapy and surgical resection, however radiotherapy may also be used to treat local and distant metastatic disease (*14*).

Standardising recurrence rates for osteosarcoma is difficult and quoted rates in the literature are based on different types of tumour grade, population age and local or widespread disease type. Nathan *et al* found local recurrence rates to be 5.6% in 407 patients with skeletal osteosarcoma (*10*), while Katagiri *et al* described a 10% recurrence in 530 patients with high grade osteosarcoma (*8*). Published Ewing's sarcoma recurrence rates are also variable ; Barker *et al* found that local recurrence was as high as 18% (*1*). In the fibula there have been a few small case series and the largest reported recurrence rates at 12% (*10*) for malignant and aggressive bone tumours. Takahashi *et al* (*15*) described a case series of 13 patients with proximal fibula osteosarcoma managed between 1975 and 1999. In their study all the patients had limb sparing surgery, however all of the 4 (31%) patients who had their common peroneal nerve preserved went on to develop local recurrence. Despite this finding, the authors found that five year survival was 76%. This study is limited in informing current practice because only 6 of the patients received preoperative chemotherapy, and also because over the last 35 years the chemotherapy regimes have changed significantly.

The lack of published recurrence rates for Ewing's sarcoma and osteosarcoma of the proximal fibula makes measuring surgical outcomes a difficult task. Given the proximity of this region to major neurovascular structures and the need for marginal excision to salvage the limb and the potential for incomplete margins in limb salvage surgery, it is vital to know whether recurrence in this region is higher than the published data as it may indicate a need for other treatment options such as primary amputation or the implementation of post-operative radiotherapy.

The aim of this study is to establish whether the recurrence rates and survival outcomes for these tumours are poorer, and whether primary amputation or post-operative radiotherapy should be instituted.

MATERIALS AND METHODS

A retrospective study of all patients treated for Ewing's tumours and osteosarcoma at a regional bone tumour unit between January 1995 and December 2009 was conducted. Inclusion criteria for the study included localised disease at presentation, ongoing follow-up or follow up of at least 5 years, and patients who had undergone adjuvant chemotherapy. Exclusion criteria included the extension of the tumour into the mid-shaft of the fibula, the tibia or the femur.

Patients treated for osteosarcoma and Ewing's sarcoma during the described period were identified through the hospital's histopathology database. A search was carried out by two of the above authors using histopathology reports, radiology reports and digitally stored clinical notes to identify the cohort in this database that had tumours of the proximal fibula. In the initial search 25 patients were identified with tumours of the proximal fibula and there clinical notes were then acquired. After the inclusion and exclusion criteria were applied 8 patients were excluded (7 with metastases at presentation and 1 who was lost to follow-up), which left 17 patients who were included in the study.

The clinical notes of these patients were then studied and basic parameters such as age, sex and presenting symptoms were recorded. Tumour size at presentation was recorded as the maximum diameter of the tumour on MRI (Fig. 1). Further to this, the patients within the group who underwent post-operative radiotherapy were also identified and this information was incorporated into the results. The surgical operation notes were used to classify the surgical technique used for each case and

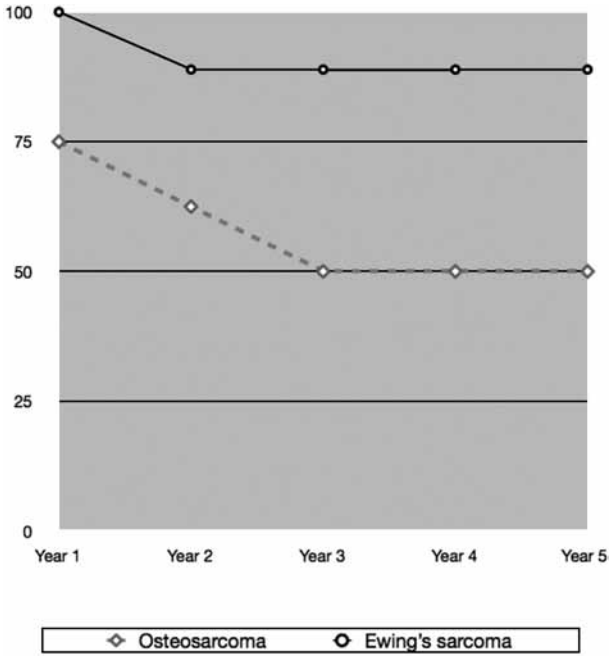

Fig. 1. — Kaplan-Meier survivorship analysis showing 5 year survival of proximal fibular osteosarcoma and Ewing's sarcoma.

the need for further surgery along with its indication was also recorded. The histopathology reports were used to acquire data on the excision margins and the response to the pre-operative chemotherapy, and all cases of recurrence were also recorded.

RESULTS

Between January 1995 and December 2009, nine male patients and eight female patients with proximal fibular Ewing's tumours and osteosarcomas were managed surgically at a regional bone tumour unit (Table I). The mean age of this group was 22.9 (12-65) years. Nine of these patients had an initial symptom of a swelling in the leg, five complained of a swelling and pain and 3 presented with just pain. Eight of these patients had osteosarcoma and nine had Ewing's sarcoma. All seventeen patients in the study had adjuvant chemotherapy, however five had post operative radiotherapy because their histology indicated a poor response to pre-operative chemotherapy. The mean maximum diameter of the tumour at presentation was 5.8 (2-8) cm.

Twelve type II en-bloc proximal fibular resections were performed (Fig. 2), four type I en-bloc resections and one above-knee amputation were performed. Histology of the specimens taken after a first surgical procedure revealed that eleven patients had a poor response to pre-operative chemotherapy (less than 90% tumour necrosis) and 6 had a good response (greater than 90% tumour necrosis). Fourteen patients had clear resection margins, however there were three cases (17.6%) where excision margins were not clear or were marginal. All three cases involved the more radical type II en-bloc resection. Of these, one patient underwent further surgery and has had no local recurrence to date, one had evidence of vascular invasion on the histology report and underwent post operative radiotherapy, however developed widespread metastasis and died a year later. The third patient had marginal excision margins and had no further surgery or radiotherapy and remained disease free at five year follow-up. Twelve patients (70.6%) have no recurrence to date or at five year follow-up, however five (29.4%) developed recurrence. Of these five, four developed widespread metastasis and one developed local recurrence first and widespread metastasis soon after. All five of these patients subsequently succumbed to the disease. Recurrence only occurred in one of the three cases where the primary excision margin was incomplete and identified evidence of vascular tumour invasion. Four of the five recurrences occurred in the eight patients with osteosarcoma (50%) and there was only one recurrence amongst the nine patients with an Ewing tumour (11.1%). When assessing the relationship between tumour size at presentation and recurrence and morbidity, the Pearson product moment correlation coefficient (r) was 0.61 which implies there is a correlation.

Of the eleven patients who had a poor response to the pre-operative chemotherapy, four (36.7%) went on to develop recurrence and of the six who had a good response to chemotherapy, one (16.7%) went on to develop recurrence. Applying Fisher's exact test this is not statistically significant ($p = 0.60$), though a small population size makes it diffi-

Table I. — Summary of results

Case	Age/Sex	Tumour type	Tumour Maximum Diameter at Presentation	Response to pre-operative chemotherapy	Resection Type	Surgical margins	Post op Radio-therapy	Tumour Recurrence	Mortality
1	19/F	Osteosarcoma	2 cm	< 90% Tumour Necrosis	Type II	Incomplete	No	No	N/A
2	22/F	Osteosarcoma	5 cm	> 90%Tumour Necrosis	Type I	Clear	No	No	N/A
3	13/F	Osteosarcoma	7 cm	> 90%Tumour Necrosis	Type I	Clear	No	No	N/A
4	20/M	Osteosarcoma	7 cm	> 90%Tumour Necrosis	Type II	Clear	No	Yes - at 2 years	At 2 years
5	11/M	Osteosarcoma	8 cm	< 90% Tumour Necrosis	Type II	Clear	Yes	Yes - at 3 years	At 3 years
6	15/M	Osteosarcoma	7 cm	< 90% Tumour Necrosis	Type II	Incomplete	Yes	Yes - at 1 year	At 1 year
7	22/F	Osteosarcoma	5 cm	< 90% Tumour Necrosis	Type II	Incomplete	No	No	N/A
8	13/M	Osteosarcoma	6 cm	< 90% Tumour Necrosis	type II	Clear	No	Yes - at 1 year	At 1 year
9	18/M	Ewings	5 cm	< 90% Tumour Necrosis	type II	Clear	Yes	No	N/A
10	54/F	Ewings	7 cm	< 90% Tumour Necrosis	Above knee amputation	Clear	No	No	N/A
11	20/F	Ewings	6 cm	< 90% Tumour Necrosis	type II	Clear	No	No	N/A
12	17/M	Ewings	6 cm	< 90% Tumour Necrosis	type II	Clear	No	No	N/A
13	65/M	Ewings	8 cm	> 90%Tumour Necrosis	type II	Clear	No	Yes - at 1 year	At 2 years
14	16/M	Ewings	5 cm	< 90% Tumour Necrosis	type II	Clear	Yes	No	N/A
15	14/F	Ewings	4 cm	> 90%Tumour Necrosis	type I	Clear	No	No	N/A
16	12/M	Ewings	6 cm	> 90%Tumour Necrosis	Type I	Clear	No	No	N/A
17	38/M	Ewings	4.5 cm	< 90% Tumour Necrosis	type II	Clear	Yes	No	N/A

cult to state that there isn't a relationship between a poor response to pre-operative chemotherapy and recurrence of disease. Interestingly, of the five patients who had post operative radiotherapy, three (60%) went on to develop disease recurrence. It must be pointed out that these five patients were identified and given post operative radiotherapy because they had a poor response to pre-operative chemotherapy or because excision margins were not complete. Survival rates were derived using

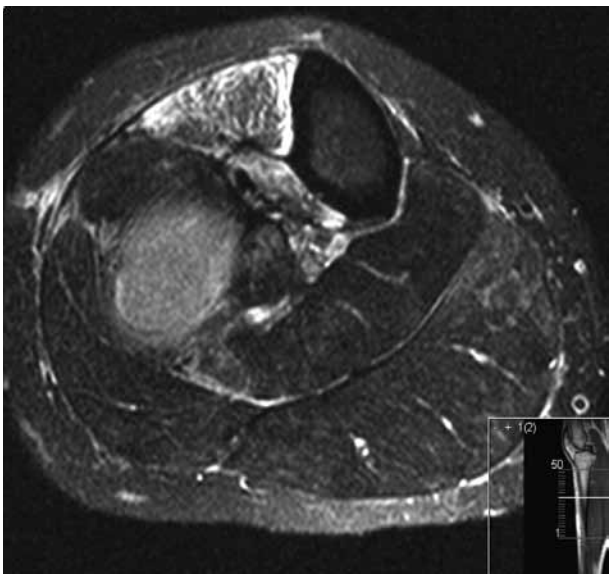

Fig. 2. — Pre-operative T1 weighted MRI showing proximal fibula Ewing's sarcoma.

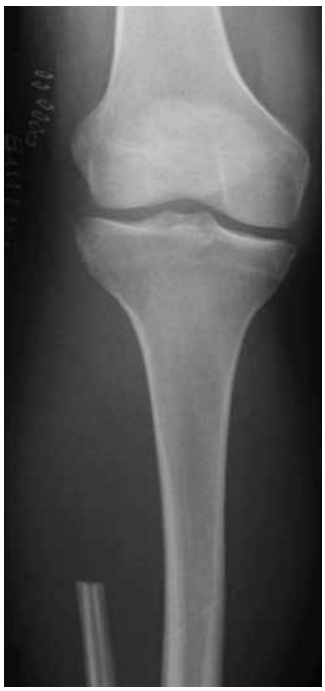

Fig. 3. — Post-operative plain radiographs showing Type II proximal fibular resection.

Kaplan-Meier survival estimates and at year 1 survival was 88.2%, at year 2 survival was 76% and from year 3 to year 5 remained at 70.5%. When separating the groups into tumour type, survival for osteosarcoma was 75% at year 1, 62.5% at year 2 and 50% from year 3 to year 5. For patients who had an Ewing tumour survival was 100% at year 1 and 88.9% from year 2 to year 5 (Fig. 3).

DISCUSSION

The hypothesis of this study was that the surgical management of malignant proximal fibular tumours is challenging because the presence of neurovascular structures within a tight compartment makes complete excision difficult and hence recurrence more likely. The overall recurrence rate was found to be 29.4% and the overall 5 year survival was 70.5%. When separating the data according to tumour type, the results in this study demonstrated a recurrence rate of 50% for osteosarcoma , compared to published rates which have ranged from 5.6% (*7*) to 10% (*8*) throughout the appendicular skeleton. Comparison to other proximal fibula osteosarcoma studies is limited to the case series reported by Takahashi *et al* (*16*) whose recurrence rates of 31% in 13 cases is also higher than rates quoted throughout the appendicular skeleton. Five year survival for osteosarcoma of the proximal fibula was 50% in this study and was found to be poor when compared to generalised five year survival rates of osteosarcoma which have localised disease at presentation which are quoted at between 60-80% (*7*). For Ewing's sarcoma outcomes appeared better, with the recurrence rate of 11.1% in this study very similar to a recurrence rate of 12% which was published by Barker *et al* (*1*). Moreover, 5 year survival for Ewing's was 88.9% compared to other published rates of 5 year survival for patients with localised disease at presentation, which have ranged from 66% (*12*) to 55% (*3*).

The results suggest that osteosarcoma of the proximal fibula has a worse prognosis in terms of disease recurrence and patient survival when compared to osteosarcoma elsewhere in the skeleton when a patient presents with localised

disease. While this study failed to show a significant difference in outcome after a good response to pre-operative chemotherapy, larger studies have demonstrated this (*2*) and adjuvant chemotherapy with local treatment remains the gold standard for treatment of non-metastatic Ewing's sarcoma and osteosarcoma. Despite the surgical technique not correlating to outcome or recurrence within this study, in view of the poorer outcomes for patients with osteosarcoma of the proximal fibula, the authors recommend consideration of the more radical en-bloc type II proximal fibula resection as well as local post-operative radiotherapy. The role for primary limb amputation in the treatment of proximal fibula osteosarcoma requires further investigation. In the past, limb salvage surgery has been adopted because of the presumption that complications rates are lower, patient psychosocial status and functional outcome is better compared to primary amputation, however more recent evidence examining outcomes in long term survivors of lower extremity osteosarcoma suggests that this is not the case (*13*). Should larger data samples indicate that recurrence and survival rates are as poor as those encountered within our case series, there would be a strong case for primary limb amputation being offered to patients as one of the first line surgical management options.

The results also suggested that larger tumours are more likely to result in recurrence and morbidity. All these cases presented initially to their general practitioners with symptoms such as pain or localised swelling behind the knee. It is important to emphasize to primary care doctors that such symptoms require immediate assessment, as earlier detection and management of malignant bone tumours are likely to improve outcomes (*6*).

The study was limited by a change in the chemotherapy regime for patients, which occurred during the fifteen year period. Moreover, the number of patients identified is small, however current evidence for malignant proximal tumours consists of small case series which are limited by out of date oncological management. This series has demonstrated that aggressive bone tumours of the proximal fibula are a difficult entity to manage and recurrence rates and patient survival are poor for osteosarcoma. While local surgical treatment and adjuvant therapy remain the standard treatment, we recommend more radical tumour resection and consideration of post-operative radiotherapy for osteosarcoma of the proximal fibula. Further research is needed to determine the role of primary limb amputation, which may have a role to play in improving long term survival for these patients.

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