Twentieth-century survival from osteosarcoma in childhood
TRENDS FROM 1933 TO 2004

We have reviewed the data from our regional Bone Tumour Registry on patients with osteosarcoma diagnosed between 1933 and 2004 in order to investigate the relationship between survival and changes in treatment. There were 184 patients with non-metastatic appendicular osteosarcoma diagnosed at the age of 18 or under. Survival was calculated using Kaplan-Meier curves, and multivariate analysis was performed using the Cox regression proportional hazards model.

The five-year survival improved from 21% between 1933 and 1959, to 62% between 1990 and 1999. During this time, a multi-disciplinary organisation was gradually developed to manage treatment. The most significant variable affecting outcome was the date of diagnosis, with trends in improved survival mirroring the introduction of increasingly effective chemotherapy. Our experience suggests that the guidelines of the National Institute for Clinical Excellence on the minimum throughput of centres for treatment should be enforced flexibly in those that can demonstrate that their historical and contemporary results are comparable to those published nationally and internationally.

Osteosarcoma is the most common malignant primary bone tumour in children and adolescents,1 and the majority of these tumours occur in this age group. In our region, with a population of just over five million, the incidence is low. In the five years between 1997 and 2001, the diagnosis of osteosarcoma was made in 53 patients aged 18 years or younger.2

The guidelines of the National Institute for Clinical Excellence (NICE) on improving outcomes for patients with sarcoma3 recommend that recognised treatment centres should treat over 50 new primary malignant bone tumours each year. Several established units have had difficulty in complying with this recommendation. This study aimed to document the trends in survival for osteosarcoma among patients aged 18 and under using notes held in our Bone Tumour Registry (Department of Pathology, University of Glasgow, Western Infirmary, Dumbarton Road, Glasgow G11 6NT, UK). This was founded in 1933 and we have used for comparison have also excluded them.6-8 Another case had no follow-up data, one patient was treated in Canada, and in two cases the pathological diagnosis was amended after the death of the patient. Pulmonary metastases were seen on presentation (Enneking stage III) in 19 cases (9%), which were excluded from survival calculations. This proportion increased from 0% prior to 1961, to 15% since 2001. Such
patients have more limited options for treatment, a poorer prognosis, and have typically been excluded in comparable reports in the literature. There remained 184 patients for analysis. Survival was calculated using Kaplan-Meier curves, and covariate analysis was performed using the Cox regression proportional hazards model.

**Results**

The epidemiological characteristics for the patients included in the analysis are shown in Table I. The five-year survival for patients diagnosed before 2000 was 30%, and the ten-year survival for patients diagnosed before 1995 was 27%. Median survival was 26 months (95% confidence interval (CI), 18 to 24). The 3% difference in the five- and ten-year survival rates suggests that the majority of patients who survive for five years will be cured.

There was no significant difference in the five-year survival between male and female patients (male 35%, female 40%; Kaplan-Meier survival analysis and log-rank test, p = 0.397). The age at diagnosis was not significant (Kaplan-Meier survival analysis and log-rank test, p = 0.824). There was a significant difference in survival at five years according to the site of the tumour, with the distal femur being associated with the best outcome (44%) and the proximal humerus the worst (14%) Kaplan-Meier survival analysis and log-rank test, p = 0.011).

Table II summarises the changes in survival if the cases are divided according to year of diagnosis. This shows that five-year survival improved from 21% to 62% during the study period, with 59% of the patients diagnosed between 1990 and 1999 still alive, as well as 79% of the group diagnosed after 2000. The median time of survival for the 1990 to 1999 group is currently 48 months, but this will increase as patients remain alive.

Chemotherapy treatment was associated with a significantly improved chance of survival. Such patients had a median survival of 39 months (95% CI 30 to 48) and a five-year survival of 48%, as opposed to 11 months (95% CI 9 to 13) and 17% in those who did not receive chemotherapy (Kaplan-Meier curve with log-rank test, p < 0.001). Figure 1 illustrates the changes in survival among the patients receiving chemotherapy if they are classified by year of diagnosis, using the divisions described by Kotz et al in Table III (Kaplan-Meier curve with log-rank test, p < 0.001).

The use of chemotherapy has increased the surgical options in the management of osteosarcoma. Figure 2 illustrates how the proportion of patients receiving amputation, wide local excision (in most cases with an endoprosthetic implant), or no surgery has changed over this period. A chi-squared test for association between the periods pre- and post-1990 and the type of surgery (amputation/wide local excision) found a significance of p < 0.001 (Kaplan-Meier curve with log-rank test).

Multivariate analysis was performed using the Cox regression model. The covariates of site (p < 0.001), date (p < 0.001) and chemotherapy (p = 0.025) were included in the final model as factors contributing to risk of death. A tumour that was diagnosed before 1980 (hazard ratio 33 to 40, compared to the most recent era), sited in the proximal humerus (hazard ratio 3.24 compared to all other sites) and was not treated with chemotherapy (hazard ratio 1.77 compared to receiving chemotherapy) was associated with the worst chance of survival.

**Discussion**

Demographic features. The demographic features of the patients in this series are similar to those published

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**Table I. Epidemiological data**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Number of patients</th>
</tr>
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<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>107</td>
</tr>
<tr>
<td>Female</td>
<td>77</td>
</tr>
<tr>
<td>Male:female ratio</td>
<td>1.4:1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age at diagnosis (years)</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 3</td>
<td>1</td>
</tr>
<tr>
<td>4 to 6</td>
<td>7</td>
</tr>
<tr>
<td>7 to 9</td>
<td>17</td>
</tr>
<tr>
<td>10 to 12</td>
<td>34</td>
</tr>
<tr>
<td>13 to 15</td>
<td>55</td>
</tr>
<tr>
<td>16 to 18</td>
<td>69</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
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</table>

<table>
<thead>
<tr>
<th>Site of tumour</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distal femur</td>
<td>81</td>
</tr>
<tr>
<td>Humerus</td>
<td>23</td>
</tr>
<tr>
<td>Proximal tibia</td>
<td>50</td>
</tr>
<tr>
<td>Other</td>
<td>30</td>
</tr>
</tbody>
</table>

**Table II. Median and five-year survival by year of diagnosis**

<table>
<thead>
<tr>
<th>Year of diagnosis</th>
<th>Median survival in months (range)</th>
<th>Five-year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1933 to 1959</td>
<td>11 (4 to 18)</td>
<td>21</td>
</tr>
<tr>
<td>1960 to 1969</td>
<td>12 (10 to 14)</td>
<td>16</td>
</tr>
<tr>
<td>1970 to 1979</td>
<td>17 (12 to 20)</td>
<td>18</td>
</tr>
<tr>
<td>1980 to 1989</td>
<td>44 (17 to 59)</td>
<td>47</td>
</tr>
<tr>
<td>1990 to 1999</td>
<td>&gt; 50% cases still alive</td>
<td>62</td>
</tr>
<tr>
<td>2000 to present</td>
<td>&gt; 50% cases still alive</td>
<td>-</td>
</tr>
</tbody>
</table>
elsewhere\textsuperscript{13,14} and the number of patients treated allows comparison to be made between this and other series. A male:female ratio of 1.4:1 is similar to that in other papers\textsuperscript{4,13} as is the finding that more than 70\% of the tumours occurred at the knee (distal femur/proximal tibia).\textsuperscript{11,15}

Tumours of the distal femur were associated with the best survival and those of the proximal humerus with the worst. It is apparent from the medical records that many osteosarcomas are discovered incidentally on radiographs taken after the child has presented with an injury sustained while playing or participating in sports. Children are more likely to sustain minor injuries to the knee than to the shoulder, which may lead to more tumours being identified at this site at an earlier stage in their growth. Although Enneking stage III tumours are excluded from this analysis, 22\% of the tumours of the proximal humerus were stage III at presentation, compared to 7\% at the distal femur, explaining the poorer prognosis for patients with lesions of the proximal humerus in this series. Improvements in detecting metastatic disease have occurred with the introduction of CT of the thorax in the 1970s, and the proportion of patients with stage III disease at presentation since then is consistent with recent reports of between 15\% and 20\%.\textsuperscript{16,17}

Survival. It is not appropriate to compare the overall survival figures at five and ten years for this group to those in other series because of the long duration of this study. However, the figures calculated for the cases divided according to the date of diagnosis can be compared to similar periods reported in other series. The size of the sample for each of these subdivisions of the overall group is in most instances somewhat smaller than those reported by other centres because of the relatively small size of our population.

Table IV\textsuperscript{4,6,7,11,14,18-23} summarises the survival figures from a number of studies, including this one, listed in approximately chronological order. Table V shows the survival figures from the National Registry of Childhood Tumours of Great Britain for children less than 15 years old.\textsuperscript{24,25}

These results show a marked improvement in survival from osteosarcoma since the early 20th century. The majority of recent studies report five-year survivals approaching 60\%. Our figures are comparable to these results, with a five-year survival for the latest period of 1990 to 1999 of 62\%.

Treatment factors. The definitive treatment of osteosarcoma must be surgical removal of the tumour. At the beginning of our study period this was largely limited to amputation of the involved limb. However, 80\% to 90\% of patients developed fatal pulmonary metastases following surgery,\textsuperscript{8} half within a ten-month period. Once pulmonary metastases were confirmed, the mean survival was six months.\textsuperscript{26} In 1955, Cade\textsuperscript{27} published the results of a study of the treatment of osteosarcoma with mega-voltage radiation, followed six months to one year later by amputation if the patient had not developed metastatic disease by then. He described his method as the natural selection of “favourable, less malignant, non-disseminated cases” for surgery, sparing those with a less favourable prognosis from having to undergo a mutilating operation only to die weeks or months later. This protocol was adopted worldwide, although it did not offer improved survival compared
to surgery alone. The use of radiotherapy is now limited to palliative treatment and or cases that are not amenable to surgery. The five-year survival increased from 47% to 62% between the periods 1980 to 1989 and 1990 to 1999. This improvement can be attributed to the advances in chemotherapy that were being made during this period. Our study shows that both the use of chemotherapy and the year of diagnosis are strong predictors of survival, the evolution of increasingly effective chemotherapy being mirrored by improvements in survival. Prior to the introduction of chemotherapy, the five-year survival from osteosarcoma had consistently been found to be approximately 20% (Table IV).

The first reported use of chemotherapy to treat osteosarcoma in our Registry was for a 14-year-old girl diagnosed in 1967. The routine implementation of chemotherapy in 1972 followed the first published reports of its successful use as an adjuvant to surgery. Cores et al\(^{28}\) and Jaffe et al\(^{29}\) described the use of the single agents doxorubicin and high-dose methotrexate in stimulating the regression of pre-existing pulmonary metastases. As the use of chemotherapy developed, it was discovered that multi-agent protocols were more effective than those with a single agent, and that the use of neo-adjuvant drugs prior to surgery could, in some cases, make the tumour easier to remove by defining its margins and in some cases shrinking it.\(^{30}\) This heralded the increased use of limb-salvage procedures rather than amputations, as the time in which the patient was receiving their neo-adjuvant medication could be used to construct a custom-made endoprosthesi.

No significant difference in survival has been found between patients treated by amputation and those treated by limb salvage.\(^{31,32}\) A recent German study reports no difference in the quality of life and wellbeing following amputations and limb salvage as perceived by the patients.\(^{31}\) However, in the upper limb salvage procedures produce a better outcome, with conservation of the hand contributing significantly to improved function.\(^{31}\)

In conclusion, survival from osteosarcoma among young people in our region improved from less than 20% to over 60% between 1933 and 2004. This is largely a result of the introduction and continued improvement of chemotherapy. Independent of the year of diagnosis, and hence whether or not a patient received chemotherapy,
the most important factor in determining survival is the site of the tumour, with the proximal humerus being associated with a worse outcome than any other site. The age or gender of the patient does not contribute significantly to the outcome. In the early years of this study period, interaction between hospitals was restricted to pathology services, but by 2004 the three major teaching hospitals merged as a managed clinical network with both political and financial support to improve sarcoma care.

Taken together, the total number of primary malignant bone tumours is insufficient to allow our managed clinical network to qualify as sufficiently large to act as a provider of services for bone tumours under the NICE guidelines, but the results provide evidence for flexibility in the implementation of these recommendations where established and successful treatment centres can demonstrate results that are consistent with those of the rest of the United Kingdom and the developed world.

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.

References

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