SELECTION BIAS IN TREATMENT OF SOFT-TISSUE SARCOMA

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We analysed 256 patients with primary soft-tissue sarcoma of the extremities diagnosed between 1970 and 1990 to see if tumour-related and host-related prognostic factors influenced both the selection of operation and the margin of clearance obtained at surgery. Amputation was more often performed in young patients, in those with distal tumours, and in those with deep-seated tumours. Inadequate surgical margins (those with a high risk of local recurrence) were more common in patients with deep-seated and large tumours than in patients with superficial and small tumours. These features of the tumour and the host, which have been shown to be prognostic for survival, also influenced the choice and performance of surgical procedures.

In soft-tissue sarcoma the relationship between treatment of the primary tumour, local recurrence, and prognosis is not clearly understood. Metastasis is more common in patients who have had surgery with inadequate margins and, therefore, an increased risk of local recurrence (Gustafson, Rööser and Rydhholm 1991), and it has been suggested that better treatment of the primary tumour would improve survival (Suit et al 1990). Amputation, which is the safest local treatment as regards local recurrence, has, however, been associated in several studies with poor survival (Shiu et al 1975; Brennan et al 1985; Collin et al 1987; Emrich et al 1989; Berlin et al 1990).

One explanation for the correlation between local recurrence and metastasis may be that highly malignant tumours combine both local and distant aggressiveness. Another contributing factor may be selection bias in treatment; that is to say that factors which govern prognosis may also influence treatment. Tumours with a high risk of metastatic spread may be treated more often with high-risk surgical margins, and therefore be at high risk of local recurrence. This selection bias may also explain the association between amputation and poor survival, patients with the most malignant tumours being selected for amputation.

Our aim was to determine retrospectively whether tumour-related and host-related prognostic factors influenced the choice between amputation or limb-sparing surgery and the surgical margins obtained in patients with soft-tissue sarcomas of the extremities.

PATIENTS AND METHODS

We treated 256 patients between 1970 and 1990 in our Orthopaedic Oncology Centre. The criteria for inclusion, definition of surgical margins, histopathological classification, and the system for grading malignancy have been described elsewhere (Rööser et al 1991; Rydhholm et al 1991). An intralesional or marginal excision was graded high-risk and one with a wide or radical margin low-risk. Our treatment principles were as follows: first option, limb-sparing surgery with low-risk margins; second option, limb-sparing surgery with high-risk margins and postoperative radiotherapy if serious complications were not expected; and third option, amputation with low-risk margins.

There were 139 men and 117 women; their median age was 62 years (20 to 87). Eight patients had metastases at the time of diagnosis of the primary tumour. Sixty-seven tumours were subcutaneous, with a mean size of 5 cm (1 to 15), and 189 were deep-seated, with a mean size of 8 cm (1 to 30). The thigh was the most common location (44%), followed by the lower leg (13%), the upper arm (9%), and the lower arm (8%). Malignant fibrous histiocytoma (MFH) was the most common histological diagnosis (45%), followed by liposarcoma (14%), leiomyosarcoma (12%), and synovial sarcoma (9%). Nine tumours were of malignancy grade I, 35 of grade II, 76 of grade III, and 136 of grade IV. Thirty-one patients were treated by amputation, one with a high-risk margin and 30 with low-risk margins; 225 patients had limb-
sparing surgery, 52 with high-risk margins and 173 with low-risk margins.

The differences between groups were assessed using the chi-squared and the Mann-Whitney U tests. The analyses were performed by J. Ranstam, MA, Department of Community Health Sciences, General Hospital, Malmö, Sweden.

RESULTS

The 31 patients who had amputation were younger and more often had distal and deep-seated tumours than those who had limb-sparing surgery (Table I). We performed amputation more often on patients with synovial sarcoma (9/22) than on those with MFH (7/114; \( p = 0.0001 \)), liposarcoma (3/37; \( p = 0.007 \)), or leiomyosarcoma (2/30; \( p = 0.008 \)).

In the analysis of surgical margins we excluded the 31 patients treated by amputation. High-risk surgical margins (\( n = 52 \)) were more common in patients with deep-seated and large tumours than in those with superficial and small tumours (Table II).

Patients with soft-tissue sarcoma who have local recurrence of the tumour have a higher rate of metastasis than those with no local recurrence, and a causal relationship has been proposed, implying that the recurrence is the source of the metastases (Suit and Tepper 1986; Emrich et al 1989). Amputation and limb-sparing surgery with high-risk surgical margins, however, are both associated with poor survival, although the local recurrence rate is low after the former and high after the latter procedure (Shiu et al 1975; Simon and Enneking 1976; Brennan et al 1985; Collin et al 1987; Emrich et al 1989; Berlin et al 1990). All these observations were made in retrospective, non-randomised studies, and one explanation may be selection bias in treatment. Patients with the most aggressive tumours, and therefore at the highest risk of metastatic spread, even before treatment, are either selected for amputation or, when treated by limb-sparing surgery, more often operated on with high-risk margins.

Few authors have compared the grade and stage of tumours in amputated and non-amputated patients. Shiu

DISCUSSION

Table I. Details of 256 patients with soft-tissue sarcoma of an extremity according to their surgical treatment

<table>
<thead>
<tr>
<th></th>
<th>Amputation (( n = 31 ))</th>
<th>Limb-sparing surgery (( n = 225 ))</th>
<th>Difference (A) Relative risk (B)</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yr)</td>
<td>49</td>
<td>60</td>
<td>10.6 (A)</td>
<td>4.1 to 17</td>
</tr>
<tr>
<td>Site*</td>
<td>Proximal</td>
<td>186</td>
<td>9 (5%)</td>
<td>1.7 (A)</td>
</tr>
<tr>
<td></td>
<td>Distal</td>
<td>70</td>
<td>22 (31%)</td>
<td>48 (69%)</td>
</tr>
<tr>
<td>Depth†</td>
<td>Subcutaneous</td>
<td>67</td>
<td>2 (3%)</td>
<td>65 (97%)</td>
</tr>
<tr>
<td></td>
<td>Deep-seated</td>
<td>189</td>
<td>29 (15%)</td>
<td>160 (85%)</td>
</tr>
<tr>
<td>Mean size (cm)</td>
<td>9.6</td>
<td>7.9</td>
<td>1.7 (A)</td>
<td></td>
</tr>
<tr>
<td>Malignancy‡</td>
<td>Low-grade</td>
<td>44</td>
<td>2 (5%)</td>
<td>42 (95%)</td>
</tr>
<tr>
<td></td>
<td>High-grade</td>
<td>212</td>
<td>29 (14%)</td>
<td>183 (86%)</td>
</tr>
</tbody>
</table>

* Distal = lower arm, hand, lower leg and foot. Proximal = all other locations
† Tumours located in or below the deep fascia were classified as deep-seated, all others as subcutaneous
‡ Low-grade = malignancy grades I and II. High-grade = malignancy grades III and IV

Table II. Details of 225 patients with extremity-located soft-tissue sarcoma, treated by limb-sparing surgery, according to surgical margin

<table>
<thead>
<tr>
<th></th>
<th>High risk* (( n = 52 ))</th>
<th>Low-risk (( n = 173 ))</th>
<th>Difference (A) Relative risk (B)</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yr)</td>
<td>64</td>
<td>59</td>
<td>5.6 (A)</td>
<td>1.0 to 12</td>
</tr>
<tr>
<td>Site†</td>
<td>Proximal</td>
<td>177</td>
<td>39 (22%)</td>
<td>138 (78%)</td>
</tr>
<tr>
<td></td>
<td>Distal</td>
<td>48</td>
<td>13 (27%)</td>
<td>35 (73%)</td>
</tr>
<tr>
<td>Depth‡</td>
<td>Subcutaneous</td>
<td>65</td>
<td>6 (9%)</td>
<td>59 (91%)</td>
</tr>
<tr>
<td></td>
<td>Deep-seated</td>
<td>160</td>
<td>46 (29%)</td>
<td>114 (71%)</td>
</tr>
<tr>
<td>Mean size (cm)</td>
<td>10.8</td>
<td>7.0</td>
<td>3.8 (A)</td>
<td>1.4 to 6.2</td>
</tr>
<tr>
<td>Malignancy§</td>
<td>Low-grade</td>
<td>42</td>
<td>13 (31%)</td>
<td>29 (69%)</td>
</tr>
<tr>
<td></td>
<td>High-grade</td>
<td>183</td>
<td>39 (21%)</td>
<td>144 (79%)</td>
</tr>
</tbody>
</table>

* High-risk = intrasional or marginal margin. Low-risk = wide or radical margin
† Distal = lower arm, hand, lower leg and foot. Proximal = all other locations
‡ Tumours located in or below the deep fascia were classified as deep-seated, all others as subcutaneous
§ Low-grade = malignancy grades I and II. High-grade = malignancy grades III and IV

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et al (1975) reported that large and unfavourably situated tumours generally required amputation. Collin et al (1987) found that patients treated by amputation more often had large, painful, deep-seated, and high-grade tumours, which were usually of an unfavourable histological type. In our series the patients treated by amputation were younger than the rest, they more often had distal and deep-seated tumours and proportionally higher incidence of synovial sarcoma, a highly malignant tumour.

Several authors (Shiu et al 1975; Brennan et al 1985; Potter et al 1986; Stotter et al 1990; Gustafson et al 1991) have questioned whether the increased rate of metastasis in patients with local recurrence is a result of the local recurrence. An alternative explanation may be that given the same surgical margin, highly malignant tumours recur locally more often than do less malignant ones (Rööser et al 1988). Selection bias in treatment may also contribute to this correlation; highly malignant tumours may be treated more often by high-risk surgery. In a large series of soft-tissue sarcomas previously reported (Gustafson et al 1991) we found no evidence for a causal relationship between local recurrence and metastasis although patients who developed metastases had been treated more often with high-risk surgical margins. In the present series we found that high-risk surgical margins were more common in patients with large and deep-seated tumours, which have a poorer prognosis per se than do small, subcutaneous tumours (Collin et al 1987; Tsujimoto et al 1988).

Our findings indicate that the prognostic properties of the host and the tumour influence the type of surgery performed. This selection bias in treatment may confound analysis of the relationship between surgical treatment and prognosis in soft-tissue sarcoma.

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REFERENCES


