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Prognostic Importance of Pathological Fractures in Osteosarcomas

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Abstract

Aims
To investigate whether pathological fractures impact on osteosarcoma patient prognosis in Ireland.
Methods
This was a retrospective study over 22 years in a National Orthopaedic Oncology Centre. There were 117 non-fracture cases and 15 fracture cases. Outcome measures included 5 and 10 year event-free (EFS) and overall survival (OS). Kaplan-Meier curves assessed length of survival and time to death.
Results
Pathological fracture has no significant effect on 10 year EFS or 10 year OS. 3 factors strongly associate with 10 year OS rates: American Joint Committee on Cancer (AJCC) classification ($p<0.001$), Metastases site ($p<0.001$) and Distant recurrence ($p<0.001$). Fractures had poorer post-chemotherapeutic necrosis rates ($p=0.005$).
Conclusion
Pathological fractures have no significant effect on survival rates or length of survival in an Irish population. The effect of pathological fractures on necrosis rates must be explored in future research.

Introduction

Osteosarcoma is the most common primary non-hematological cancer of bone [1]. Overall survival (OS) is relatively poor with recent figures suggesting a 5 year survival of 69% [2]. Davis et al. described tumour necrosis as the most important prognostic variable [3]. Tumour site, size and alkaline phosphatase (ALP) levels have been described as prognostic also [4]. Intuitively, early and local recurrence has been associated with poorer outcomes [5,6]. Disseminated disease and negative surgical margins have been associated with poorer outcomes and proximal tumour location in peripheral bones has a poorer outcome than distally located tumours [7].

Sun et al. confirmed that 3 and 5 year OS and event free survival (EFS) was significantly reduced in patients with pathological fractures [8]. Yang et al. confirmed that pooled hazard ratios for overall and disease- free survival were higher in the pathological fracture group also [9]. A meta-analysis by Salunke et al. concluded that pathological fracture is a negative prognostic indicator associated with poorer rates of 5 year EFS [10]. Lee et al. in 2013 examined a paediatric group and concluded that the control group had longer overall 5 year survival rates [11].

There is a controversy, however illustrated by Cates et al. in 2016 [12]. Their retrospective cohort study shows no statistically significant reduction in overall and disease-free survival rates. Bacci et al. excluded pathological fracture as an indicator of 5 year event-free and overall survival [13]. In 2009, Kim et al. performed a cohort and case-control study showing a tendency to poorer metastasis-free 5 year survival, which did not reach statistical significance. Their case-control study found no survival effect between the fracture and non-fracture group [14].

There is controversy in the literature regarding the effect of pathological fractures on the prognosis of osteosarcoma patients. The research question for this study was to confirm whether or not a prognostic relationship could be confirmed for pathological fractures in osteosarcoma patients using a well-designed study controlling for known confounding variables. Anecdotal observation in our institution has raised the novel question of a negative effect of pathological fractures on post-chemotherapeutic necrosis rates and so this relationship was also questioned and investigated.

Methods

This was a retrospective, single-centre cohort study conducted at the National Orthopaedic Oncology Centre in Ireland. One cohort of osteosarcoma patients had never suffered a pathological fracture during the course of their disease while the other group had.

The inclusion criterion was patient attendance at the National Orthopaedic Oncology Centre in Ireland over a 22 year period with the diagnosis of an osteosarcoma. Patients were identified using histological records. The exclusion criteria consisted of misdiagnosed histology, treatment at an alternative location and an inadequate dataset regarding fracture status and survival outcomes

After application of the exclusion criteria, 156 were reduced to 132 eligible participants. 117 of these had never suffered a pathological fracture at any time in the course of their disease whereas 15 had. Of the 132 eligible for analysis, 17 patients had been lost to follow-up. ‘Time to death’ was used as an outcome only for those deceased patients with complete and current datasets. Regarding the impact of a pathological fracture on prognosis, six dependent outcome variables were used including 5 year EFS, 5 year OS, 10 year EFS, 10 year OS, length of survival and time to death

The second aim was to assess the independent prognostic variables associated with osteosarcomas. These independent variables are tabulated in table 1. The effect of a fracture on post-chemotherapeutic necrosis rates was assessed using the Huvos classification that segregates the scores based on the percentage of necrosis seen after chemotherapy using intraoperative histological samples.

Table 1. Variables Recorded

Variable name	Value recorded	Variable name	Value recorded
Gender	male/female	*Exact size*	size in centimetres
Age of onset	age in number	*Deceased*	yes/no
Site	*name of bone including region*	*<5yr follow-up*	yes/no
Size	*≤8cm, >8cm*	*5yr follow-up*	yes/no
Metastasis site	*0, 1A, 1B*	*10yr follow-up*	yes/no
Metastasis postoperative	*yes/no*	*Chemotherapy*	no/preop/postop/ preop and postop
Haemaglobin	*low/normal/high*	*Necrosis rate*	grade I/II/III/IV
Bone	*name of bone*	*5 year EFS*	yes/no
Bone region	*proximal/ diaphyseal/distal*	*5 year OS*	yes/no
Fracture	*yes/no*	*10 year EFS*	yes/no
Age of surgery	*age in number*	*10 year OS*	yes/no
Surgery type	*amputation/limb sparing surgery*	*Radiotherapy*	yes/no
Local recurrence	*none/<5year/ <10year*	*Histology*	type recorded as per legend
AJCC classification	*stage* IA/IB/IIA/IIB/III/ IVA/IVB	*Identification number*	patient encrypted identification number
Alkaline Phosphatase	*low/normal/high*	*Postoperative recurrence*	none/local/ distant/both
Distant recurrence	*none/<5year/ <10year*	*Margins*	positive/negative
Age of recurrence	*age in number*	*Stage*	high/Intermediate /low

Follow-up time was recorded in years as the time elapsing between initial presentation and either current review or date of death. These data were accurately collected for 115 patients. An independent reviewer confirmed interobserver reliability. Adjusted cox regression models were used for the most significantly prognostic variables reported on univariate analysis. Univariate analyses of fracture against 5 and 10 year EFS and OS were firstly performed. Depending on sample size, Chi-squared and Fisher exact tests were used to analyze these relationships. In order to investigate the effect of fracture against the length of survival, an unadjusted Cox regression model was used and a Kaplan-Meier curve was generated. The effect of fracture on deceased patient time to death was then assessed to see whether those patients who died would die quicker in the presence of a fracture. The failure event was set to 'Time to death' before conducting these analyses. The range of this interval variable was from 1 to 12 years.

Separate univariate analyses of all variables against 5 and 10 year EFS and OS were conducted, with the aim of identifying the strongest predictors of outcome. Adjusting for each of these allowed assessment of whether or not a fracture impacts on survival outcomes once relevant confounders have been adjusted for.

When analyzing whether presence of fracture could predict the type of necrosis response a patient would have, a one-way ANOVA test with Bartlett's test for equal variances was used. The boundaries for the interval variable were Huvos grade 1 to 4.

The statistical package used was Stata/IC 13.1 for Mac (64-bit Intel) by StataCorp, STATAPC 4905 Lakeway Dr, College Station, TX 77845, USA. Statistical significance was taken to be a p-value of <0.05.

Results

Patient demographics

The gender profile showed a male preponderance of 60%. Mean age of onset was 23 with a range of 6 to 83 years of age. This cohort was taken from a predominantly homogenous Caucasian population. The mean length of follow-up per patient was 5.55 years with a range of 1 to 22 years. 17 patients were lost to follow-up despite efforts to get a current status update on them. Importantly, no fracture case was lost to follow-up, therefore strengthening the findings in relation to this cohort.

Prognostic effect of a pathological fracture

The effect of fracture on 5 year EFS (p=0.918) and 5 year OS (p=0.358) was not significant. The presence of a fracture had no correlation with 10 year EFS (p=1.00) or 10 year OS (p=0.717). When investigating the effect of fracture against the length of survival (figure 1), the hazard ratio was reported as 1.23 (95% C.I. 0.72-2.12, p=0.44). When adjusting for the 3 variables with the strongest independent prognostic effect, none of these adjustments demonstrated a significant effect between fracture and 'Length of survival'. The Kaplan-Meier curve generated using unadjusted Cox regression analysis showed the tendency of deceased patients with a fracture to die sooner than patients without a fracture (Figure 2). This was not significant (p=0.136). The hazard ratio was 1.938 (95% C.I. 0.81-4.62). Adjustment for the three significant confounding variables showed no significant effect between fracture and 'Time to death'.

Figure 1. Kaplan-Meier Curve: Fracture Effect on Length of Survival

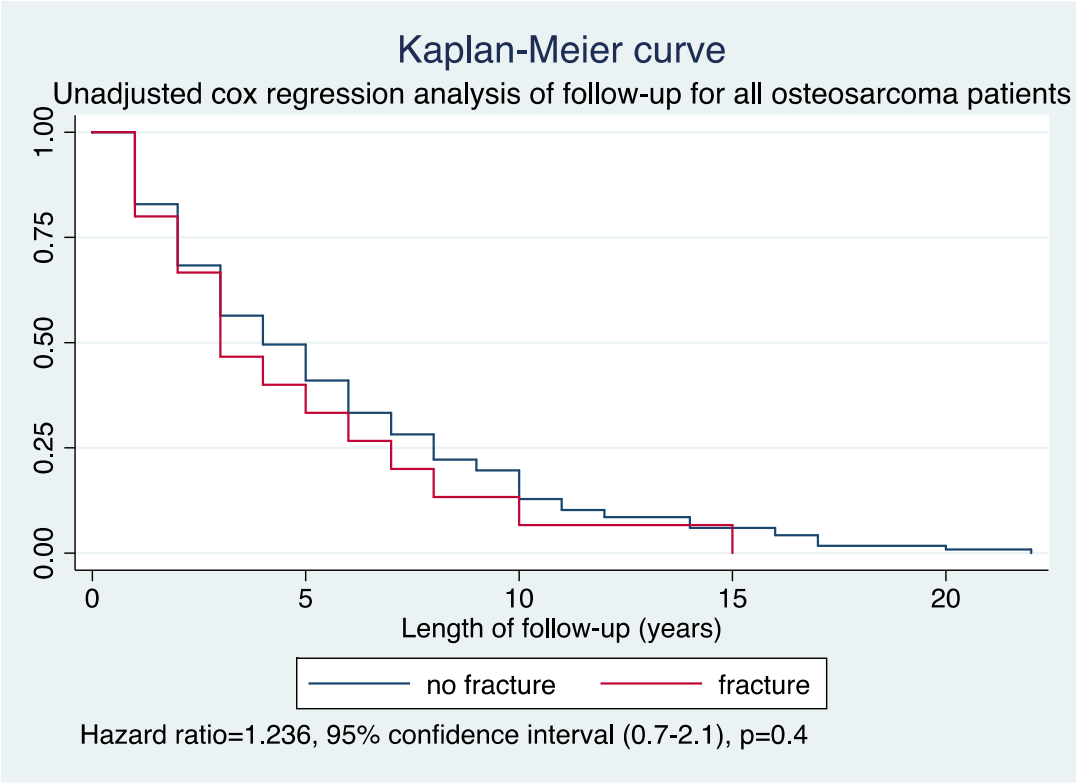
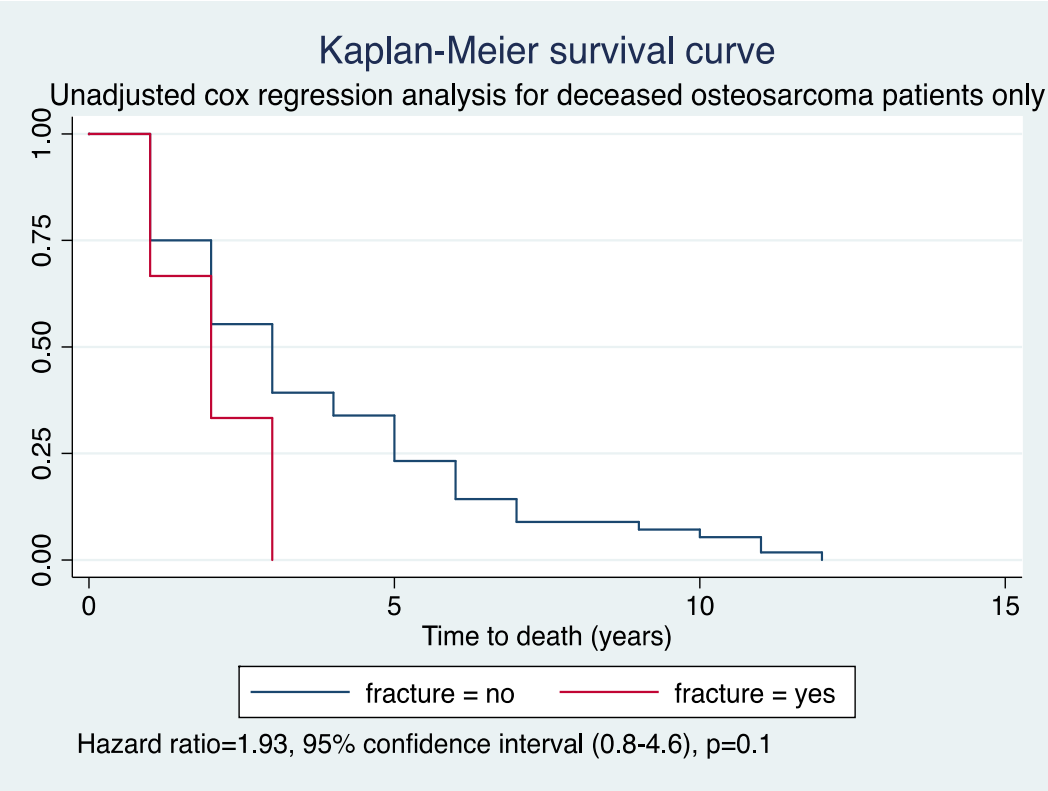


Figure 2. Kaplan-Meier Curve: Fracture Effect on Time to Death



Prognostic factors

10 variables were deemed to have a statistically significant effect on outcome measures (Table 2). Only 3 variables however had a significant effect on all 4 survival outcome variables. These variables were 'distant recurrence' ($p<0.001$), 'metastases site' ($p<0.001$) and 'AJCC classification' ($p<0.001$). Patients with distant recurrence had poorer survival rates than those with local recurrence only. Patients with extrapulmonary metastases had significantly poorer survival rates when compared to patients with pulmonary metastases only. An increasing 'AJCC classification' correlated with a significantly poorer outcome also.

Table 2. Predictors of Event-Free and Overall Survival

Variable	5 year EFS	5 year OS	10 year EFS	10 year OS
Surgery type	P<0.05	-	-	-
Size	-	P<0.05	-	-
Stage	P<0.05	-	-	-
Haemoglobin	-	-	P<0.05	-
Exact tumour size	-	P<0.01	-	-
Local recurrence	P<0.01	-	-	-
Necrosis grade	P<0.05	P<0.05	-	-
AJCC classification*	P<0.001	P<0.001	P<0.01	P<0.001
Metastases site*	P<0.001	P<0.001	P<0.01	P<0.001
Distant recurrence*	P<0.001	P<0.001	P<0.001	P<0.001
Postoperative metastases*	P<0.001	P<0.001	P<0.001	P<0.001
Postoperative recurrence*	P<0.001	P<0.001	P<0.001	P<0.001

Fracture relationship to necrosis rates

Sixty-three percent of non-fracture patients had a poor necrosis rate after chemotherapy (Huvos grade 1 or 2) compared to 80% of fracture patients who had a poor response. This demonstrates the significant effect of fracture status on the grade of post-chemotherapeutic necrosis rates (p=0.005).

Discussion

Recently in the literature, contention has arisen as to whether the presence of a pathological fracture is prognostic of survival in osteosarcomas [12]. Based on the findings of this study, pathological fractures in an osteosarcoma population have no statistically significant effect on survival outcomes when controlling for known prognostic confounders. These results therefore support the findings of Cates et al. in 2016 [12]. Pathological fractures are shown to have no significant effect on 5 and 10 year EFS and OS rates. There is a non-significant trend toward poorer overall survival times and time to death. One must consider the concept of clinical significance in this circumstance. Kim et al. have already acknowledged the concept of a statistically non-significant trend [14]. Visual analysis of Kaplan-Meier curves supports this same trend, especially when considering 'Time to death' (Figure 2).

However, at present, in light of our findings and within the scope of the best available evidence in the literature to date, one must conclude that there is no significant relationship between pathological fracture status and patient survival. A recent study by Schlegel et al. demonstrated a significantly negative impact of pathological fracture on survival outcomes [15]. This study combined Ewing's sarcomas with osteosarcomas however, limiting the relevance of their findings for a group consisting exclusively of osteosarcomas. We also report findings in a larger sample size of osteosarcomas also. Of the 10 prognostic variables, 3 had a strong independent effect on all 4 survival outcomes. Many of the variables found to be prognostic in this condition have been confirmed in prior research already. Weeden et al. has confirmed that local recurrence is prognostic [6]. We agree that local recurrence has a significant effect on 5 year EFS in this cohort. Davis et al. described tumour necrosis as the most important prognostic variable [3]. Tumour necrosis in this dataset has an effect on 5 year EFS and OS. Manoso et al. confirmed that absence of recurrence was a considerable prognostic factor for improved overall survival [16]. This study shows that 'metastases site' and 'distant recurrence', as well as 'AJCC classification', are the strongest predictors of prognosis in this patient cohort. These findings add to our clinical knowledge when managing osteosarcoma patients who present with fractures from the outset.

Interestingly, there seems to be a significant effect of fracture status on the grade of post-chemotherapeutic necrosis rates as classified by the Huvos grading system (p=0.005). This effect is not well described in the literature to date and occurs independent of histological subtype. Given that this effect is independent of histological subtype, it may be possible that the fracture process somehow limits the chemotherapeutic efficacy against the tumour. Further research as to why this effect might be should be performed in the future.

Limitations of this study include sample size. The fracture group is much smaller than the non-fracture group and does limit the power of our findings. Our sample sizes are still comparable with other studies in this area. Seventeen patients were lost to follow-up. Observer bias was addressed using an independent reviewer confirming interobserver reliability. Bias due to confounding variables was addressed by using adjusted cox regression models for the most significantly prognostic variables reported on univariate analysis.

In conclusion, pathological fractures in an Irish cohort do not significantly affect prognosis. The significant prognostic variables were distant recurrence, metastatic location and AJCC staging. Pathological fractures do seem to have a significant impact on post-chemotherapeutic tissue necrosis rates, an effect that should be investigated in future studies.

Declaration of Conflicts of Interest:
No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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References:

1. Hogendoorn PC, Athanasou N, Bielack S, De Alava E, Dei Tos AP, Ferrari S, et al. Bone sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2010;21 Suppl 5:v204-13.
2. Society AC. Cancer Facts & Figures (2016) Atlanta, GA. 2016.
3. Davis AM, Bell RS, Goodwin PJ. Prognostic factors in osteosarcoma: a critical review. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 1994;12(2):423-31.
4. Bramer JA, van Linge JH, Grimer RJ, Scholten RJ. Prognostic factors in localized extremity osteosarcoma: a systematic review. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2009;35(10):1030-6.11
5. Gelderblom H, Jinks RC, Sydes M, Bramwell VH, van Glabbeke M, Grimer RJ, et al. Survival after recurrent osteosarcoma: data from 3 European Osteosarcoma Intergroup (EOI) randomized controlled trials. European journal of cancer (Oxford, England : 1990). 2011;47(6):895-902.
6. Weeden S, Grimer RJ, Cannon SR, Taminiau AH, Uscinska BM. The effect of local recurrence on survival in resected osteosarcoma. European journal of cancer (Oxford, England : 1990). 2001;37(1):39-46.
7. Chen Z, Guo J, Zhang K, Guo Y. TP53 Mutations and Survival in Osteosarcoma Patients: A Meta-Analysis of Published Data. Disease markers. 2016;2016:4639575.
8. Sun L, Li Y, Zhang J, Li H, Li B, Ye Z. Prognostic value of pathologic fracture in patients with high grade localized osteosarcoma: a systemic review and meta- analysis of cohort studies. Journal of orthopaedic research : official publication of the Orthopaedic Research Society. 2015;33(1):131-9.
9. Yang M. Prognostic role of pathologic fracture in osteosarcoma: Evidence based on 1,677 subjects. Journal of cancer research and therapeutics. 2015;11(2):264-7.
10. Salunke AA, Chen Y, Tan JH, Chen X, Khin LW, Puhaindran ME. Does a pathological fracture affect the prognosis in patients with osteosarcoma of the extremities? : a systematic review and meta-analysis. The bone & joint journal. 2014;96-B(10):1396-403.
11. Lee RK, Chu WC, Leung JH, Cheng FW, Li CK. Pathological fracture as the presenting feature in pediatric osteosarcoma. Pediatric blood & cancer. 2013;60(7):1118-21.
12. Cates JM. Pathologic fracture a poor prognostic factor in osteosarcoma: Misleading conclusions from meta-analyses? European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2016.
13. Bacci G, Longhi A, Versari M, Mercuri M, Briccoli A, Picci P. Prognostic factors for osteosarcoma of the extremity treated with neoadjuvant chemotherapy: 15-year experience in 789 patients treated at a single institution. Cancer. 2006;106(5):1154-61.12
14. Kim MS, Lee SY, Lee TR, Cho WH, Song WS, Cho SH, et al. Prognostic effect of pathologic fracture in localized osteosarcoma: a cohort/case controlled study at a single institute. Journal of surgical oncology. 2009;100(3):233-9.
15. Schlegel M, Zeumer M, Prodinger PM, Woertler K, Steinborn M, von Eisenhart-Rothe R, et al. Impact of Pathological Fractures on the Prognosis of Primary Malignant Bone Sarcoma in Children and Adults: A Single-Center Retrospective Study of 205 Patients. Oncology. 2018;94(6):354-62.
16. Manoso MW, Healey JH, Boland PJ, Athanasian EA, Maki RG, Huvos AG, et al. De novo osteogenic sarcoma in patients older than forty: benefit of multimodality therapy. Clinical orthopaedics and related research. 2005;438:110-5.