Prognostic factors and late effects of treatment in localised high grade extremity osteosarcoma
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Do Pathological Fractures influence Survival and Local Recurrence Rate in Bony Sarcomas?

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6.1 Introduction

Pathological fracture through a bony sarcoma can theoretically worsen prognosis by spreading tumour via the fracture haematoma, or by spreading micro-metastases. It can also lead to joint involvement. If the fracture is not recognized as being pathological, there is a risk of inappropriate procedures, delaying diagnosis and potentially spreading the disease more than necessary. The literature is unclear about the implications of a pathologic fracture on the outcome for patients with bony sarcomas(1-6). The aim of the current study was to establish whether pathological fracture had any influence on surgical management, local recurrence or survival in patients treated for a localised high grade extremity sarcoma of bone (osteo-, Ewing’s, or chondrosarcoma). For osteosarcoma and chondrosarcoma the influence of subtype was established as well.

6.2 Patients and methods

A retrospective survey was performed, using a prospectively kept database in which patient, tumour, treatment and outcome details were recorded. We included all patients, treated between 1983 and 2003, for a localised, primary, high grade, bony osteosarcoma, chondrosarcoma or Ewing’s sarcoma of an extremity. All patients were treated in the Royal Orthopaedic Hospital in Birmingham (UK), which is a national referral centre for bone tumours. We excluded those patients who did not receive “standard treatment”. In osteosarcoma and Ewing’s sarcoma this consisted of pre-operative chemotherapy, followed by resection of the tumour, and post-operative chemotherapy. For osteosarcoma chemotherapy was administered according to the protocol of the European Organisation for Research and Treatment of Cancer (EORTC) current at the time(7;8), for Ewing’s sarcoma according to the protocol of the UKCCSG or the EICESS groups(9;10). Tumours, located in, or extending into the proximal half of the humerus and femur were considered to be proximal”, the others “distal”. Radical and wide margins, according to Enneking(11), were considered to be “adequate”, marginal or intralesional margins “inadequate”. Chemotherapy response was defined according to the protocol of the European Osteosarcoma Intergroup as good if less then 10% of viable tumour was found in the resection specimen(12;13). Outcome parameters were local recurrence and estimated 10-years overall survival. We compared the outcome in patients with and without a pathological fracture through the tumour, occurring before or during treatment. To evaluate safety of limb saving surgery in patients with a fracture, type of surgery was evaluated in respect to local recurrence and survival.
Other evaluated prognostic variables included proximity of the tumour, surgical margins, and chemotherapy response (for osteo- and Ewing’s sarcomas). The influence of subtype on the occurrence of fracture and on survival was established for osteosarcoma (telangiectatic as opposed to “other” subtypes), and for chondrosarcoma (dedifferentiated as opposed to grade 2 or grade 3). In a total of 620 eligible patients who were treated for osteosarcoma in the mentioned period, 83 had metastatic disease at diagnosis and were excluded. The fraction of patients with metastasis at diagnosis was equal in the fracture and non fracture group (15% and 13% respectively, p=0.58, chi square). Fifty three further patients were excluded, 45 because they did not receive standard treatment (41 had no or incomplete chemotherapy, 4 no resection), and 8 because they died of an unrelated cause. Thus 484 patients were analysed. The mean follow-up in survivors was 117 months (7-252 months). Completeness of follow-up was 97% after 2 years and 94% after 3 years.

For chondrosarcoma, 152 patients were treated, 13 of them had metastatic disease at diagnosis. Again no difference in percentage of patients with and without fracture was found between these 2 groups (13% and 7%, p=0.30, chi square). A further 9 patients were excluded, 2 because resection was impossible, 7 because of unrelated death. This left 130 patients with localised, primary, high grade chondrosarcoma of an extremity to analyse. All included patients were diagnosed with a chondrosarcoma grade 2 or 3, or a dedifferentiated chondrosarcoma. The mean follow-up in survivors was 81 months (3-263 months). Completeness of follow-up was 88% after 2 years and 76% after 3 years.

Of the 223 patients with Ewings sarcoma, 52 had metastatic disease at the time of diagnosis. The percentage of metastatic disease in the fracture and no fracture groups did not differ significantly (14% and 11%, p=0.56, chi square). Fifteen patients were excluded because they did not receive standard treatment (5 had palliative chemotherapy, 7 had chemo- and radiotherapy but no surgery, 3 did not have chemotherapy). This left 156 patients with Ewing’s sarcoma to analyse. The mean follow-up in survivors was 120 months (19-253 months). Completeness of follow-up was 99% after 2 years and 92% after 3 years.

**Statistical analysis**

Comparability of the groups with and without fracture was assessed with the Chi-Square test for nominal variables and with a Mann/Whitney test for age. Local recurrence was compared between the groups with a Chi-square test as well. Overall survival was determined by Kaplan Meier survival analysis and compared between groups with a log rank test. For assessment of (independent) predictive value of factors a Cox proportional hazards model was used (level of significance p≤0.05).
6.3 Results

6.3.1 Osteosarcoma: Patient and tumour characteristics and treatment. Comparability of fracture- and control groups

Of the 484 patients in the osteosarcoma group, 56 had a fracture (12%). The groups with or without a fracture were comparable regarding sex and age at diagnosis. The site of the osteosarcoma in both groups was predominantly in the distal femur. The second most common place was the proximal tibia, followed by the humerus (figure 6.1-A). Location of the tumours in the bone was different in both groups: in the fracture group 41% of the tumours were proximal, compared to only 13% of tumours in the control group (p<0.01). The fraction of telangiectatic subtype was higher in the fracture group (23% versus 6% in the control group, p<0.01). In the group of patients with a telangiectatic osteosarcoma the incidence of fracture was higher (34%) than in the group with other subtypes (10%).

Treatment in both groups was comparable. Adjuvant radiotherapy was given in 9% of patients in the fracture group and in 8% in the non-fracture group (p=0.90). All fractures were treated conservatively apart from 1 which was treated with osteosynthesis elsewhere, which did not influence further treatment. Limb saving surgery was done in the majority of cases and percentages of ablative and limb saving surgery were comparable between the 2 groups, as were surgical margins and chemotherapy response (see table 6.1).

FIGURE 6.1 Number of fractures and total number of tumours on specified sites (% of fractures between brackets) in the eligible patients: 484 with osteosarcoma (A), 130 with chondrosarcoma (B), and 156 with Ewing’s sarcoma (C).
6.3.2 Chondrosarcoma: Patient and tumour characteristics and treatment. Comparability of fracture- and control groups

Of the 130 analysed chondrosarcoma patients 33 (25%) had a fracture. The groups of patients with or without a fracture were comparable concerning age, sex, treatment and surgical margin. The fracture group showed a tendency towards more proximal tumours and towards a higher fraction of dedifferentiated subtypes, but these differences did not reach the level of significance. Tumour site was different from that in osteosarcoma, the majority being localised at the proximal, rather than the distal femur or proximal tibia (figure 6.1-B; Table 6.1).

Table 6.1 - Comparability of fracture- and no-fracture group in Osteosarcoma, Chondrosarcoma, and Ewing’s sarcoma

<table>
<thead>
<tr>
<th></th>
<th>Osteosarcoma Fracture (n=56)</th>
<th>Osteosarcoma No-fracture (n=428)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>36/20</td>
<td>254/174</td>
<td>0.48</td>
</tr>
<tr>
<td>Median age (yrs+range)</td>
<td>16 (4-57)</td>
<td>16 (5-57)</td>
<td>0.52</td>
</tr>
<tr>
<td>Proximal tumour (%)</td>
<td>23 (41)</td>
<td>54 (13)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Teleangiectatic subtype (%)</td>
<td>13 (23)</td>
<td>25 (6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Grade 2:</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Dedifferentiated (%)</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Grade 3 (%)</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Grade 2 (%)</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Limb salvage (%)</td>
<td>44 (79)</td>
<td>357 (83)</td>
<td>0.37</td>
</tr>
<tr>
<td>Adequate margin (%)</td>
<td>35 (63)</td>
<td>288 (67)</td>
<td>0.58</td>
</tr>
<tr>
<td>Poor Chemotherapy response (%)</td>
<td>43 (78)</td>
<td>320 (75)</td>
<td>0.91</td>
</tr>
<tr>
<td>Adjuvant radiotherapy (%)</td>
<td>5 (9)</td>
<td>36 (8)</td>
<td>0.90</td>
</tr>
</tbody>
</table>

1 For osteosarcomas, 2 For chondrosarcomas

6.3.3 Ewing’s sarcoma: Patient and tumour characteristics and treatment. Comparability of fracture- and control groups

In the Ewing’s sarcoma group, 16 of 156 (10%) had a fracture. Again, the groups with or without a fracture were comparable for age, sex, treatment and surgical margin. Also in Ewing’s sarcoma the fracture group showed significantly more proximal tumours (Figure 6.1-C; Table 6.1).
6.3.4 Local Recurrence and overall survival in osteosarcoma

The local recurrence rate was similar (e.g., 14 %) in the fracture group and the control group in osteosarcoma patients (p=0.96). Comparing local recurrence between patients in the fracture group only, treated with ablative or limb saving surgery, revealed no statistically significant differences with local recurrence in 17% of the ablative group and 14% of the group treated with limb saving surgery (p=0.79 in Chi-Square test). The estimated 10-year overall survival in the entire group of osteosarcoma patients was 55%. The overall survival in the group with a fracture was lower (34%) than in the control group (58%; p<0.01). Table 6.2 shows the results of univariate analysis. It appears that, apart from fracture, proximal tumour location, poor chemotherapy response, inadequate margin, and ablative surgery are correlated with worse survival. Comparing survival in fracture and control group, shows that fracture is a predictor of worse survival in most subgroups, but not in patients with proximal tumours, telangiectatic subtype, good chemotherapy response, or ablative surgery. In multivariate analysis (table 6.3), fracture, proximal tumour location, ablative surgery, inadequate margin, and poor chemotherapy response appear to be independent predictors of worse survival.
6.3.5 Local Recurrence and Overall survival in Chondrosarcoma

The local recurrence rate was not statistically different between the fracture and the control group in chondrosarcoma, although a tendency towards more local recurrence in the fracture group seemed to exist (local recurrence in fracture group 33%, in control group 20%, p=0.11). No statistical difference in local recurrence was found in the fracture group comparing ablative and limb saving surgery (39% in the ablative group, and 20% in the group treated with limb saving surgery; p=0.28 in Chi-Square test).

### Table 6.2 Estimated 10 year survival in osteosarcoma (%); Univariate analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>All patients (n=484)</th>
<th>Fracture (n=56)</th>
<th>No-fracture (n=428)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>55</td>
<td>34</td>
<td>58</td>
<td>0.0002</td>
</tr>
<tr>
<td>Proximal tumours</td>
<td>39</td>
<td>33</td>
<td>42</td>
<td>0.24</td>
</tr>
<tr>
<td>Distal tumours</td>
<td>58</td>
<td>36</td>
<td>60</td>
<td>0.006</td>
</tr>
<tr>
<td>p-value ↑</td>
<td>0.0002</td>
<td>0.3757</td>
<td>0.0043</td>
<td></td>
</tr>
<tr>
<td>Telangiectatic</td>
<td>47</td>
<td>43</td>
<td>52</td>
<td>0.221</td>
</tr>
<tr>
<td>Other subtype</td>
<td>56</td>
<td>33</td>
<td>58</td>
<td>0.0004</td>
</tr>
<tr>
<td>p-value ↑</td>
<td>0.6284</td>
<td>0.7886</td>
<td>0.9975</td>
<td></td>
</tr>
<tr>
<td>Poor chemo response</td>
<td>48</td>
<td>24</td>
<td>51</td>
<td>0.0002</td>
</tr>
<tr>
<td>Good chemo response</td>
<td>79</td>
<td>66</td>
<td>81</td>
<td>0.112</td>
</tr>
<tr>
<td>p-value ↑</td>
<td>&lt;0.0001</td>
<td>0.0233</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Inadequate margin</td>
<td>43</td>
<td>21</td>
<td>46</td>
<td>0.043</td>
</tr>
<tr>
<td>Adequate margin</td>
<td>61</td>
<td>42</td>
<td>63</td>
<td>0.0043</td>
</tr>
<tr>
<td>p-value ↑</td>
<td>0.0024</td>
<td>0.3752</td>
<td>0.0045</td>
<td></td>
</tr>
<tr>
<td>Limb saving surgery</td>
<td>59</td>
<td>37</td>
<td>62</td>
<td>0.0001</td>
</tr>
<tr>
<td>Ablative surgery</td>
<td>35</td>
<td>21</td>
<td>37</td>
<td>0.5278</td>
</tr>
<tr>
<td>p-value ↑</td>
<td>&lt;0.0001</td>
<td>0.3181</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

### Table 6.3 - Overall survival in osteosarcoma; Multivariate analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds ratio</th>
<th>Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Fracture</td>
<td>0.59</td>
<td>0.401 - 0.869</td>
<td>0.0076</td>
</tr>
<tr>
<td>Distal Tumour</td>
<td>0.649</td>
<td>0.456 - 0.924</td>
<td>0.0166</td>
</tr>
<tr>
<td>“Other” Subtype¹</td>
<td>1.25</td>
<td>0.749 - 2.087</td>
<td>0.3937</td>
</tr>
<tr>
<td>Ablative Surgery</td>
<td>2.48</td>
<td>1.743 - 3.528</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Adequate Margin</td>
<td>0.56</td>
<td>0.412 - 0.761</td>
<td>0.0002</td>
</tr>
<tr>
<td>Good Chemo Response</td>
<td>0.336</td>
<td>0.208 - 0.543</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

¹as opposed to osteoblastic subtype

6.3.5 Local Recurrence and Overall survival in Chondrosarcoma

The local recurrence rate was not statistically different between the fracture and the control group in chondrosarcoma, although a tendency towards more local recurrence in the fracture group seemed to exist (local recurrence in fracture group 33%, in control group 20%, p=0.11). No statistical difference in local recurrence was found in the fracture group comparing ablative and limb saving surgery (39% in the ablative group, and 20% in the group treated with limb saving surgery; p=0.28 in Chi-Square test).
The estimated 10-year overall survival in the entire group with chondrosarcoma was 57%. The overall survival in the fracture group was lower (35%) than in the control group (63%) (p=0.04). Apart from fracture, only dedifferentiated and grade 3 subtypes were correlated with worse survival in univariate analysis (table 6.4). As in osteosarcoma, patients treated with ablative surgery, showed a worse survival.

**Table 6.4** - Estimated 10 year survival in chondrosarcoma (%); Univariate analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>All patients (n=130)</th>
<th>Fracture (n=33)</th>
<th>No-fracture (n=97)</th>
<th>p-value ←</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>57</td>
<td>35</td>
<td>63</td>
<td>0.04</td>
</tr>
<tr>
<td>Proximal tumours</td>
<td>50</td>
<td>33</td>
<td>56</td>
<td>0.3556</td>
</tr>
<tr>
<td>Distal tumours</td>
<td>65</td>
<td>50</td>
<td>70</td>
<td>0.0268</td>
</tr>
<tr>
<td>p-value ↑</td>
<td>0.2378</td>
<td>0.5432</td>
<td>0.1919</td>
<td></td>
</tr>
<tr>
<td>Dedifferentiated</td>
<td>36</td>
<td>20</td>
<td>45</td>
<td>0.2531</td>
</tr>
<tr>
<td>Grade 3</td>
<td>48</td>
<td>80</td>
<td>48</td>
<td>0.89</td>
</tr>
<tr>
<td>Grade 2</td>
<td>67</td>
<td>42</td>
<td>71</td>
<td>0.13</td>
</tr>
<tr>
<td>p-value ↑</td>
<td>&lt;0.0001</td>
<td>0.0164</td>
<td>0.0017</td>
<td></td>
</tr>
<tr>
<td>Inadequate margin</td>
<td>60</td>
<td>52</td>
<td>63</td>
<td>0.0749</td>
</tr>
<tr>
<td>Adequate margin</td>
<td>53</td>
<td>47</td>
<td>55</td>
<td>0.9207</td>
</tr>
<tr>
<td>p-value ↑</td>
<td>0.3093</td>
<td>0.6933</td>
<td>0.1664</td>
<td></td>
</tr>
<tr>
<td>Limb saving surgery</td>
<td>60</td>
<td>41</td>
<td>65</td>
<td>0.0595</td>
</tr>
<tr>
<td>Ablative surgery</td>
<td>43</td>
<td>27</td>
<td>46</td>
<td>0.7206</td>
</tr>
<tr>
<td>p-value ↑</td>
<td>0.1208</td>
<td>0.6779</td>
<td>0.1896</td>
<td></td>
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</tbody>
</table>

**Table 6.5** - Overall survival in chondrosarcoma; Multivariate analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds ratio</th>
<th>Confidence Interval</th>
<th>p-value Wald test</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Fracture</td>
<td>0.948</td>
<td>0.453 - 1.982</td>
<td>0.8868</td>
</tr>
<tr>
<td>Distal Tumour</td>
<td>0.787</td>
<td>0.370 - 1.675</td>
<td>0.787</td>
</tr>
<tr>
<td>Subtype¹:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dedifferentiated</td>
<td>1.868</td>
<td>0.698 – 4.999</td>
<td>0.2135</td>
</tr>
<tr>
<td>Grade 2</td>
<td>0.367</td>
<td>0.133 – 1.014</td>
<td>0.0532</td>
</tr>
<tr>
<td>Global Wald test</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ablative Surgery</td>
<td>1.922</td>
<td>0.831 - 40443</td>
<td>0.1267</td>
</tr>
<tr>
<td>Adequate Margin</td>
<td>1.382</td>
<td>0.623 - 3.066</td>
<td>0.4257</td>
</tr>
</tbody>
</table>

¹Wald test related to grade 3
but this difference was not statistically significant. Studying subgroups, fracture correlated with worse survival only in distally located tumours, although a tendency existed in all subgroups. In multivariate analysis, subtype appeared to be the only independent predictor of survival (table 6.5).

### 6.3.6 Local Recurrence and Overall survival in Ewing’s sarcoma

In patients with a Ewing’s sarcoma, no difference between the groups was found for local recurrence, which was 0% and 9% for fracture and no-fracture group

#### Table 6.6 - Estimated 10 year survival in Ewing’s sarcoma (%); Univariate analysis

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=156)</th>
<th>Fracture (n=16)</th>
<th>No-fracture (n=140)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>65</td>
<td>75</td>
<td>64</td>
<td>0.5</td>
</tr>
<tr>
<td>Proximal tumours</td>
<td>70</td>
<td>78</td>
<td>69</td>
<td>0.8216</td>
</tr>
<tr>
<td>Distal tumours</td>
<td>63</td>
<td>71</td>
<td>62</td>
<td>0.5817</td>
</tr>
<tr>
<td>p-value ↑</td>
<td>0.2887</td>
<td>0.7749</td>
<td>0.319</td>
<td></td>
</tr>
<tr>
<td>Poor chemo response</td>
<td>64</td>
<td>71</td>
<td>63</td>
<td>0.6736</td>
</tr>
<tr>
<td>Good chemo response</td>
<td>62</td>
<td>67</td>
<td>61</td>
<td>0.8464</td>
</tr>
<tr>
<td>p-value ↑</td>
<td>0.2878</td>
<td>0.9944</td>
<td>0.273</td>
<td></td>
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<tr>
<td>Inadequate margin</td>
<td>68</td>
<td>67</td>
<td>69</td>
<td>0.8915</td>
</tr>
<tr>
<td>Adequate margin</td>
<td>67</td>
<td>73</td>
<td>66</td>
<td>0.7539</td>
</tr>
<tr>
<td>p-value ↑</td>
<td>0.4396</td>
<td>0.8815</td>
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</tr>
<tr>
<td>Limb saving surgery</td>
<td>66</td>
<td>75</td>
<td>65</td>
<td>0.5378</td>
</tr>
<tr>
<td>Ablative surgery</td>
<td>66</td>
<td>na</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>p-value ↑</td>
<td>0.428</td>
<td>na</td>
<td>0.4571</td>
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</tbody>
</table>

#### Table 6.7 - Overall survival in Ewing’s sarcoma; Multivariate analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds ratio</th>
<th>Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Fracture</td>
<td>1.186</td>
<td>0.403 - 3.492</td>
<td>0.7564</td>
</tr>
<tr>
<td>Distal Tumour</td>
<td>0.833</td>
<td>0.394 - 1.763</td>
<td>0.6333</td>
</tr>
<tr>
<td>Ablative Surgery</td>
<td>1.082</td>
<td>0.243 - 4.823</td>
<td>0.9179</td>
</tr>
<tr>
<td>Adequate Margin</td>
<td>0.851</td>
<td>0.369 - 1.965</td>
<td>0.7053</td>
</tr>
<tr>
<td>Good Chemo Response</td>
<td>0.687</td>
<td>0.336 - 1.406</td>
<td>0.687</td>
</tr>
</tbody>
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respectively (p=0.22). All patients in the fracture group were treated with limb saving surgery. Fracture in Ewing’s sarcoma was not correlated with estimated 10-year overall survival, which was 75% and 64% for fracture and no-fracture group (p=0.50). None of the studied factors showed any statistically significant correlation with survival in univariate (table 6.6) or multivariate analysis (table 6.7).

6.4 Discussion

Although a fracture through a bony sarcoma may theoretically have an adverse effect on the outcome of the disease after treatment(14;15), this is not consistently reflected by the literature. Zeifang and colleagues studied 336 patients with bony sarcomas of different type and stage, 30 of whom had a fracture. They found a similar local recurrence rate but a worse survival in patients with a fracture. Limb saving surgery was considered safe if an adequate resection margin can be obtained(5). This is confirmed by Ebeid and colleagues, who presented a series of 31 patients with a fracture through different types of stage IIIB tumours of bone, who were all treated with limb saving surgery. Local recurrence in this series occurred in 6%. Survival was 81% and seemed worse for patients who sustained their fracture during chemotherapy as opposed to those who presented with a fracture. The follow-up period however in this study was short and the type of tumour differed, making this comparison rather weak(16).

For osteosarcoma the literature is contradictory on the implications of pathological fracture. In 1996 Abudu presented a series of patients with a fracture who showed similar survival to a comparable group in the literature without a fracture(1). Glasser and colleagues reported worse survival for patients with a fracture(17). Scully showed an unfavourable influence of fracture on both local recurrence and survival in a multicentre evaluation(4). This study could be biased by the fact that a considerable part of the patients did not receive pre-operative chemotherapy, as was correctly noted in a comment by Bacci(18). Bacci himself did not find a difference for either local recurrence or survival(3). Both Abudu(1) and Scully(4) compared oncological outcome between patients who presented with a fracture, and those who sustained it during treatment, and both did not find any difference. Abudu reported a higher chance of local recurrence if patients with a fracture were treated with limb saving surgery. This difference disappeared however after correction for surgical margin. Scully(4) as well as Bacci(3) compared limb saving and ablative surgery in their studies and did not find any difference in oncological outcome between them.
In the current study, fracture- and control group consisted of osteosarcoma patients, treated in the same period in one institution. All had similar treatment. The groups were comparable, apart from the fact that tumours in the fracture group were located more proximally, and that telangiectatic subtype was more frequent in the fracture group. This is consistent with the concept that proximal tumours, as well as telangiectatic subtypes, are more aggressive\(^\text{19}\). Fracture was found to be an independent predictor for worse survival, but no difference in local recurrence was found. This seems to indicate that it is probably not spreading of tumour cells in the fracture haematoma that leads to a worse prognosis. More likely, the fracture is a symptom of a more aggressive tumour, and therefore heralds a lower survival chance.

For chondrosarcoma several authors highlighted the importance of local control\(^\text{20-25}\), but few mentioned the influence of pathological fracture. Lee et al\(^\text{2}\) reported on 227 patients with chondrosarcoma, 141 of which were high grade. Pathological fractures occurred predominantly in the group with high grade tumours (38 compared to 46 in the entire group). In their series, fracture did not have an influence on oncological outcome, although it is not clear how exactly this analysis was done. The authors did not comment on the type of surgery in comparison to local recurrence or oncological outcome. They did find a correlation between achieved surgical margin and survival in high grade lesions, as is reported in other publications. In most publications, histological grade is found to be an, independent, prognostic factor in chondrosarcoma. In our patients with high grade non metastatic chondrosarcoma, surgical margins were comparable between fracture and control group. No difference in local recurrence was found. Patients with a fracture did show a lower survival rate. In multivariate analysis however, only subtype appeared to be an independent predictor of survival, which decreased with increasing grade of malignancy. This fits with the idea that a fracture is more likely to occur in a more aggressive tumour, which would also be supported by the abovementioned literature. The fact that more patients with dedifferentiated chondrosarcomas are in the fracture group in our study supports this theory.

For Ewing’s sarcoma, Wagner reported that tumours in the proximal femur are at higher risk for fracture and that late fracture, occurring after completion of therapy, should raise the suspicion of local recurrence\(^\text{26}\). They did not report on the difference in survival or local recurrence between patients with or without a fracture. Fuchs found similar results concerning location, and reported no significant difference in survival or local recurrence comparing 14 patients with a fracture through a Ewing’s sarcoma, sustained before or during treatment, with the entire group of patients\(^\text{27}\). It is not clear in this paper whether the fracture patients are included
in the control group and whether fracture and no-fracture group were matched for treatment, stage, and other characteristics. Hoffmann and colleagues compared 42 fracture patients with a control group of 350 patients with Ewing’s sarcoma or PNET stage 2, and found no difference in relapse free or overall survival(6).

Our study seems consistent with the abovementioned. None of the studies compares ablative and limb saving surgery in fractured Ewing’s sarcoma patients, which in our study does not reveal a difference. The explanation why Ewing’s sarcoma does not show a difference in overall survival between fracture and no-fracture group, whereas osteo-and chondrosarcoma do show worse survival in fractured patients, could be that Ewing’s sarcoma generally is more chemotherapy -sensitive(28). This idea is strengthened by our finding that in osteosarcoma, good chemotherapy responders do not show a difference in survival between fracture and control group.

Another factor that might influence both survival and the chance of pathological fracture in all of the three studied tumours is tumour volume. Bacci and colleagues found tumour volume to be an independent predictor for survival in osteosarcoma, but in their patients pathological fracture did not correlate with survival, not even in a univariate analysis(29). Scully found exactly the opposite, worse survival for fractured patients, but no influence of tumour size(4). For chondrosarcoma Lee and colleagues report a correlation of larger tumour volume with a worse prognosis, but they did not find fracture to be of influence(2). Hoffmann and colleagues found no influence of fracture in Ewing’s sarcoma, and worse survival for patients with larger tumours. Volume, however, lost its predictive value in the fracture group(6). Unfortunately we did not have sufficient information about tumour volume in the three studied patient groups to establish the influence of tumour volume.

We conclude that a pathological fracture in a bony sarcoma does not increase the chance of local recurrence, provided oncological principles are adhered to and the tumour and fracture site can be excised with clear margins. Overall survival is worse in patients with a fracture in osteo- or chondrosarcoma, but not in Ewing’s sarcoma. Fracture is an independent predictor of survival in osteosarcoma only. The fracture is probably not in itself the cause of the lower survival, but rather a symptom of a more aggressive tumour. The influence of tumour volume should be further studied. Limb saving surgery in fractured patients does not seem to have an influence on local recurrence or survival and therefore is thought to be safe, as long as adequate margins can be obtained. We recommend that patients with a pathological fracture through a bony sarcoma be treated by non-operative stabilisation of the fracture (e.g. by means of a splint) and appropriate analgesia, followed by chemotherapy according to the standard protocol. After this, resection of the tumour should, as
usual, be done with wide margins. We have not been able to clarify the benefit, or otherwise, of adjuvant radiotherapy following limb salvage after a pathological fracture.

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Reference List


