The prognosis for patients with osteosarcoma who have received prior manipulative therapy

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We evaluated the long-term outcome of patients with an osteosarcoma who had undergone prior manipulative therapy, a popular treatment in Asia, and investigated its effects on several prognostic factors. Of the 134 patients in this study, 70 (52%) patients had manipulative therapy and 64 (48%) did not. The age, location, and size of tumour were not significantly different between the groups. The five-year overall survival rate was 58% and 92% in the groups with and without manipulative therapy (p = 0.004). Both the primary and overall rates of lung metastasis were significantly higher in the manipulative group (primary: 32% vs 3%, p = 0.003; overall lung metastasis rate: 51.4% vs 18.8%, p < 0.001). Patients who had manipulative therapy had higher local recurrence rates in comparison to patients who did not (29% vs 6%, p = 0.011). The prognosis for patients with osteosarcoma who had manipulative therapy was significantly poorer than those who had not. Manipulative therapy was an independent factor for survival.

This form of therapy may serve as a mechanism to accelerate the spread of tumour cells, and therefore must be avoided in order to improve the outcome for patients with an osteosarcoma.

Osteosarcoma is the most common primary malignant bone tumour and occurs with greater frequency in childhood and adolescence.1-5 The usual treatment is a combination of chemotherapy and surgery, giving a long-term survival for approximately 60% to 70% of patients.6 The factors associated with a poor prognosis include elevated levels of serum alkaline phosphatase,7-9 size of tumour10,11 and a low tumour necrotic rate.12,13 However, the relationship between treatment before diagnosis and outcome is seldom discussed.

The most common symptoms of osteosarcoma are pain and swelling. Treatment of the affected areas before diagnosis can include manipulative therapy, a traditional Chinese method. There are a variety of techniques for manipulation. Usually, the practitioner provides powerful, even and persistent force to the affected areas using hands, fingers, wrist and elbows. In many Asian countries, it is a popular approach for musculoskeletal symptoms. Thus, Tuina, or Chinese therapeutic massage, can be practised at home, in offices, clinics, and hospitals.14 Similarly, in many Western countries, the symptoms of osteosarcoma may be treated with massage or other types of manipulative therapy before diagnosis.

The aim of this study was to evaluate the long-term outcome of patients with an osteosarcoma who have undergone prior manipulative therapy and to investigate its effects on key prognostic factors. To our knowledge, this is the only such study to date. This was also a historical prospective study, before 1995 we found a trend in our institution suggesting that manipulative therapy was related to survival rate, therefore, in 1995 we began a prospective study of its influence on the prognosis of patients with osteosarcoma.

Patients and Methods
A total of 170 patients with osteosarcoma were enrolled in this study between July 1995 and February 2005. Those with axial tumours (n = 6), low-grade malignancies (n = 13) and previous surgery at another hospital (n = 16) were excluded. One patient was lost to follow-up, leaving 134 patients consisting of 92 males and 42 females with a mean age of 19.7 years (5 to 67). Of these, 70 had manipulative therapy and 64 did not. All patients were treated by the two senior authors (WMC, THC).

General factors such as age, gender, duration of the symptoms and tumour-related factors, including the volume, histological subtype, rate of post-chemotherapy necrosis and...
biological markers were recorded and analysed in each case. All patients gave written, informed consent.

The history of manipulative therapy was recorded from the notes at presentation to the institution which administered the initial chemotherapy. The patients answered a detailed questionnaire which addressed; a) whether manipulation was administered near the site of tumour; b) the duration and frequency of therapy; c) the name and location of the institution where it was performed; and d) whether the therapist requested further therapy or follow-up at another institution. The patients who received manipulative therapy without direct massage to the involved area (for example, to the back or foot) were considered not to have received manipulative therapy. None of the patients had further visits from a manipulative therapist once the diagnosis was confirmed.

All the patients received neoadjuvant chemotherapy according to two protocols in two different periods. Period 1 was from July 1995 to July 1998 (protocol 1) and period 2 was from August 1993 to February 2005 (protocol 2). A total of 40 (29.9%) patients were treated during period 1 and 94 (70.1%) during period 2. In period 1, they received combination therapy with 12 mg/m² methotrexate, 1.8 mg/m²/day ifosfamide, 25 mg/m²/day epirubicin and 120 mg/m²/day cisplatin whereas in period 2 they received therapy with 12 mg/m² methotrexate, 37.5 mg/m²/day adriamycin, 3.0 mg/m²/day ifosfamide and 60 mg/m²/day of cisplatin.

After chemotherapy, all patients underwent wide excision and reconstruction, except for those who underwent an amputation. Among the parameters for assessment of the response to treatment was a pulmonary survey using plain film and CT. Scans were performed at the time of diagnosis, before surgery, every three months in the first two years post-operatively, every six months during the third to fifth years, and then annually.

The length, width and depth of tumour were measured using MRI. Thereafter, these parameters were calculated using the ellipsoid formula.9 The levels of two biological markers, serum alkaline phosphatase and serum lactate dehydrogenase were measured prior to chemotherapy. Based on published data,13 the normal levels of serum alkaline phosphatase were classified, after adjusting for age and gender, as follows: 2 to 10 years of age, 100 UI/l to 350 UI/l; 10 to 13 years of age (female), 110 UI/l to 400 UI/l; 13 to 15 years of age (male), 125 UI/l to 500 UI/l; 20 to 50 years of age, 25 UI/l to 100 UI/l; and other childhood ages, 73 UI/l to 300 UI/l.

A skip lesion was defined as one that was separated anatomically from the primary lesion by an interval of non-reactive normal tissue beyond the zone of the perineoplastic reaction.16 The response to pre-operative chemotherapy was assessed according to the scale of Huvos et al,13 in which grades I to IV denoted 0% to 50%, 51% to 90%, 91% to 99% and 100% necrosis, respectively. Grades III and IV were defined as a good response.

**Statistical analysis.** The survivorship analysis was calculated according to the Kaplan-Meier method and these curves were compared statistically using the log-rank test. The differences in the demographics and presenting characteristics between the groups were evaluated by Fisher’s exact or the exact Pearson chi-squared tests. Variables, such as age, volume and duration of the symptoms between the groups were analysed by Student’s t-test. A p-value of < 0.05 was considered statistically significant.

### Results

The overall mean follow-up for the 134 patients in the study was 50.2 months (7 to 160) and the gender and age were not significantly different between the groups with or without manipulation (Table I; p = 0.982 and 0.13, respectively). A total of 70 patients had received manipulative therapy. Of these, 48 were male (69%) and 22 were female (31%) with a mean age of 18.2 years (5 to 67) and a mean follow-up of 41.8 months (7 to 132). It was performed in a bone-setter’s office in 36 cases (51%), a Chinese medical clinic in 32 cases (46%), and in a physiotherapy clinic in two cases (3%). The patients received a mean of 2.6 manipulative sessions (1 to 6; Fig. 1a) over a mean period of 2.8 weeks (1 to 8; Fig. 1b). There were no local complications such as skin erosion or tendon rupture after manipulation.

The most common presenting symptom was pain in the involved limb. The mean duration from onset of symptoms to diagnosis was 4.3 months for the patients who had manipulation therapy and 4.1 months for those who did not

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**Table I. Patient profiles and tumour characteristics**

<table>
<thead>
<tr>
<th>Characteristic*</th>
<th>Manipulative therapy (n = 70)</th>
<th>No manipulative therapy (n = 64)</th>
<th>p-value</th>
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<tr>
<td>Gender (%)</td>
<td></td>
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<tr>
<td>Male</td>
<td>48 (68.8)</td>
<td>44 (68.8)</td>
<td>0.982</td>
</tr>
<tr>
<td>Female</td>
<td>22 (31.2)</td>
<td>20 (31.2)</td>
<td></td>
</tr>
<tr>
<td>Mean age in years (range)</td>
<td>18.2 (5 to 67)</td>
<td>21.5 (0.5 to 24)</td>
<td>0.13</td>
</tr>
<tr>
<td>Symptoms duration in months (range)</td>
<td>4.3 (7 to 67)</td>
<td>4.1 (0.5 to 12)</td>
<td>0.487</td>
</tr>
<tr>
<td>Mean volume (ml)</td>
<td>285.1</td>
<td>275.7</td>
<td>0.821</td>
</tr>
<tr>
<td>Tumour location (around the knee) (%)</td>
<td>54 (77.1)</td>
<td>44 (68.8)</td>
<td>0.439</td>
</tr>
<tr>
<td>Serum lactate dehydrogenase increase (%)</td>
<td>40 (57.1)</td>
<td>24 (37.5)</td>
<td>0.026</td>
</tr>
<tr>
<td>Serum alkaline phosphatase increase (%)</td>
<td>46 (66.7)</td>
<td>42 (65.6)</td>
<td>0.889</td>
</tr>
</tbody>
</table>
This lack of statistical significance suggests that the poor clinical outcome of the patients who had manipulative therapy was not due to a delay in diagnosis.

The tumours were mostly located in the distal femur (n = 62, 46%), proximal tibia (n = 34, 25%), proximal humerus (n = 20, 15%) with the remaining 18 in other locations. There was no difference in the location of the tumour between the groups (Table I; p = 0.439). The volume of the tumour was also comparable between the groups. Their mean volumes were 285 ml (15 to 896) and 276 ml (25 to 1000) respectively (Table I; p = 0.821).

The serum lactate dehydrogenase levels were elevated in 40 patients (57.1%) in the manipulation group and 24 (37.5%) in the non-manipulation group (p = 0.026). This finding strongly suggests that patients who received manipulative therapy may have a poorer outcome, since a low serum level of lactate dehydrogenase is a good prognostic indicator for disease-free survival.\(^{17}\)

The serum alkaline phosphatase levels were raised in 46 patients (65.7%) in the manipulation group and 42 (65.6%) in the non-manipulation group (Table I; p = 0.889).

In relation to tumour necrosis, a total of 26 patients (37%) in the manipulative group and 24 (38%) in the non-manipulative group showed a favourable response (Huvos’ grade III or IV) (Table II; p = 0.446).

Skip lesions were seen in eight patients who had manipulation (Table II; p = 0.005). Two of these died, 16 and 17 months after surgery respectively. However, the overall survival rate between patients with and without skip lesions was not statistically different between the groups (p = 0.54). Pathological fracture occurred in six patients (8.6%) in the manipulation group and four patients (6.3%) in the non-manipulation group (p = 0.610).

Lung metastases occurred in 48 (36%) of the 134 patients, and the mean five-year survival rate was 87% in the non-metastasis group and 58% in the metastasis group (p < 0.001). Compared with the non-manipulative group, patients who received manipulative therapy were more likely to develop lung metastases (51% versus 19%; p < 0.001; Table II).

The rate of lung metastasis at initial diagnosis was also significantly higher in the group which had manipulative therapy (31% vs 3%, p = 0.003; Table II). The onset of lung involvement, there were 33 (47%) cases with more than three nodules, 37 (58%) with invasion of more than one lobe in the manipulation group and there were 21 (33%) cases with more than three nodules and 43 (40%) with invasion of more than one lobe in the non-manipulation group. The extent of the lung metastases was not significantly different between the groups (33% vs 40%).

After wide excision of the primary tumour, 24 (18%) patients developed a local recurrence. The mean interval between excision and local recurrence was 13.8 (4 to 45.6) months. After this was confirmed, 14 cases underwent

![Bar charts showing a) frequency and b) duration of prior manipulative therapy and number of patients.](image-url)
amputation and ten had palliative treatment because of metastases. Among those with local recurrence, 20 patients (84%) had received manipulation. Of these, 18 died at a mean of 24.5 months (10 to 40) post-operatively. The local recurrence rate was significantly higher in the group which had undergone manipulative therapy (29% vs 6%, p = 0.001; Table II), suggesting a relationship with manipulative therapy.

At a mean follow-up of 55.2 months (7 to 160), 108 patients (81%) were disease-free or alive with disease. The five-year overall survival rate was 92.0% in the non-manipulative group and 58% in the manipulative group (p = 0.004; Fig. 2 and Table III).

A multivariate Cox regression analysis was performed to evaluate the influence on survival rate. In this, if four factors were included (manipulative therapy, metastasis, metastasis at initial diagnosis, and necrotic rate), manipulation was found to be an independent factor for the survival rate (Table III).

**Table III. Multivariate Cox regression model of prognostic factors**

<table>
<thead>
<tr>
<th></th>
<th>RHR*</th>
<th>95% CI†</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manipulation</td>
<td>2.2</td>
<td>0.41 to 1.18</td>
<td>0.038</td>
</tr>
<tr>
<td>Primary lung metastasis</td>
<td>5.3</td>
<td>1.60 to 17.8</td>
<td>0.006</td>
</tr>
<tr>
<td>Local recurrence</td>
<td>6.2</td>
<td>1.90 to 20.0</td>
<td>0.002</td>
</tr>
</tbody>
</table>

* RHR, relative hazard rate  † CI, confidence interval

**Discussion**

As recently as 30 years ago, the survival rate for patients with osteosarcoma was poor. The five-year survival rate has improved dramatically to between 50% and 80% due to advances in chemotherapy and surgical intervention.8,18-20
Several poor risk factors for osteosarcoma, such as large tumour volume, elevated serum alkaline phosphatase or serum lactate dehydrogenase levels, poor tumour necrosis, pathological fractures and skip lesions are reported. However, some of our patients without these risk factors eventually died. Furthermore, they were treated similarly with chemotherapy and surgery. These observations prompted us to look for additional risk factors. From 1995, we investigated whether manipulative therapy was another risk factor and, in our patients who had undergone manipulation, the five-year survival rate was low (58%).

More than half of our patients (52%) initially sought manipulative therapy rather than Western medicine because of the non-specific symptoms. Although the patient demographics were similar between the groups, our results show that manipulation affects the long-term survival, as well as the development of lung metastases, skip lesions and local recurrence. The lung is the most common site for the metastases, and between 11% and 20% of these patients develop lung metastases. Also several studies have shown that the outcome for patients with lung metastases is between 10% and 40%. In our study, the patients who received manipulative therapy had an increased incidence of both primary and overall lung metastases.

The Cooperative Osteosarcoma Study Group reported a 2% incidence of skip lesions in osteosarcoma and several studies reported an average six-month survival rate after the development of a skip lesion. Furthermore, Enneking and Kagan recommended that these patients should be classified as stage III disease and suggested stronger chemotherapy protocols. In our study although all the patients with a skip lesion had received manipulative therapy. We found that the development of a skip lesion did not affect the outcome.

Limb salvage has become the most popular form of surgical treatment for patients with osteosarcoma. Inadequate excisional margins will cause local recurrence and lead to poor outcome. Whereas the local recurrence rate of osteosarcoma is reported as 5% to 10%, it was 20% (26 patients) in our study and 22 (85%) of these patients had received manipulative therapy. Furthermore, during follow-up, 18 died within two years.

The multivariate Cox regression analysis, using several factors, demonstrated that manipulation was an independent factor for survival in our study. We initially believed that patients who received manipulative therapy had an increased risk of the development of a skip lesion, local recurrence and lung metastasis due to delayed diagnosis. However, we did not find a significant difference in the time between the onset of symptoms and the diagnosis for the two groups. Therefore, delayed diagnosis is not a likely cause of the poor outcome. Manipulative therapy may cause the formation of micrometastases leading to a poor outcome. There is a high probability that local mechanical compression, such as surgical manipulation or manipulative therapy, may result in dissemination of tumour cells via local spread or the circulation. Also, an increase in local vascularity after manipulation may favour the formation of micrometastases. While these cannot be controlled by chemotherapy, occult disease will become overt metastases.

In this study, the five-year survival rate of the patients who had manipulative therapy was 58%. This influence on clinical outcome was comparable to that of 55% for lung metastases. Those patients who develop lung metastases have a poor outcome. Intensive therapy such as high dose chemotherapy and peripheral blood stem cells may be used. Thus, more intensive chemotherapy may be indicated for patients with an osteosarcoma who have received manipulative therapy.

We have shown that in patients with osteosarcoma, receiving manipulative therapy before the diagnosis is made is an independent factor for survival. Because some of these patients do not respond favourably to current chemotherapy regimes, new or more intensive regimes, gene therapy, stereotactic radiotherapy and immunotherapy should be considered. Also manipulative therapy should be stopped once the diagnosis of osteosarcoma is made. Furthermore, symptoms of tumour, such as a mass and night pain should be a contraindication to manipulative therapy.

There were two limitations in this study. Firstly, the various techniques, strength, and quality of therapists could not be analysed further; and, secondly, we were unable to define the mechanism by which manipulative therapy may promote the formation of micrometastases and influence the outcome.

References

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