The Prognosis of Patients with Primary Osteosarcoma Who Have Undergone Unplanned Therapy

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Objective: For diagnosing osteosarcoma correctly, a combination of clinical, radiological and histological examinations is required. Erroneous treatment may cause local contamination and systemic seeding in patients. The purpose of this study was to compare outcomes of planned and unplanned treatment for osteosarcoma.

Methods: A retrospective review of patients with high-grade osteosarcoma who received appropriate surgical treatment and chemotherapy (n = 134) and those who were misdiagnosed and received unplanned surgery (n = 16) between July 1995 and February 2005.

Results: Patients who received unplanned treatment were older (mean age: 29.7 vs. 19.7 years; P = 0.003) and had a smaller mean tumor volume (119 vs. 280 ml; P = 0.015). The 5-year survival rate was not statistically different between the groups. Patients who had unplanned treatment had a higher local recurrence rate (43.8 vs. 17.9%; P = 0.024) and a shorter mean time for recurrence (11.9 vs. 20.8 months; P = 0.036). Furthermore, in patients who underwent unplanned treatment, lung metastases occurred earlier (6.1 vs. 16.2 months P = 0.021) and the final limb salvage rate was less (68.7 vs. 87.3%; P < 0.001).

Conclusions: Unplanned treatment for high-grade osteosarcoma can result in failure of local control and earlier systemic metastases.

Key words: orthopedics/sarcoma – orthopedics/sarcoma-surg – orthopedics/sarcoma-med

INTRODUCTION

Osteosarcoma (OS) is the most common primary malignant bone tumor in teenagers and the estimated worldwide incidence is ~4 per million (1). The current management of high-grade OS is multi-agent neoadjuvant chemotherapy followed by wide tumor resection, limb reconstruction and adjuvant chemotherapy (2–4). Different combinations of platinum, ifosfamide, doxorubicin and high-dose methotrexate, along with limb salvage surgery, have resulted in a survival rate of 50–70% (5–7). Accurate diagnosis of high-grade OS requires integration of clinical, radiological and histological data. The relatively low incidence of malignant bone tumors and limited experience with such tumors in non-specialized centers likely accounts for misdiagnosis and inappropriate treatment such as inadequate surgical procedures and lack of neoadjuvant chemotherapy (8–10).

Studies for unplanned surgery of soft tissue sarcoma have been discussed recently (11,12). However, the outcome of unplanned treatment for high-grade OS was less discussed.
The purpose of the current study was to compare the prognosis of patients who had received unplanned management and treatment with that of patients who underwent planned therapy. The limb salvage rates of the two groups were also compared.

**PATIENTS AND METHODS**

The medical records of 150 patients diagnosed with high-grade OS who received surgical treatment between July 1995 and February 2005 were analyzed. Those with axial tumors \( n = 6 \) and low-grade OS \( n = 16 \) were excluded. The patients were divided into two groups: Group A were patients who were diagnosed with high-grade extremity OS and received appropriate surgical treatment and neoadjuvant chemotherapy \( n = 134 \) and Group B were patients who were initially incorrectly diagnosed at other hospitals and underwent inadequate surgical procedures and did not receive neoadjuvant chemotherapy \( n = 16 \).

Among the patients who received inadequate surgical treatment, the initial diagnoses included benign bone tumor \( n = 10 \), fracture \( n = 4 \), meniscus tear \( n = 1 \) and osteonecrosis of the femoral head \( n = 1 \). All patients underwent inadequate surgical treatment including intralesional curettage for bone tumors, open reduction and internal fixation for fractures and core decompression for osteonecrosis of the femoral head. No patient received neoadjuvant chemotherapy before the initial surgical treatment. After high-grade OS was confirmed by biopsy or histopathological review of prior surgical specimens at our hospital, neoadjuvant chemotherapy was administered. All patients subsequently received wide tumor excision and a limb salvage procedure, except for two patients who underwent amputation due to massive tumor contamination during the first surgery.

All patients with planned treatment received chemotherapy according to two different protocols (Protocol 1 and Protocol 2). All patients who underwent prior inadequate surgery received Protocol 3 chemotherapy, except for two patients (5 and 6) who received initial limb disarticulation without neoadjuvant chemotherapy. In Protocol 1 (from July 1995 to July 1998), patients received combination chemotherapy of 12.0 mg/m² methotrexate, 1.8 g/m²/day ifosfamide, 25.0 mg/m²/day epirubicin and 120.0 mg/m²/day cisplatin and in Protocol 2 (from August 1993 to February 2005) patients received 12.0 mg/m² of methotrexate, 37.5 mg/m²/day adriamycin, 3.0 g/m²/day ifosfamide and 60.0 mg/m²/day of cisplatin. Protocol 3 was more aggressive therapy, which consisted of 12.0 mg/m² methotrexate, 45.0 mg/m²/day adriamycin, 3.0 g/m²/day ifosfamide and 75.0 mg/m²/day cisplatin (Fig. 1).

Figure length, width and depth were measured on preoperative magnetic resonance imaging (MRI) scans and tumor volume \( V \) was calculated by the cylinder formula.

For identification of pulmonary metastases and local tumor recurrence, plain radiographs, chest computed tomography scanning and MRI were performed at the time of diagnosis, ending of neoadjuvant chemotherapy, every 3
months the first 2 years postoperatively, every 6 months during the third to the fifth years and then annually. The presence of lung metastasis and local recurrence was observed and recorded.

The 5-year survival rate was estimated by the Kaplan–Meier method and compared using the log-rank test. Differences of demographic characteristics were analyzed by Pearson’s chi-squared test. Variables including patient age and tumor volume were evaluated by Student’s t-test. A value of \( P < 0.05 \) was considered to indicate statistical significance and all analyses were performed with SPSS software version 13.0 (SPSS, Inc., Chicago, IL, USA).

**RESULTS**

Of 150 patients diagnosed with high-grade OS who received surgical treatment between July 1995 and February 2005, 16 patients (10.7%) with high-grade OS received unplanned treatment. Among these patients, there were 10 who were misdiagnosed with benign bone tumors and underwent intralesional curettage; 4 were misdiagnosed as simple fractures and underwent metal implant fixation (Cases 4, 5, 12 and 13; Figs 2 and 3); 1 (Case 7) was misdiagnosed as early-stage osteonecrosis of the femoral head and underwent core decompression; and 1 (Case 8) was misdiagnosed as a meniscus tear and underwent arthroscopic partial meniscectomy.

The average follow-up of the 150 patients was 49.5 months (range: 7–160 months). Gender was not significantly different between the groups (Table 1; \( P = 0.99 \)); however, the mean age of patients who had planned and unplanned treatment (19.7 and 29.7 years, respectively) was significantly different (Table 1; \( P = 0.003 \)). Among patients of the planned treatment group, only 9% (\( n = 12 \)) were over the age of 30 years, whereas 31.3% (\( n = 5 \)) of the patients of the unplanned treatment group were below the age of 30 years (\( P = 0.021 \)).

The average tumor volume in patients who underwent planned treatment was 280.6 ml (range: 65.5–4875.2 ml) and was 119.2 ml (range: 18.7–473.2 ml) in patients who underwent unplanned treatment (Table 1; \( P = 0.015 \)). Furthermore, there were six patients with a very small tumor volume (range: 18.7–31 ml) in the unplanned treatment group (Table 2).

Lung metastasis occurred in eight (50%) patients who received unplanned treatment and in 35.8% of those who underwent planned treatment and the difference was not

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**Figure 2.** (A) Radiograph of a 40-year-old male (Case 4) with osteosarcoma (OS) involving the left femur diaphysis with pathological fracture. The patient was misdiagnosed and underwent open reduction internal fixation with a plate. (B) Radiograph 4 months later. The patient underwent secondary surgery by re-fixation with an interlocking nail. (C) Magnetic resonance imaging showed extensive tumor seeding from the proximal femur to the distal femur. (D) Radiograph after wide excision and reconstruction by total femur prosthesis.
statistically significant (Table 1; $P = 0.29$). Seven of these eight (87.5%) patients who had unplanned treatment, had involvement of more than three tumor nodules. Compared with metastatic patients who received planned treatment, the difference was not significant. (Table 1; $P = 0.19$). Of these eight patients, seven received thoracotomies for an average of 1.8 times. However, patients who received unplanned treatment were more likely to develop lung metastases earlier (6.1 vs. 16.2 months, respectively) as determined from the time of diagnosis (Table 1; $P = 0.021$).

In the unplanned treatment group, 7 patients (43.8%) experienced local recurrences as compared with 24 patients (17.9%) in the planned treatment group (Table 1; $P = 0.024$) and the mean time intervals for local recurrence were 11.9 and 20.8 months, respectively ($P = 0.036$). Among the seven patients in the unplanned treatment group, two patients underwent repeat wide excision and five patients underwent amputations. Two patients (Cases 5 and 6) received limb disarticulation initially after being referred to our hospital due to massive tumor seeding from the previous surgical wound. At the current follow-up, the rate of limb salvage was less in patients who underwent unplanned surgery (Table 1; $P < 0.001$).

Three patients (Cases 5, 6 and 7) who underwent unplanned treatment expired at the last follow-up. The 5-year survival rates of patients who received planned surgery and those who received unplanned treatment were 60.9 and 75.3%, respectively ($P = 0.850$; Fig. 4), and the difference was not significant.

**DISCUSSION**

The outcome of unplanned excision for soft tissue sarcoma has been recently discussed, and in most studies, after re-excision of the residual tumor bed, the long-term outcome was comparable with that of planned excision (25, 26). Our study was conducted to determine if this finding would be present with respect to malignant bone tumors such as OS. The primary difference in the treatment of soft tissue sarcomas with OS is the use of chemotherapy. Since the 1970s, the standard treatment for high-grade OS has been neoadjuvant chemotherapy, wide tumor excision and adjuvant chemotherapy (22). This regimen has resulted in long-term survival of $\sim 60-70\%$ of patients (23, 24, 27). The outcomes of patients who have initially received inadequate treatment, including those with inadequate surgical margins and no neoadjuvant chemotherapy before the first surgery, have been rarely studied.
OS commonly occurs in teenagers and a second peak occurs in individuals >60 years of age (13). With regard to the patients who underwent unplanned treatment in our study, about 30% of patients were >30 years, and the mean age was 10 years older than for patient who underwent planned treatment. Both differences were statistically significant. According to our results, we strongly considered that OS might not be the initial diagnosis in adult patients with bone lesions or fractures, and result in unplanned and inadequate treatment.

In addition to age, tumor volume may be a factor contributing to unplanned treatment. Six patients who underwent unplanned treatment had a relatively small tumor volume (range: 18.7–31.0 ml), and the mean tumor volume in the unplanned treatment group was only 40% less than in the planned treatment group (119.2 and 280.6 ml, respectively; *P* = 0.015). A relatively small lesion on radiographic studies may lead to a misdiagnosis of a benign bone tumor and subsequent inadequate treatment.

The local recurrence rate of OS has been estimated to range from 5 to 10% (14). Factors influencing local recurrence include surgical margins, tumor location and histological response to chemotherapy (15). Unplanned excision of high-grade OS may cause inappropriate surgical manipulation, inadequate surgical margins, and wrong skin incision and drain position. These factors may explain the higher local recurrence rate and earlier local recurrence time in the patients who underwent unplanned treatment in our study.

The lung is the most common location of OS metastases. It has been reported that 10–20% of patients have lung metastasis at initial diagnosis and 50% develop lung metastasis later (16,17). Of the patients who underwent unplanned treatment, eight (50%) developed lung metastases during follow-up, a rate not higher than that reported for patients with an appropriate initial diagnosis (35.8%, *n* = 48). There was no statistical significance of lung metastases rate or extension of tumor between patients among these two groups (*P* = 0.29 and 0.19, respectively). The causation of the result

### Table 2. Profiles and outcomes of patients who underwent unplanned surgery

<table>
<thead>
<tr>
<th>No.</th>
<th>Age</th>
<th>Gender</th>
<th>Location</th>
<th>Previous diagnosis</th>
<th>Tumor volume (ml)</th>
<th>Lung metastasis</th>
<th>Local recurrence</th>
<th>Limb salvage</th>
<th>Status</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>45</td>
<td>M</td>
<td>Distal femur</td>
<td>Benign bone tumor</td>
<td>94</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Alive</td>
<td>64</td>
</tr>
<tr>
<td>2</td>
<td>27</td>
<td>M</td>
<td>Distal femur</td>
<td>Benign bone tumor</td>
<td>145</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Alive</td>
<td>105</td>
</tr>
<tr>
<td>3</td>
<td>16</td>
<td>M</td>
<td>Proximal tibia</td>
<td>Benign bone tumor</td>
<td>19</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Alive</td>
<td>38</td>
</tr>
<tr>
<td>4</td>
<td>68</td>
<td>M</td>
<td>Femur shaft</td>
<td>Simple fracture</td>
<td>197</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Alive</td>
<td>42</td>
</tr>
<tr>
<td>5</td>
<td>59</td>
<td>F</td>
<td>Proximal femur</td>
<td>Simple fracture</td>
<td>23</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Expired</td>
<td>12</td>
</tr>
<tr>
<td>6</td>
<td>14</td>
<td>M</td>
<td>Proximal humerus</td>
<td>Benign bone tumor</td>
<td>218</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Expired</td>
<td>14</td>
</tr>
<tr>
<td>7</td>
<td>24</td>
<td>F</td>
<td>Proximal femur</td>
<td>ONFH</td>
<td>78</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Expired</td>
<td>13</td>
</tr>
<tr>
<td>8</td>
<td>18</td>
<td>M</td>
<td>Distal femur</td>
<td>Meniscus tear</td>
<td>204</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Alive</td>
<td>77</td>
</tr>
<tr>
<td>9</td>
<td>23</td>
<td>M</td>
<td>Distal radius</td>
<td>Benign bone tumor</td>
<td>23</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Alive</td>
<td>93</td>
</tr>
<tr>
<td>10</td>
<td>53</td>
<td>F</td>
<td>Proximal tibia</td>
<td>Benign bone tumor</td>
<td>83</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Alive</td>
<td>67</td>
</tr>
<tr>
<td>11</td>
<td>15</td>
<td>F</td>
<td>Proximal tibia</td>
<td>Benign bone tumor</td>
<td>27</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Alive</td>
<td>30</td>
</tr>
<tr>
<td>12</td>
<td>15</td>
<td>M</td>
<td>Femur shaft</td>
<td>Simple fracture</td>
<td>188</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Alive</td>
<td>20</td>
</tr>
<tr>
<td>13</td>
<td>20</td>
<td>F</td>
<td>Proximal femur</td>
<td>Simple fracture</td>
<td>31</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Alive</td>
<td>23</td>
</tr>
<tr>
<td>14</td>
<td>14</td>
<td>F</td>
<td>Metatarsal</td>
<td>Benign bone tumor</td>
<td>21</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Alive</td>
<td>25</td>
</tr>
<tr>
<td>15</td>
<td>48</td>
<td>M</td>
<td>Distal femur</td>
<td>Benign bone tumor</td>
<td>473</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Alive</td>
<td>32</td>
</tr>
<tr>
<td>16</td>
<td>16</td>
<td>M</td>
<td>Proximal tibia</td>
<td>Benign bone tumor</td>
<td>83</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Alive</td>
<td>53</td>
</tr>
</tbody>
</table>

No., number; M, male; F, female; ONFH, osteonecrosis of the femoral head.
might be the more aggressive treatment for unplanned treatment group patients, including the higher dosage of chemotherapy or more extensive surgical treatment. However, patients who underwent unplanned surgery developed pulmonary metastases statistically earlier (~10 months) than those who received planned surgery.

Our results indicated that unplanned surgery was not a risk factor for poorer long-term outcome. The 5-year survival rate was 60% for patients who underwent unplanned treatment and 75% for patients who received planned treatment. However, this result was affected by differences among patients, tumor characteristics and treatment methods. The tumor volume at the time of diagnosis has been shown to be a significant predictive factor of outcome (16,18). In our study, the mean tumor volume was smaller in the unplanned treatment group, and this may explain why there was no difference in 5-year survival rates between the two groups. Before patients underwent repeated wide tumor excision, they received more aggressive chemotherapy, except for two patients who underwent limb disarticulation due to massive tumor contamination. This may also be a factor contributing to the similar 5-year survival rates.

With improvements in imaging modalities, chemotherapy and surgical techniques in recent years, limb salvage surgeries can be performed in most patients with OS. In our study, ~90% of patients who underwent planned surgery had their limbs preserved at the last follow-up; however, only 10 (62.5%) patients who underwent inadequate initial treatment had their limbs preserved. We found that if the patient was treated as a case of a benign bone tumor, limb salvage surgery was more likely to succeed. If the patient was treated otherwise, amputation was more likely to be the best option left. This may be because when treating a benign bone tumor, the surgeon would transfer the patient to an orthopedic oncologist based on the final pathology report. On the other hand, for those treated with arthroscopy or fracture fixation, the surgeon might be less alert and thus did not request a pathology report. Even under the same risk of tumor seeding at initial surgery, earlier referral to an orthopedic oncologist might have a significant impact on applicable treatment options and even patient survival.

CONCLUSIONS

By advanced adjuvant chemotherapy and improvement of the surgical technique, the long-term survival and limb salvage rate of OS have been improved in recent years. However, for patients who received unplanned treatment for high-grade OS, having a lack of neoadjuvant chemotherapy and inadequate surgical margins can result in failure of local control and earlier systemic tumor metastases. With regard to further study, using a larger sample size is crucial to confirming our results. We highly recommended reasonable consideration of the possibility of a malignant bone tumor before surgery is performed for bone lesions as well as the consideration of a pathological fracture for an unreasonable trauma mechanism.

Conflict of interest statement

None declared.

References


