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Pathological Fracture in Osteosarcoma: Is it Always an Indication for Amputation?

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SUMMARY

Background. The presence of a pathological fracture due to osteosarcoma (OS) has been considered a high risk factor for dissemination and an indication for immediate amputation. With current neoadjuvant chemotherapy regimens there is a trend towards limb salvage procedures in selected cases. The aim of this study is to assess the outcome of patients treated with amputation versus patients treated with limb salvage surgery focusing on local recurrence, mortality rates and metastatic dissemination.

Material and methods. A retrospective study of patients with OS treated at our institution was performed. Fifteen patients with a mean age of 25.6 years (8 to 66) were identified with an average follow up of 7 years (2 to 29). Patients were treated either with amputation (8) or limb salvage procedure (6). One patient was not treated surgically.

Results. Four patients developed local recurrence (1 in the amputation group and 3 in the limb salvage group, treated with secondary amputation). Six patients developed pulmonary metastasis (4 in the amputation group and 2 in the limb salvage) and 3 patients died (all of them in the amputation group).

Conclusions. 1. A pathologic fracture in an OS is not always a contraindication for limb salvage because the oncologic results are acceptable. 2. In selected cases limb salvage has similar success rates to amputation.

Key words: osteosarcoma, pathologic fracture, prognosis, amputation, limb salvage

BACKGROUND

Osteosarcomas (OS) are the most frequently seen primary bone tumour in children and young adults [1]. It is a malignant lesion with a reported annual incidence of 2 per 1,000,000 of the population [2,3]. A pathological fracture in an osteosarcoma is rare with an incidence, either at diagnosis or during the pre-operative treatment, of 5-10% [4].

In these cases, a pathological fracture results in a local haematoma with potential dissemination of tumour cells throughout the adjacent tissues and into the surrounding vessels and joints [5]. For this reason, amputation has classically been the treatment of choice [4]. However, current neoadjuvant chemotherapy regimes are effective and modern limb salvage procedures have lead to a reassessment of the surgical treatment of these fractures. A number of groups have reported no difference in survivorship following limb-preserving surgery in non-randomized studies [6,7,8,9].

The objective of this study is to review our results in treating pathological fractures secondary to osteosarcoma and to compare the survival and recurrence in those patients treated with amputation versus those treated with limb salvage surgery. Our hypothesis is that patients treated with limb salvage surgery have similar outcomes to those treated with amputation with regards to mortality, local recurrence and metastatic spread.

MATERIAL AND METHODS

We reviewed our tumour database consisting of a total of 455 new cases of primary bone tumours between 1983 and 2011. These were classified depending on their histologic type into: 214 osteosarcomas (47%), 122 chondrosarcomas (27%), 97 Ewing Sarcomas (21%), and 22 malignant Fibrohistiocitomas (5%).

Inclusion criteria were patients who were diagnosed with an osteosarcoma and who sustained a pathological fracture. Exclusion criteria were patients who were treated non-operatively. All patients gave their informed consent to participate in the study.

Overall we found 25 cases (5.49%) of pathological fracture. Of these 25 pathological fractures, 15 (60%) occurred in Osteosarcomas, accounting for the most frequent group in which a pathological fracture can occur.

Our study focusses on the 15 patients (7%) who sustained a pathological fracture in an osteosarcoma. One patient was excluded as no surgical treatment was performed and therefore 14 patients were eligible for analysis.

Information regarding the clinical and radiological characteristics, treatment, and outcome of OS patients was collected through a review of the medical records. An experienced pathologist retrospectively reviewed all available pathology material for these patients. Imaging studies included a combination of plain radiography, computerized tomography (CT), and magnetic resonance (MR), which were reviewed by experienced radiologists.

The presence of a pathological fracture was determined on the basis of clinical and radiological findings (plain radiography, CT, or MR imaging).

The sub-types of osteosarcoma were 4 telangiectatic, 4 osteoblastic, 2 fibroblastic, 2 osteogenic fibrocellular, 1 chondroblastic fusocellular, 1 parosteal fibrosarcoma. Amongst these patients there were 9 males and 5 females with a mean age of 25.6 years (8 to 66) at diagnosis and a mean follow-up of 84.3 months (24 to 348).

All of the fractures were localised within the femur; 13 in the distal femur and 1 in the proximal femur. We performed 8 amputations (6 coxofemoral disarticulations, 2 above-knee amputations) and 6 limb salvage surgeries (femur modular prostheses). The decision as to the operation to be undertaken was based on the involvement of the neurovascular structures, the extent of the haematoma (MRI), tumour or haematoma invasion of a joint, and the response to neoadjuvant chemotherapy (Figures 1-2). In one patient, no surgical procedure was performed due to widespread metastatic disease and a very poor prognosis at the time of diagnosis.

All patients with osteosarcoma and a pathological fracture received neoadjuvant and adjuvant chemotherapy on the basis of the current GEIS (Grupo Español de Investigación de Sarcomas – Spanish Group for Research on Sarcoma) guidelines. It is based on the use of polychemotherapy with 3 chemotherapeutic agents including at least 2 of the following drugs: doxorubicin methotrexate, cisplatin, and vincristin. For adjuvant chemotherapy 2-6 cycles of the same drugs were used. After surgery the pathologist studied the degree of necrosis within the tissue. Necrosis > 90-95% is considered a good response to chemotherapy. Changing chemotherapy regimens was considered whenever necrosis was < 90%. A pre-therapy workup, including an echocardiogram and blood tests, was routinely performed as a baseline to evaluate cardiac and renal function before beginning potentially toxic treatment. Semen or ovarian tissue cryopreservation was offered prior to surgery in young patients. Only one patient received radiotherapy, which was for palliative reasons.

All patients undergoing amputation or limb salvage had a wide resection performed which was confirmed by histological assessment of the tumour.

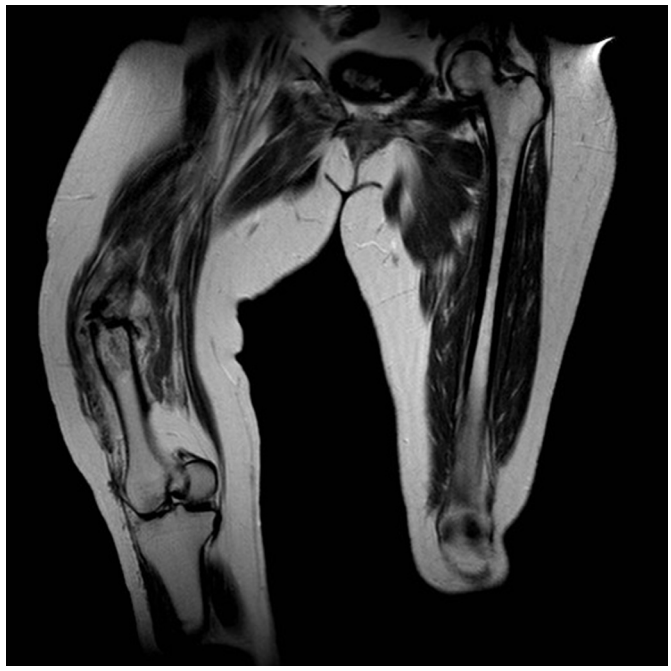

Fig. 1. MRI Image of a pathological fracture of a distal femur underlying an osteosarcoma. Arthrography showing no vascular involvement

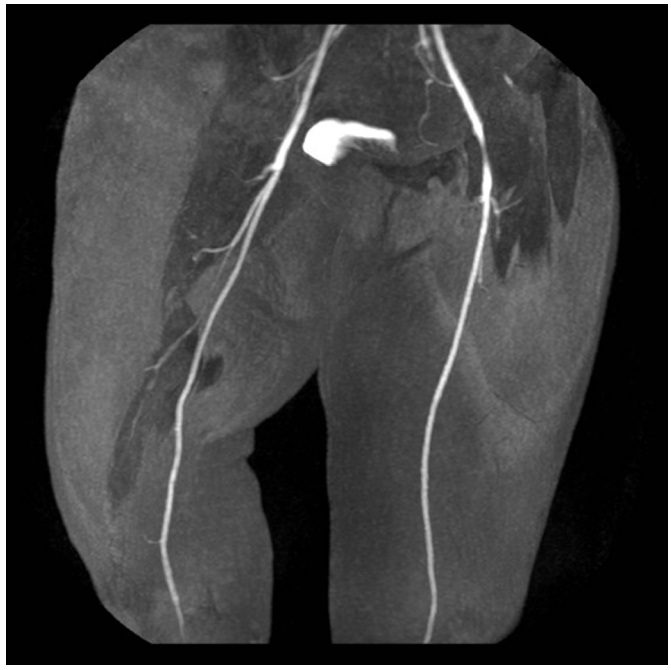

Fig. 2. MRI Image of a pathological fracture of a distal femur underlying an osteosarcoma. Arthrography showing no vascular involvement

For the statistical analysis we computed a p value from a contingency table using Fisher's exact test for the three quantitative variables of mortality, metastatic spread and local recurrence. Unless otherwise indicated, the statistical significance was established as $p<0.05$.

RESULTS

All cases were classified according to Enneking staging system [10]. Results are summarized in Table 1.

The time of presentation of the pathologic fracture was at a mean of 1.6 months (0 to 5 months) after

Tab. 1. Patients classified according to Enneking staging system
*One patient did not undergo surgical treatment and was classified as IIIB

	Limb Salvage group	Amputation group	Total
II A	3	-	3
II B	2	4	6
III A	1	1	2
III B	-	3	3 (+ 1Excluded)*
Total	6	8	14 (+ 1Excluded)*

osteosarcoma diagnosis. In the limb salvage group 3 patients presented with pathologic fracture at the time of diagnosis of osteosarcoma and 3 during neo-adjuvant chemotherapy (mean of 2.7 months after osteosarcoma diagnosis) whereas in the amputation group there were 4 patients with fracture at diagnosis and 4 during chemotherapy (mean of 3.5 months after osteosarcoma diagnosis).

There were 3 deaths in the amputation Group (n= 3/8, 37.5%) and one death (n=1/6, 16.7%) in the limb salvage group. This difference was not statistically significant (p=0,580).

At the time of follow up, 1 (12.5%) of the amputated patients presented with local recurrence in comparison to 3 (50%) in limb salvage cases. This was not statistically significant (p=0.245). The recurrences appeared at 6 months, 7 months and 36 months respectively (mean = 16.3 months) in the limb salvage group and at 16 months in the amputation group (Figure 3).

Three patients (37.5%) who underwent amputation presented at diagnosis with metastasis, compared to one patient (16.7%) in the limb salvage group. Two of the patients with amputation (25%) developed metastatic dissemination during the course of the treatment: one patient developed pulmonary metasases at 24 months and the other developed pulmonary and cerebral metastases 36 months after diagnosis. In the limb salvage group 2 patients (33%) developed metastatic dissemination during the course of the treatment: one at 18 months and one at 17 months after diagnosis. Again the metastases were pulmonary in one patient and pulmonary and cerebral in another (p=1.000). None of these results were statistically significant (p<0.05) (Table 2).

Patients undergoing amputation suffered more complications following surgical treatment with 3 cases of phantom limb, 2 infections of the surgical site (*Staphylococcus epidermidis, Klebsiella oxytoca*), 2 cases of pancytopenia and 1 urinary tract infection.

After undergoing limb salvage procedures one complication was detected in the form of an allograft nonunion that required further surgical intervention. Patients undergoing amputation required 4 further surgical interventions for pulmonary or cerebral metastasis excision. In the group of limb salvage 3 patients needed further surgical interventions in the form of amputation secondary to local recurrence and one pulmonary metastasis excision.

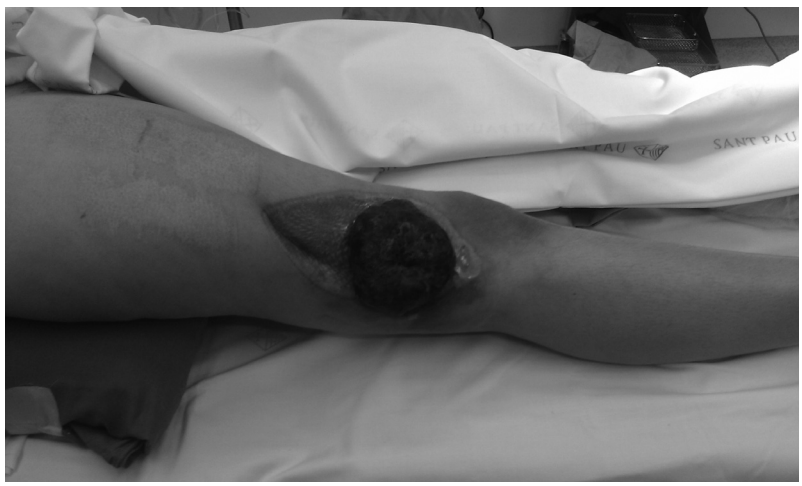

Fig. 3. Local recurrence in a patient that underwent limb salvage procedure using a mega-prosthesis

Tab. 2. Results in both treatment groups

	Limb Salvage	Amputation	p value
Mortality	16.7 % (n= 1/6)	37.5 % (n= 3/8)	p = 0.580
Metastatic Spread	33 % (n= 2/6)	25 % (n= 2/8)	p = 1.000
Local Recurrence	50% (n= 3/6)	12.5% (n= 1/8)	p = 0.245

DISCUSSION

In our institution we offer limb salvage to patients affected by a pathological fracture with an underlying OS except in cases where there is involvement of the neurovascular structures, an uncontained haematoma (MRI), tumour or haematoma invasion of a joint, or poor response to neoadjuvant chemotherapy (Figure 4). In these cases amputation is performed. The decision for limb salvage depends on a complete assessment of the imaging before and after chemotherapy and satisfactory preoperative surgical planning (with good margins) which would permit limb salvage surgery. Using these indications, 53% (n=8) of our patients were treated with an amputation, which differs from other studies that report 15% and 33% amputation rates (11,5). This difference may be due to the higher number of patients with advanced grade tumours (IIB, IIIA, IIIB) found in our series which were unsuitable for limb salvage. Some factors that predict a better outcome, such as the response to chemotherapy and fracture union, should be taken into account when limb salvage is considered [12]. Despite the fact that chemotherapy itself causes a delay in the healing process, it has been reported that fractures which healed were associated with a significantly higher percentage of tumoral necrosis than those which did not heal [13]. The tumour response to chemotherapy was a predictive factor for fracture healing, better global survivorship and local tumour control [12]. Fracture healing is correlated with a high percentage of tumour necrosis, which indicates a good response to chemotherapy [14]. In some studies within the paediatric population it has been suggested that the use of neoadjuvant chemotherapy promotes fracture healing and enables limb salvage [4,13,15].

In malignant high grade primary bone tumours, fractures occur spontaneously after minimal trauma because of the high cellularity, poor differentiation and loose extracellular matrix. The stress or mechanical weakness caused by a diagnostic biopsy and the tumour necrosis after chemotherapy can also contribute in the development of pathological fractures [16]. It has been reported that the occurrence of a pathological fracture in a primary bone tumour is associated with a poorer survival rate and the local treatment in these cases is controversial [5,17]. Patients who sustain a pathological fracture, either at the time of diagnosis of the tumour or during the neoadjuvant chemotherapy, have an increased risk of

Fig. 4. Distal femoral modular prosthesis used in a limb salvage procedure

local recurrence and a diminished survival rate compared with patients that have not sustained a pathological fracture [12]. A pathological fracture in a primary bone sarcoma has previously been considered a contraindication for limb salvage for two reasons: 1) the fracture results in a local haematoma with tumour cell dissemination to surrounding tissues and joints; and 2) microcirculation damage that might facilitate metastasis [5,18]. Some authors believe that a pathological fracture is an indication for an amputation rather than resection due to the risk of disease progression caused by the fracture [4,5].

With the development of effective neoadjuvant chemotherapy there has been an overall improvement in survivorship of patients with an OS [19] and modern techniques of limb salvage have changed the treatment trends. Preoperative chemotherapy results in tumour mass reduction and occasionally fracture healing [4,20,14]. A retrospective case-control matched study reported that limb salvage surgery, in selected patients with a pathologic fracture, did not significantly increase the local recurrence rate nor mortality compared to amputation [12]. Effective neoadjuvant chemotherapy has been a revolution in the management of patients with ostosarcomas. It has improved the survival rate at 5 years from 20% without chemotherapy [21,22] to 60% with chemotherapy [19,23, 24]. Similar survivorship has been noted in osteosarcoma patients treated with amputation or limb salvage (9,25). In the occurrence of a pathological fracture, the survival rate has been reported to be worse than in an unfractured control group (34% versus 58%, $p<0.01$) [26].

The timing of the fracture does not seem to have an influence on the outcome. Various authors have found no significant difference in overall survivorship and local recurrence between patients having a pathological fracture at diagnosis or those having the fracture during the preoperative chemotherapy period. Therefore, the presence of a pathological fracture at the time of diagnosis should not be an absolute indication for an immediate amputation [5,11,27]. When the complete excision of the tumour is anatomically possible and neo and/or adjuvant chemotherapy is used, limb salvage can improve the functional outcome without sacrificing control of the local tumour [9,28]. In a series of patients with pathological fractures where amputation was undertaken in 33% of patients, none developed local recurrence [5]. In another study the rate of local recurrence for all patients treated with limb salvage was 19% compared with 4.5% of all patients with osteosarcoma [11]. However when using wide margins during resection, the range was similar to those of limb salvage procedures in general [9,11,29]. Limb salvage surgery was not found to significantly increase the risk of local recurrence or death. In other series of pathological fractures in osteosarcomas, the local recurrence is reported to be 6.5% [30], which is less than the 23% reported by Scully [12] and 19% reported by Abudu [5]. It should be noted that many patients in the latter study had contaminated excision margins. [30]. The most common locations reported for tumours are the distal femur, proximal tibia and proximal humerus [29,31]. In our study we found the majority (93%) to be in the distal femur.

Due to the possible spreading of tumoral cells during a surgical procedure for managing a pathological fracture in OS, immobilisation in plaster of paris has been considered the standard treatment for the initial chemotherapeutic period and we have been using this treatment method at our institution [5,27]. There are studies that conclude that the preoperative treatment method for the fracture (surgical fixation compared to non-operative treatment) does not influence the local dissemination control nor the overall survivorship. However these studies had small patient cohorts [12,32]. There has also been reported a correlation between an OS patient's survival and the size of the primary tumour, with the larger tumours having a poorer prognosis [33]. However others did not measure the size of the tumour due to doubts over the accuracy of measurement with the presence of significant haematoma and oedema related to the fracture. [5].

There is further controversy regarding the role of radiotherapy following limb salvage surgery, however the majority of studies recommend against its use. Radiotherapy is not successful in preventing local recurrences nor metastases in osteosarcomas, and the adverse effects induced might jeopardize the functional outcomes and result in the need for further procedures [34,5]. Only one of our patients received radiotherapy and this was for palliative reasons in a non-operative case.

In our case series we did not observe an increased mortality following a limb salvage procedure (1 death (16.7%) in the salvage group versus 3 deaths (37.5%) in the amputation group). The metastatic spread was found to be slightly higher in the limb salvage procedure group (33% (n=2/6)) than the amputation group (25% (n=2/8)). Local recurrence was also seen more frequently in the limb salvage group 50% (n=3/6) than in the amputation group 12.5% (n=1/8). Our results were similar to the available current literature with regard to the relationship between type of operative treatment and mortality, metastatic spread or local recurrence control.

These figures show similar results in both groups treated either by limb salvage or amputation. The results are based on patients who fulfill our strict selection criteria. However, we realise that a limitation of our study is the small sample size which is due to the rarity of the condition in question. Other limitations of the current study are its retrospective observational nature and the small number of patients included. Our median follow up was 7 years with a minimum follow-up of 2 years. Six of our patients have less than 4 years follow-up. The heterogeneity of chemotherapy treatment protocols over the years may also introduce a bias. Both studied groups have important differences in terms of grade malignancy, which affects the type of surgery indicated and the prognosis, thus introducing a selection bias. However, the rarity of pathological fractures in OS renders a prospective clinical trial of this OS subtype unfeasible.

The groups are comparable in terms of number of cases, observation time, and safe margins accomplished at surgery. However, response to chemotherapy or stage at diagnosis were not matched for the two study groups. These can be explained because patients were classified to each group depending on the aforementioned selection criteria in each group. The risks that would be undertaken if patients with advanced disease were not treated agressively do not outweight the benefits and jeopardize ethical considerations. Scully et al. also recommend different surgical approaches depending on factors such as response to chemotherapy or fracture union [12]. With the advance of therapeutic oncology, studies that allow for identical groups might arise, but at the present time this is unacheivable.

The classic treatment of pathologic fractures in primary bone tumours has been amputation. Recently in patients with OS there has been a trend towards treating pathological fractures with limb salvage procedures. Even though local recurrence is higher in limb salvage surgery than in amputation there are no significant differences in survival or metastatic spread. We feel that new chemotherapeutic agents with strict selection of cases (i.e. no multi-metastatic spread, contained haematoma on MRI, good response to neoadjuvant chemotherapy, correct planning with wide margins) allows successful limb salvage. There are limited studies in the literature describing the approach to pathologic fractures of bone tumours. Further multi-institution studies or metaanalysis with larger numbers of patients are needed to assist in the treatment of this specific patient population.

CONCLUSIONS

1. A pathologic fracture in an OS is not always a contraindication for limb salvage because the oncologic results are acceptable.
2. In selected cases limb salvage has similar success rates to amputation.

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