THE EFFECT OF BIOPSY ON SURVIVAL OF PATIENTS WITH
OSTEOSARCOMA

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A retrospective study of patients with osteosarcoma was undertaken to determine whether there was a relationship between biopsy and survival. Fifty-seven patients treated at the Karolinska Hospital, Stockholm, between 1938 and 1959 were included in this study, all of whom were less than thirty years old, had a metaphysical osteosarcoma in a long bone but had no pulmonary metastases at the time of diagnosis; all were treated by amputation. No clinical variants of osteosarcoma were included. Twenty-four of the fifty-seven patients had an amputation without a prior biopsy; the others had biopsies before amputation. These two groups were fairly closely matched in age, sex, site and size of tumour, and in the level of amputation; some patients in each group received radiation before operation. Evaluation of these two groups of patients revealed that the performance of a biopsy, with or without a delay of not more than thirty days between the biopsy and the definitive operation, had no adverse effect on survival.

The iatrogenic spread of cancer in man has been the subject of observations for almost a century (Gerster 1885; Ward 1913; Mayo 1913; Knox 1922). Recently, many investigators have isolated tumour cells in the blood of patients with various solid tumours (Engell 1959; Peterson et al. 1960; Potter et al. 1960; Foss et al. 1966; Roberts et al. 1967; Turnbull et al. 1967). These studies have demonstrated increased numbers of cancer cells in the blood after manipulation or biopsy of the malignant lesion. None of the investigations has demonstrated conclusively, however, that the presence of tumour cells, or of an increased number of tumour cells, in the blood is correlated with long-term survival. It has been pointed out that not all circulating neoplastic cells form secondary deposits, and that little is known about the pathophysiology of the formation of metastases.

Animal studies have consistently demonstrated that manipulation of the tumour results in a higher metastatic rate (Tyzzer 1913; Knox 1922; Marsh 1927). However, few clinicians manipulate suspected human tumours as severely as was done by the investigators.

The concern about manipulation has been transferred to surgical practice. Turnbull reported on a large series of patients on whom he used "no-touch isolation" techniques for operations on the colon in which the vascular drainage of the area was occluded before handling the tumours (Turnbull et al. 1967). Evidence points to the safety of aspiration biopsy of breast lumps, but obtaining sufficient tissue by this technique is still a problem (Robbins et al. 1954). In patients with breast cancer, a delay of two weeks or even more between biopsy and operation gave a survival rate which did not differ from that of patients who had an immediate operation after analysis of a frozen section (Pierce et al. 1956). For patients with solid tumours, however, no randomised studies with appropriate stratification and concurrent controls have been published.

For patients with osteosarcoma, it is standard practice to perform an open biopsy with an ablative procedure soon afterwards. This approach, rather than diagnosis by frozen section and immediate operation, is used because the incidence of osteosarcoma is low and the pathological findings are difficult to interpret. Neither pathologists nor orthopaedic surgeons are willing to make a definitive diagnosis on the basis of small amounts of tissue or on the analysis of a frozen section. Some authors have suggested doing either no biopsy or a biopsy below a proximal vascular occlusion, followed by immediate amputation above the occlusion to prevent embolisation (Lindbom, Söderberg and Spjut 1961; Dahlin and Coventry 1967; Kuehn, Tamoney and Gossling 1970; Enneking 1975). Other authors feel that a biopsy with a short delay before the definitive operation is not a hazard to the patient (Sweetnam 1969). All of these studies are inconclusive. Lindbom et al. (1961) published results of treatment of osteosarcoma in Sweden and concluded that a biopsy may
decrease the chance of survival. Although insufficient
detail was presented on matching of patients according
to the site of the tumour, the age of the patient, and the
treatment and stage of disease, this study raised
questions about the advisability of biopsy in osteosar-
coma.

Since a biopsy should always be performed before
ablation of the osteosarcoma, it is not a question of
whether or not the biopsy should be done. The question
to be answered is: does a biopsy compromise survival,
and if so, should precautions be taken during the
operation to prevent embolisation by tumour cells? To
find an answer, we undertook a retrospective study of
patients with osteosarcoma who were included in the
Bone Tumour Registry at the Karolinska Hospital in
Stockholm between 1938 and 1959. Some of the
patients with osteosarcoma had undergone amputation
without a biopsy.

Table I. Five-year survival rates in each group

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of patients</th>
<th>Surviving patients*</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Amputation without biopsy</td>
<td>Subtotal 24</td>
<td>5 (21 per cent)</td>
</tr>
<tr>
<td>II. A. Biopsy, frozen section, and immediate amputation above a proximal tourniquet</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>B. Biopsy, frozen section, and immediate amputation without a tourniquet</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>C. Biopsy and delayed amputation within 30 days</td>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td>D. Biopsy and delayed amputation more than 30 days later</td>
<td>Subtotal 33</td>
<td>7 (21 per cent)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>57</td>
<td>12 (21 per cent)</td>
</tr>
</tbody>
</table>

*Number surviving more than 60 months without evidence of disease

MATERIALS AND METHODS

Between 1938 and 1959, a series of 105 consecutive cases
of osteosarcoma was reviewed and catalogued at the Bone Tumour
Registry of the Karolinska Hospital. The pathological and radi-
ographic features have been reviewed elsewhere (Lindbom et al. 1961).
For our study, all parosteal and extra-osseous osteosarcomata, and all
diaphysial osteosarcomata, as well as osteosarcomata arising
from previously diseased or irradiated bone, were excluded from the series.
The only patients evaluated were those who were less than thirty years
old, had an intra-osseous metaphysical osteosarcoma in a long bone,
and were without metastases at the time of clinical diagnosis; all had an
amputation with or without biopsy.

A total of forty-eight patients were excluded from the study:
twenty-five who were more than thirty years old; thirteen who refused
amputation and had only a biopsy; six who were below the age of thirty,
but had tumours of the axial skeleton or of small bones; one who
had a multicentric osteosarcoma; one who was lost to follow-up; one
whose records were incomplete; and one who had suffered a delay of

Table II. The age and sex of the patients and the site of the tumour

<table>
<thead>
<tr>
<th>Site of the tumour</th>
<th>Group I</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal femur</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Distal femur</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Proximal tibia</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Proximal fibula</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Distal tibia</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Proximal humerus</td>
<td>2</td>
<td>6</td>
</tr>
</tbody>
</table>

The information analysed included the age and sex of the patient,
and time of onset of the symptoms; the site and size of the tumour;
whether or not there had been radiation therapy before operation; the
date of biopsy, and the date and level of amputation. All of the patients
had been followed up for at least five years, or until death.

RESULTS

We classified the amputation into two main groups: those
who had an amputation without a biopsy (Group I) and
those who had a biopsy before amputation (Group II),
the latter group being made up of four subcategories
based on the interval between biopsy and amputation.
The survival rates for the main groups and subgroups are
shown in Table I. There were no significant differences
between Group I and Group II.

The age and sex of the patients, and the sites of the tumour
in each group are shown in Table II. In Group II,

The average interval from biopsy to amputation was
thirty-five days, with a range of 0–351 days and a mode
of four days. There was no difference between groups in
regard to the size of the tumour.

Table III lists the level of amputation and the sites
of the tumour for the two groups. There were similar
numbers of through-bone amputations for tumours of
the distal femur. In Group II five procedures were
possibly inadequate: a disarticulation of the hip for a
tumour of the proximal femur and four disarticulations
of the shoulder for tumours of the proximal humerus.

No patient received any form of chemotherapy
during the course of the disease. Radiation therapy was
given sporadically before operation to occasional patients, with various doses in each group. Seven patients in Group I received between 3600 and 9600 rads to the primary tumour before amputation, only one of whom survived. No patient in Group IIA or IIB received radiation therapy. Seven of the sixteen patients in Group II received from 450 to 5600 rads locally before amputation, two of whom survived. Six of the nine patients in Group IID received between 3000 and 6000 rads before amputation, and none survived.

The patients who are long-term survivors in each group are listed in Tables IV and V. There seems to be no common denominator for these patients except that all had amputations.

### DISCUSSION

This study had all the problems of an uncontrolled retrospective study. It was difficult to gather the data, and the patients had not been treated according to any specific protocol. The reasons for the choice of treatment for a given patient could not be ascertained from the records. The interest in this group stems from the presence of twenty-four patients who had an amputation without any operative manipulation of the tumour (biopsy). These twenty-four patients would, in theory, have experienced the greatest possible precautions regarding operative manipulation of the tumour during a surgical procedure.

### Table III. The site of the tumour and the level of amputation for each group

<table>
<thead>
<tr>
<th>Site</th>
<th>Group I</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of patients</td>
<td>Level of amputation</td>
</tr>
<tr>
<td>Proximal femur</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Distal femur</td>
<td>13</td>
<td>2 through hip</td>
</tr>
<tr>
<td>Proximal tibia</td>
<td>7</td>
<td>5 mid-femur</td>
</tr>
<tr>
<td>Proximal fibula</td>
<td>2</td>
<td>2 mid-femur</td>
</tr>
<tr>
<td>Distal tibia</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Proximal humerus</td>
<td>2</td>
<td>2 forequarter</td>
</tr>
</tbody>
</table>

### Table IV. Group I survivors

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Site of tumour</th>
<th>Level of amputation</th>
<th>Radiation therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24</td>
<td>F</td>
<td>Proximal tibia</td>
<td>Mid-femur</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>F</td>
<td>Distal femur</td>
<td>Through hip</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
<td>F</td>
<td>Distal femur</td>
<td>Mid-femur 7200 rads</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>19</td>
<td>M</td>
<td>Distal femur</td>
<td>Proximal femur</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>17</td>
<td>F</td>
<td>Proximal tibia</td>
<td>Distal femur</td>
<td>None</td>
</tr>
</tbody>
</table>

### Table V. Group II survivors

<table>
<thead>
<tr>
<th>Patient</th>
<th>Subgroup</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Site of tumour</th>
<th>Delay between biopsy and amputation (days)</th>
<th>Level of amputation</th>
<th>Radiation therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>13</td>
<td>M</td>
<td>Proximal tibia</td>
<td>0</td>
<td>Mid-femur</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>B</td>
<td>22</td>
<td>F</td>
<td>Proximal humerus</td>
<td>0</td>
<td>Through shoulder</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>C</td>
<td>16</td>
<td>F</td>
<td>Proximal tibia</td>
<td>26</td>
<td>Distal femur</td>
<td>460 rads</td>
</tr>
<tr>
<td>4</td>
<td>C</td>
<td>14</td>
<td>M</td>
<td>Proximal tibia</td>
<td>1</td>
<td>Distal femur</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>C</td>
<td>14</td>
<td>F</td>
<td>Distal femur</td>
<td>10</td>
<td>Proximal femur</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>C</td>
<td>26</td>
<td>F</td>
<td>Distal femur</td>
<td>4</td>
<td>Mid-femur</td>
<td>None</td>
</tr>
<tr>
<td>7</td>
<td>C</td>
<td>16</td>
<td>M</td>
<td>Distal femur</td>
<td>29</td>
<td>Proximal femur</td>
<td>3600 rads</td>
</tr>
</tbody>
</table>
To minimise the effect of other variables in osteosarcoma, we studied only those patients who were less than thirty years old. All had a metaphyseal osteosarcoma in a long bone that was confirmed by histological and radiological examination. All had an amputation and all were without metastases at the time of diagnosis. The patients came from a single geographical location and from a homogeneous population, and they were evaluated during the same period. We eliminated from consideration variants of osteosarcoma as well as secondary osteosarcomata.

The two main groups were comparable in age and sex of the patients, size of tumour, and the use of radiation therapy, but differed in the location of the tumour and in the type of operation undergone. Whether such differences influenced the prognosis, either favourably, or unfavourably is open to conjecture (Dahlin and Coventry 1967; O'Hara et al. 1968; Marcove et al. 1970). The two groups were comparable in regard to the level of amputation relative to the site of the tumour, except that Group II contained five patients whose operations may have been inadequate (one of these is a survivor). Therefore, the data may be biased unfavourably for Group II.

Another problem related to differences in the biopsy procedure. We had difficulty in deciding into which group the two patients should be placed who had a biopsy, frozen-section analysis, and immediate amputation above a proximally placed tourniquet, since optimal precautions against embolisation were taken during operation. If this subgroup is deleted, however, the results are not changed significantly. The same is true for Group IIB. In addition, if Group IID (biopsy with amputation more than thirty days later) is omitted, there is still no significant difference between Group I and Group II.

Since modern clinical practice dictates the need for a pathological diagnosis before amputation, should some attempt be made to control tumour embolisation during the operation by proximal vascular control and by immediate amputation above the tourniquet? The results of this study show that an open biopsy with a minimal delay before the definitive operation had no deleterious effect on the long-term survival of patients with classical osteosarcoma. The fact that there was no survivor among the nine patients whose operation was more than thirty days after biopsy indicates that it is probably prudent to limit the delay.

The authors are grateful to Dr Lindbom, Dr Söderberg and Dr Spjut who carefully collected much of the data upon which this study was based, and especially Dr Lindbom whose continuing interest in this project made its completion possible.

REFERENCES


