The Treatment of Soft-tissue Sarcomas of the Extremities

Prospective Randomized Evaluations of (1) Limb-sparing Surgery Plus Radiation Therapy Compared with Amputation and (2) the Role of Adjunct Chemotherapy

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SOFT-TISSUE SARCOMAS are malignant tumors that arise in the extraskeletal connective tissues of the body. Though a large number of different pathologic diagnoses, based on the cell of origin, comprise the soft-tissue sarcomas, these tumors are grouped together because of similarities in pathologic appearance, clinical presentation, and natural history. The clinical behavior of soft-tissue sarcomas is characterized by a tendency to extensively invade surrounding soft tissues as well as early metastatic dissemination, mainly to the lungs.1,3

The extensive local invasion of soft-tissue sarcomas along anatomic structures such as fascial layers, blood vessels, nerve sheaths, and muscle fibers has resulted in local recurrence rates of 30 to 50% when local surgical excision is utilized as sole therapy for these lesions.1-6 These high local recurrence rates have led to the use of radical compartmental excisions or amputations in an attempt to achieve local control and the utilization of these extensive surgical resections has reduced local recurrence rates to 5 to 20%.7,8 Recently several workers have advocated the use of local surgical excision followed by wide field radiation therapy as a means of obtaining adequate local control of these lesions.9,10 No comparative studies of these two approaches to achieving local control of soft-tissue sarcomas have been undertaken. The problems of poorly defined criteria for patient selection and the use of historical controls for analysis of treatment results have made reasonable comparison between the efficacy of these two approaches difficult. In this article the authors report the results of a prospective randomized comparison of the role of limb-sparing surgery plus radiation

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therapy compared with amputation in the treatment of patients with soft-tissue sarcomas of the extremities.

The tendency of soft-tissue sarcomas to metastasize to the lungs and the poor survival of patients treated for soft-tissue sarcomas (around 40% in most series) has led to a search for systemic treatments that might be applied early in the course of the disease. The authors also present the results of a prospective randomized evaluation of the value of adjuvant chemotherapy in the treatment of patients with soft-tissue sarcomas of the extremities. A more detailed presentation of this latter study has been presented elsewhere. 14

Methods

All patients with soft-tissue sarcomas of the extremities included in these protocols were evaluated and treated in the Surgery Branch of the National Cancer Institute. To be eligible for these protocols, patients had a diagnosis of either round cell or pleomorphic liposarcoma, pleomorphic rhabdomyosarcoma, synovial cell sarcoma, fibrosarcoma, neurofibrosarcoma, leiomyosarcoma, malignant fibrous histiocytoma, or undifferentiated sarcoma. All patients had lesions of the extremities defined as being distal to the shoulder or hip joints.

All patients underwent a standard workup including history, physical examination, blood chemistries, chest radiograph, lung tomograms, liver scan, bone scan, and computerized axial tomography through the area of the primary lesion. All patients in this protocol were free of clinical evidence of metastatic disease, either in regional lymph nodes or more distant sites.

Pathologic material, including biopsies and definitive resection specimens, were reviewed by the same pathologist, and only patients fulfilling the above histologic diagnosis were included.

Patients were excluded from the protocols if they had received any prior chemotherapy or radiation therapy before referral to the National Cancer Institute (NCI) or if they had a history of any other malignant disease except for basal cell carcinoma. Patients who had severe infections, active bleeding disorders, or concomitant severe disease such as cirrhosis, ischemic heart disease or evidence of severe impairment of renal function that made them ineligible to receive the chemotherapy used in the protocols were also excluded. Patients below the age of 30 with a diagnosis of embryonal or alveolar rhabdomyosarcoma were also excluded.

Before randomization in each of the protocols all patients signed an informed consent in accord with the guidelines of the Clinical Research Committee of the National Cancer Institute.
Four of the 27 patients randomized to the limb-sparing treatment arm of the protocol had a resection margin pathologically positive for tumor cells. No patient who underwent amputation had a positive pathologic margin. All patients who underwent limb-sparing surgery also received radiation therapy designed to treat areas at risk for tumor spread between the joints proximal and distal to the tumor including all involved muscle groups. Daily treatments were given at 180 to 200 rads per treatment to a dose of 4500 to 5000 rads. A shrinking field technique was then used, and a total of 6000 to 7000 rads was delivered to the tumor bed and completed in the sixth and seventh week of radiation therapy. The radiation therapy used in these patients has been presented in detail elsewhere. When possible, some portion of the circumference of the limb was excluded from the treatment portals. When possible, the adjacent joint space was also eliminated from the radiation portal, however, this was often not feasible because of the location of the tumor. Radiation therapy was begun as soon as the wound was healed. Wedge filters, compensator filters, complex field arrangements, wedged pairs, tangential fields, and rotational therapy were all used in an attempt to maximize radiation exposure to tissues at risk and to minimize radiation of normal tissues.

All patients in this protocol received chemotherapy beginning in the immediate postoperative period. Patients receiving radiation therapy received the first chemotherapy dose three days before the first radiation dose. Patients received doxorubicin (Adriamycin) and cyclophosphamide (Cytoxan) intravenously on day 21 of a 28-day cycle. Doxorubicin was begun at a dose of 30 mg/m² and was escalated by 10 mg/m² to a maximum of 70 mg/m² depending on bone marrow toxicity. A maximum cumulative dose of doxorubicin of 550 mg/m² was given. Cyclophosphamide was started at a dose of 500 mg/m² and was escalated by 100 mg/m² in conjunction with doxorubicin to a maximum of 700 mg/m². When the maximum cumulative dose of doxorubicin was reached, patients received high-dose methotrexate with leukovorin rescue, again on a 28-day cycle for a total of six doses. The initial dose of methotrexate was 40 mg/kg in a six-hour infusion followed two hours after completion of the infusion by 15 mg/m² of leukovorin intravenously. Intravenous leukovorin was repeated every six hours for a total of eight doses. Methotrexate dosage was escalated by 50 mg/kg in each cycle to a maximum dose of 250 mg/kg. Patients were well-hydrated, and urine was alkalized before each drug infusion. Forty-eight-hour blood levels of methotrexate were determined by radioimmunoassay, and all patients with methotrexate levels greater than 4 × 10⁻⁷ Molar received additional leukovorin.

Comparison of Patients Receiving Adjuvant Chemotherapy with Patients Receiving No Adjuvant Chemotherapy

In a study separate from that described above, patients with soft-tissue sarcoma of the extremities were prospectively randomized to be treated by either surgery alone or by surgery followed by adjuvant chemotherapy. All patients in this protocol received either amputation or limb-sparing surgery plus radiation therapy as described above. Patients were prospectively randomized to receive either adjuvant chemotherapy with doxorubicin, cyclophosphamide, and high-dose methotrexate as described above or randomized to receive no chemotherapy.

To assure comparability of the patient groups in this protocol, randomized patients were stratified based on the degree of differentiation of the primary lesion, whether patients received an amputation or limb-sparing surgery, and whether the lesions were in a proximal or distal portion of the involved extremity.

Patient Follow-up

All patients were seen at least every two months for the first three years after surgery and at three monthly intervals thereafter for the first five years. Complete blood chemical evaluation and chest radiographs were obtained at each visit. Full lung tomography was obtained every six months for the first three years. Histologic confirmation of recurrent disease was obtained in all patients who recurred.

Statistical Analysis

For comparing the disease-free survival and overall survival, the test of Mantel and Haenszel was used. In comparisons in which there were fewer than five total failures, the exact version of the Mantel–Haenszel test as described by Thomas was used to compute p values. Estimates of the “survival” curves were computed using the method of Kaplan and Meier. In looking at these curves the reader should keep in mind that toward the right hand side of these curves, where relatively few patients are at risk, the estimates are not very reliable. In comparing proportions in two groups the authors have used the Fisher exact test.

During the course of the adjuvant chemotherapy trial, interim analyses were performed at approximately six-month intervals. In order to guard against prematurely stopping the study, the method of monitoring...
TABLE 1. Soft-tissue Sarcomas of the Extremities

<table>
<thead>
<tr>
<th>Sex</th>
<th>Limb-Sparing Surgery</th>
<th>Amputation + Radiotherapy</th>
<th>Number of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>10 (63)</td>
<td>23 (85)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>6 (37)</td>
<td>4 (15)</td>
</tr>
<tr>
<td>Age:</td>
<td>0-20 years</td>
<td>2 (13)</td>
<td>4 (15)</td>
</tr>
<tr>
<td></td>
<td>21-40 years</td>
<td>9 (56)</td>
<td>9 (33)</td>
</tr>
<tr>
<td></td>
<td>41-65 years</td>
<td>5 (31)</td>
<td>14 (52)</td>
</tr>
<tr>
<td>Race:</td>
<td>Caucasian</td>
<td>13 (81)</td>
<td>22 (81)</td>
</tr>
<tr>
<td></td>
<td>Black</td>
<td>3 (19)</td>
<td>5 (19)</td>
</tr>
<tr>
<td>Site:</td>
<td>Arm</td>
<td>2 (12)</td>
<td>3 (11)</td>
</tr>
<tr>
<td></td>
<td>Forearm-hand</td>
<td>1 (6)</td>
<td>2 (7)</td>
</tr>
<tr>
<td></td>
<td>Thigh</td>
<td>10 (63)</td>
<td>17 (63)</td>
</tr>
<tr>
<td></td>
<td>Leg-foot</td>
<td>3 (19)</td>
<td>5 (19)</td>
</tr>
<tr>
<td>Histology:</td>
<td>Fibrosarcoma</td>
<td>0 (0)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Malignant fibrous</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>histiocytoma</td>
<td>1 (6)</td>
<td>3 (11)</td>
<td></td>
</tr>
<tr>
<td>Liposarcoma</td>
<td>7 (44)</td>
<td>4 (15)</td>
<td></td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>1 (6)</td>
<td>4 (15)</td>
<td></td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>0 (0)</td>
<td>3 (11)</td>
<td></td>
</tr>
<tr>
<td>Synoviosarcoma</td>
<td>4 (25)</td>
<td>7 (25)</td>
<td></td>
</tr>
<tr>
<td>Neurofibrosarcoma</td>
<td>1 (6)</td>
<td>3 (11)</td>
<td></td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>2 (13)</td>
<td>5 (19)</td>
<td></td>
</tr>
<tr>
<td>Grade:</td>
<td>1</td>
<td>1 (6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>4 (24)</td>
<td>3 (11)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>11 (70)</td>
<td>24 (89)</td>
</tr>
<tr>
<td>Total</td>
<td>16</td>
<td>27</td>
<td></td>
</tr>
</tbody>
</table>

described by Peito, et al. was employed. An overall test of disease-free survival for all patients randomized to chemotherapy or no chemotherapy was performed at each interim analysis using the test of Mantel Haenszel. At none of the interim analyses was the value of the chi square statistic extreme enough to warrant stopping the trial.

Results

Comparison of Patients Receiving Limb-Sparing Surgery Plus Radiation Therapy with Patients Receiving Amputation

Between May 1975 and April 1981, 43 patients with soft-tissue sarcoma of the extremities were randomized into this treatment protocol. Follow-up is complete in all patients as of October 1981 with a median follow-up of four years and eight months. The characteristic of the patients randomized in this protocol are presented in Table 1. Sixteen patients randomized to receive amputation and 27 patients randomized to receive limb sparing surgery and radiotherapy. Only about one third of eligible patients with soft-tissue sarcomas of the extremities agreed to enter this protocol and only these patients are considered here. There were no significant differences in patient characteristics in the two treatment arms with regard to sex, race, site, histology, or histologic grade of the primary lesions. Patients randomized to receive amputation tended to be younger than patients randomized to receive limb-sparing surgery plus radiation therapy.

The results of treatment as a function of site, histology, and grade of the primary lesion is presented in Table 2. Three patients randomized to the amputation

<table>
<thead>
<tr>
<th>Amputation</th>
<th>Limb-Sparing Surgery + Radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Number of Patients)</td>
<td>(Number of Patients)</td>
</tr>
<tr>
<td>Local + Distant</td>
<td>Local + Distant</td>
</tr>
<tr>
<td>Total</td>
<td></td>
</tr>
<tr>
<td><strong>Recurred</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Arm</strong></td>
<td>2</td>
</tr>
<tr>
<td><strong>Forearm-hand</strong></td>
<td>1</td>
</tr>
<tr>
<td><strong>Thigh</strong></td>
<td>10</td>
</tr>
<tr>
<td><strong>Leg-foot</strong></td>
<td>3</td>
</tr>
<tr>
<td><strong>Fibrosarcoma</strong></td>
<td>0</td>
</tr>
<tr>
<td><strong>Malignant fibrous histiocytoma</strong></td>
<td>1</td>
</tr>
<tr>
<td><strong>Liposarcoma</strong></td>
<td>7</td>
</tr>
<tr>
<td><strong>Leiomyosarcoma</strong></td>
<td>1</td>
</tr>
<tr>
<td><strong>Rhabdomyosarcoma</strong></td>
<td>0</td>
</tr>
<tr>
<td><strong>Synoviosarcoma</strong></td>
<td>4</td>
</tr>
<tr>
<td><strong>Neurofibrosarcoma</strong></td>
<td>1</td>
</tr>
<tr>
<td><strong>Undifferentiated</strong></td>
<td>2</td>
</tr>
<tr>
<td><strong>Grade:</strong></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>16</td>
</tr>
</tbody>
</table>
SOFT-TISSUE SARCOMAS OF EXTREMITIES

1. Prospective randomized evaluation of continuous disease-free survival in patients receiving either amputation or limb-sparing surgery plus radiation therapy. The results show a higher proportion in remission for patients receiving limb-sparing surgery. The graph indicates that limb-sparing surgery plus radiation therapy (p=0.75) results in a better disease-free survival compared to amputation (p=0.99).

Six patients have recurred in the limb-sparing surgery plus radiation therapy arm of the protocol, and three of these patients have died. There were a total of four local recurrences in these patients. One patient developed a local recurrence in the distal thigh. This patient subsequently underwent a hip disarticulation and remains disease-free 35 months later. Three patients developed simultaneous local recurrence and distant metastases, and two patients developed only distant metastases. These latter two patients underwent resection of all pulmonary metastases and remain alive 28 and 40 months later.

Actuarial analysis of the time to recurrence for all patients in the protocol is presented in Figure 1. There was no significant difference in time to recurrence in patients randomized to receive amputation compared with those randomized to receive limb-sparing surgery plus radiation therapy (p=0.75). Actuarial five-year disease-free survival was 78% in the amputation group and 71% in the limb-sparing group. Similarly there was no difference in overall survival between these two patient groups as shown in Figure 2 (p=0.99). Actuarial five-year overall survival in the amputation group was 88% compared with 83% in the group undergoing limb-sparing surgery. When analyzed for local recurrence there is a suggestion that patients undergoing limb-sparing surgery plus radiation therapy have a higher local recurrence rate than patients undergoing amputation as shown in Figure 3 (p=0.06). This difference in local recurrence rates did not result in improved survival in patients in this protocol though the number of patients in this comparison is small and this conclusion is a tentative one.

Detailed studies of the quality of life of patients in these two treatment arms have been performed and presented elsewhere. The authors found no significant differences in the quality of life parameters that were evaluated between these two patient groups.

The disease-free and overall survival of patients in
this protocol was markedly improved compared with virtually all reported series of patients with soft-tissue sarcomas of the extremities.\textsuperscript{1-10} All patients in this protocol received adjuvant chemotherapy and this is the likely explanation for the improved disease-free and overall survival seen in these patients as will be addressed in the next section.

\textit{Adjuvant Chemotherapy in Patients with Soft-Tissue Sarcomas of the Extremities}

Between May 1975 and June 1977 all patients with soft-tissue sarcomas of the extremities treated in the Surgery Branch of the National Cancer Institute in the protocol described in the previous section, as well as patients not eligible or refusing randomization in the above protocol, were treated with adjuvant chemotherapy. Preliminary results of this treatment in 26 patients with extremity soft-tissue sarcomas were reported in 1978.\textsuperscript{19} Despite the short follow-up at that time, it appeared that disease-free and overall survival in the patients receiving chemotherapy was prolonged compared with 46 historical controls from our own institution treated by surgery alone. In June 1977, therefore, we began a prospective randomized trial of the value of adjuvant chemotherapy in patients with soft-tissue sarcomas of the extremities. Patients underwent local therapy by either amputation or limb-sparing surgery plus radiation therapy and were then prospectively randomized to receive chemotherapy with doxorubicin, cyclophosphamide, and high-dose methotrexate as described above or to receive no adjuvant chemotherapy. This patient population differs from that previously described in the protocol comparing amputation and limb-sparing surgery plus radiation therapy though 16 of the 92 total patients in these protocols overlap the two protocols.

Sixty-five patients were evaluated in this randomized protocol before its termination in July 1981. Follow-up is presented here as of October 1981 with a media
follow-up of 653 days. Thirty-seven patients randomized to receive chemotherapy and 28 patients randomized to receive no chemotherapy. Actuarial analysis reveals a marked improvement in continuous disease-free survival in patients randomized to receive chemotherapy compared with those receiving no chemotherapy as shown in Figure 4 (p1 = 0.0008). The actuarial three-year disease-free survival for patients randomized to receive chemotherapy was 92% compared with 60% for patients receiving no chemotherapy. Improved survival in patients receiving chemotherapy was seen in patients who underwent either amputation or limb-sparing resection plus radiation therapy (Table 3). The overall survival of patients receiving chemotherapy was also improved compared with those randomized to receive no chemotherapy (Table 3) with actuarial three-year survivals of 95% and 74%, respectively (p1 = 0.04).

Three patients randomized to receive chemotherapy recurred with disease confined to the lung. Two of these patients underwent resection of all pulmonary disease and remain alive and free of disease without further recurrence eight and 23 months later. Nine patients who randomized to receive no chemotherapy recurred. Five patients recurred solely in the lung and four of these patients underwent resection of all known pulmonary disease, though only one has remained disease-free four months later. The remaining three patients recurred in the lungs a second time and were all rendered disease-free at repeat thoracotomy and are alive with no evidence of disease at one, two, and three months later. Though follow-up in this randomized trial is short, it appears that adjuvant chemotherapy is of benefit in the treatment of patients with soft-tissue sarcomas of the extremities. This prospective randomized trial confirms the results of the authors’ pilot, historically controlled trial conducted in the Surgery Branch of the National Cancer Institute between 1975 and 1977. Updated analysis of the 26 patients entered into that pilot trial as of October 1981 with a minimum follow-up of over four years continues to show benefit
for patients who received chemotherapy compared with historical controls who did not receive chemotherapy ($p < 0.001$).

**Discussion**

Soft-tissue sarcomas are malignant tumors of the extraskeletal connective tissues that are characterized by an aggressive tendency to invade into surrounding soft tissues and by a tendency for early metastatic spread to the lungs. There are about 4500 new cases of soft-tissue sarcomas in the United States each year. Soft-tissue sarcomas represent about 0.7% of cancers and about 6.5% of all cancers in individuals below the age of 25. Many different diagnoses comprise the soft tissue sarcomas, though all have a similar clinical behavior and can be considered as a single entity in evaluating proper therapy. The degree of differentiative (histologic grade) of the lesion is the major prognostic factor in patients with soft-tissue sarcomas.

The extensive local invasion of soft-tissue sarcomas into surrounding tissues has led to local recurrence rate of approximately 30 to 50% when wide local excision alone is used as treatment of these lesions. Two approaches that have been used to attempt to improve local control rates are the use of extensive radical con partmental excisions or amputations and the use of loco excisional surgery to remove gross tumor followed by aggressive radiation therapy to all areas at risk for loco tumor spread. Though this latter approach is effective in the control of childhood rhabdomyosarcoma, the application of this combined modality treatment adult patients with soft-tissue sarcomas has not yet been evaluated in well-designed clinical trials in the adult.

![Figure 4. Prospective randomized evaluation of continuous disease-free survival in patients randomized to receive adjuvant chemotherapy or no chemotherapy.](chart.png)

**Table 3. Soft-tissue Sarcomas of the Extremities**

<table>
<thead>
<tr>
<th></th>
<th>Chemotherapy (number of patients)</th>
<th>No Chemotherapy (number of patients)</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total recurred</td>
<td>3/37</td>
<td>9/28</td>
<td>0.0008</td>
</tr>
<tr>
<td>Total dead</td>
<td>1/37</td>
<td>4/28</td>
<td>0.04</td>
</tr>
<tr>
<td>Amputation-recurred</td>
<td>3/16</td>
<td>6/11</td>
<td>0.006</td>
</tr>
<tr>
<td>Limb sparing-recurred</td>
<td>0/21</td>
<td>3/17</td>
<td>0.04</td>
</tr>
</tbody>
</table>
The current clinical trial was undertaken in an attempt to compare the standard treatment for extremity sarcomas, i.e., amputation to treatment with limb-sparing resection surgery followed by radiation therapy.

In virtually all reported series of patients with soft-tissue sarcomas, five-year survival is in the range of 30-45%. Several chemotherapeutic agents exist with proven effectiveness in the treatment of adult patients with soft-tissue sarcomas, including doxorubicin, cyclophosphamide, DTIC, methotrexate, and vincristine.12-14 Objective response rates of approximately 30 to 45% can be achieved in patients with metastatic soft-tissue sarcomas when appropriate combinations of these chemotherapeutic agents are utilized. The use of aggressive adjuvant chemotherapy following surgery in the treatment of patients with soft-tissue sarcomas of the extremities has not been subjected to rigorous clinical evaluation. In the studies reported here, the authors have evaluated the combination of doxorubicin, cyclophosphamide, and high-dose methotrexate in patients following definitive resection for the treatment of soft-tissue sarcomas. Though follow-up is limited in this latter protocol, previous studies have shown that 80% of all sarcoma patients who recur, manifest a recurrence within two years of definitive therapy.15,3,28 This allows for relatively rapid evaluation of new therapies in this disease.

Between 1975 and 1981, the authors conducted a prospective randomized evaluation in adult patients with soft-tissue sarcomas of the extremities, comparing amputation with limb-sparing resection followed by radiation therapy. Only about one third of all patients with soft-tissue sarcomas of the extremities seen in the Surgery Branch of the NCI suitable for entrance into this protocol consented to join the protocol, and the data presented here deals only with this patient group. Although many patients refused amputation, a smaller number insisted on this treatment compared with the more experimental limb-sparing surgical treatment combined with radiation therapy. All patients included, however, were prospectively randomized. Patients randomized to receive amputation had removal of all involved tissues in the compartment of the tumor. Patients randomized to receive limb-sparing resection all underwent resection of all gross disease with maintenance of a functional extremity as a primary goal. In four of 27 patients undergoing limb-sparing surgery, positive margins of resection were present at the completion of surgery because of the proximity of tumor to essential nerves and vessels. Approximately 15% of patients presented with extremity lesions that were so extensively invasive into local tissues that local resection of all gross disease with maintenance of reasonable function of the extremity was not thought to be possible. These patients all underwent amputation and were not entered into this randomized protocol.

Appropriate stratification for prognostic factors resulted in a similar distribution of patients in the two treatment arms with respect to sex, age, race, site, histology, and histologic grade. Actuarial analysis of the results of this protocol with a median follow-up of four years and eight months revealed no difference in disease-free or overall survival between the two patient groups. The local recurrence rate was somewhat higher in the group receiving limb-sparing surgery plus radiation therapy (p = 0.06) though this difference did not result in decreased survival of patients undergoing limb-sparing surgery plus radiation therapy. Though the lack of impact of increased local recurrence on survival may be due to the small number of patients involved in this comparison, it may also indicate that patients with lesions that locally recur are also patients that are highly likely to develop disseminated disease even if local control were achieved by more radical surgery.

In a further attempt to analyze the prognostic factors responsible for recurrence the authors performed a multivariate analysis of the treatment results of all patients who received chemotherapy for the treatment of soft-tissue sarcomas in both protocols considered in this article. No correlation existed with local recurrence, overall recurrence or survival with respect to site, histology, grade, sex, race, age, time from surgery to onset of chemotherapy and nadir white count or platelet counts during chemotherapy. However, a high correlation did exist with local recurrence and the final margin of surgical resection with a marked increase in local recurrence in patients whose final surgical margins were positive for tumor (p < 0.0001). In this combined group patients with negative surgical margins had an improved survival compared with those with positive surgical margins (p = 0.007). This analysis, however, includes patients from the chemotherapy randomization study who were not randomized to the surgical treatments, and it is thus possible that this survival difference is caused by factors other than the surgical treatment performed. Patients who had positive surgical margins who recurred might well have recurred if amputative surgery to achieve negative margins had been performed. On the basis of the authors' randomized trial it does not appear essential that negative surgical margins be achieved if radiation therapy and chemotherapy are administered in the postoperative period. However, this conclusion is based on a small number of patients and must be considered tentative. A very conservative interpretation of these results, however, would indicate that if negative surgical margins can be obtained with limb-sparing surgery, and radiation therapy and chemotherapy are used in the postoperative period, these...
patients will have a long-term, disease-free and overall survival comparable with those patients who undergo amputation.

Because of the improved survival that was observed in the early pilot trials utilizing chemotherapy in patients with soft-tissue sarcomas of the extremities, the authors undertook a prospective randomized trial of the value of chemotherapy. The adjuvant chemotherapy regimen selected was a combination of doxorubicin, cyclophosphamide, and high-dose methotrexate that appeared successful in the early pilot trials.

A recent analysis of the results of treatment in the 26 patients in the pilot chemotherapy trial treated between May 1975 and June 1977 compared with our historical controls, with a minimum follow-up of four years, revealed an improvement in survival because of the adjuvant chemotherapy (p = 0.001). The prospective randomized trial comparing patients receiving chemotherapy with those receiving no chemotherapy conducted between June 1977 and July 1981 revealed a marked improvement in disease-free and overall survival for those patients receiving chemotherapy. This trial has been analyzed in more detail elsewhere. It should be emphasized, however, that follow-up in this trial is short (one year, eight months), and further follow-up will be necessary to verify this conclusion.

In summary it appears that limb-sparing surgery plus radiation therapy is effective treatment for most patients with soft-tissue sarcomas of the extremities. Postoperative adjuvant treatment with the combination chemotherapy regimen that has been described appears capable of significantly improving disease-free and overall survival of these patients.

References


Discussion

Dr. LaSalle D. Leffall, Jr. (Washington, D.C.): I would like to compliment Dr. Rosenberg and his colleagues on this paper, in particular for their continued study on a very important area in surgical oncology, and that is the management of soft sarcomas. Even though we don't see very many of these malignant tumors, very often when we do see them, some of these patients have been subjected to amputations, and I think, based on the study of Dr. Rosenberg and others who has alluded to in his manuscript, we have evidence to show that we do not need to perform some of these amputative procedures.

In the manuscript, he gives recognition to the work of Suit and Lindberg, both of these men called attention to the role that radiotherapy plays in the management of soft sarcomas. At one time we
taught that there were radioresponsive tumors, radioresistant sarcomas, and radioinert sarcomas, and I think that our colleagues have told us there is no such thing as a radioresistant tumor.

I think they are radioresponsive, or there are varying degrees of radioresponsive using that information, Dr. Rosenberg and his colleagues had the first prospective, randomized controlled trial, using adjuvant surgery and radiation therapy.

In the second group, recognizing that histologic grade was the most important criterion affecting survival if all other things were equal, we added chemotherapy to the management of these patients, and that's something that we must keep in mind, histologic grade. Going back several years, we have come from the time of talking about and-cell sarcomas and spindle-cell sarcomas; we have come to speculate on histologic types, and now we have recognized the great importance of histologic grade. Pathologists usually will say either "low grade" or "high grade," or sometimes an intermediate grade.

The majority of patients in this series, as in most series, have high-grade tumors.

I think it's important, however, that we keep in mind that most recurrences occur in the first 12 to 18 months. I think that we probably will see what he has described here as being shown when the patients are followed for longer periods of time, that is, prolonged disease-free survival periods.

There are two questions that I would like to ask Dr. Rosenberg. Is there any role for intraoperative radiotherapy in patients in whom we suspect, because of the size of the tumor and the closeness of your margin, from a clinical point of view, that this treatment may have some adjuvant role?

What size must a tumor be, how small or how large, before you make the statement to yourself that this patient can have limited surgery, radiotherapy, and chemotherapy or having amputation?

DR. MURRAY F. BRENNAN (New York, New York): At my current institution, we see in excess of a hundred new soft tissue sarcomas each year, and have been led by the insightful way in which Dr. Rosenberg has examined the problem. As a consequence, I have thought about his data, and question, and I really only have one question, which is, I don't think the radiation therapy you deliver is noninvasive, particularly in the proximal thigh lesions. It can be extremely morbid, and it makes recurrence hard to detect. As I understand your data, both in the abstract and in your presentation, even in the positive margin patients the radiotherapy did not help, and all of the patients received chemotherapy, certainly in the first protocol.

My question is, can you comment on whether the radiation therapy is necessary at all? Eventually, you will you have that data from your chemotherapy arm.

DR. C. E. CARMACK HOLMES (Los Angeles, California): I am too concerned, as were the two previous discussants, regarding the morbidity of the radiation therapy, especially in the proximal thigh. Our group, which is headed by Dr. Fred Eifler at UCLA, has employed the use of intraarterial Adriamycin and preoperative radiation therapy, the dose being 3500 rads, with very low morbidity, to obtain equal, or better, control.

I would like to suggest that Dr. Rosenberg, if he has any thoughts about other techniques that he could use to decrease the local recurrence on the proximal thigh lesions, in particular, the intraoperative radiation therapy modality that you have available to you at NTH that the rest of us do not have.

The second question has to do with the chemotherapy. I would like to compliment Dr. Rosenberg and his group for their very brave study, to prove that a prospective randomized trial that adjuvant chemotherapy is efficacious in these patients. I would, however, like to ask him to give us some idea of the morbidity associated with this chemotherapy. I happen to know that Dr. Rosenberg has decreased the dose of Adriamycin from 350 mg per meter square to 350 mg per meter square, to minimize the toxicity. Our experience has been that when the patients do recur, it is almost never during the course of Adriamycin but following its discontinuation, and I wonder if by decreasing the dose from 350 to 350, one might not see earlier recurrences, and indeed, if that will decrease the cardiotoxicity, or whether just discontinuing the cytoxan might diminish the cardiotoxicity.

DR. STEVYN A. ROSENBERG (Closing discussion): Our prospective randomized study of the role of adjuvant chemotherapy has a median follow-up of one year and ten months. This trial of adjuvant chemotherapy was based on our experience with 29 patients that were treated between 1975 and 1977 with chemotherapy in a pilot trial. We have updated follow-up of all of those patients with a minimum follow-up of four years. The overall survival in that patient population is 92%, which is quite remarkable for a patient population with high-grade soft-tissue sarcomas. In that experience as well in the report of studies of many others, over 80% of all recurrences in patients with soft-tissue sarcomas take place in the first two years; so, although the follow-up in our adjuvant chemotherapy trial is short, we have every expectation that these early results will be maintained.

Both Dr. Leffall and Dr. Holmes mentioned the possible use of intraoperative radiation therapy. This is a treatment modality that is being extensively evaluated at the National Cancer Institute by Drs. Sindelar, Kinsella & Glugstein of the Surgery & Radiation Oncology Branches. We are currently conducting three prospective randomized trials comparing intraoperative radiation therapy to conventional adjuvant radiation therapy. The only one of these trials that deals with sarcoma patients deals with patients with retroperitoneal sarcomas and it is too early in the trial to draw any conclusions.

In answer to Dr. Leffall's question about which patients were eligible for our adjuvant trial, all patients with extremity soft-tissue sarcomas for whom we felt a limb-saving operation could result in removal of the entire tumor. Without elimination of function of that extremity, were included in the protocol. There is no evidence to my knowledge, that size is an important prognostic correlate in patients with high-grade soft-tissue sarcoma. I would estimate that about 85% of all of the soft-tissue sarcoma patients of the extremities referred to the National Cancer Institute were eligible for this trial because of the size of their lesion.

Dr. Brennan has raised a very important question concerning the necessity for radiation therapy for the treatment of these lesions. Dr. Holmes has referred to the morbidity of the radiation therapy, which tends to be magnified somewhat when simultaneous radiation-sensitizing chemotherapy, such as doxorubicin is used. I think this is an important point.

In our current trials, our three-year survival figures appear to be in the 85 to 90% range. It is, therefore, going to be difficult to design trials that will look for improvements over that figure. Certainly, very large numbers of patients will be required.

It then becomes reasonable to attempt to reduce morbidity of treatment without losing therapeutic efficacy. In fact, this is the exact direction that our current clinical trials have taken.

Our next generation trial, which is a prospective randomized trial, is attempting not to eliminate radiation therapy, but rather to reduce the chemotherapy dose. The most serious toxic side effect of the use of this chemotherapy regimen is the cardiomyopathy associated with doxorubicin. About 11% of patients who receive full-dose doxorubicin will develop congestive heart failure. An additional 35% of patients will show decrease in left ventricular ejection fraction with this chemotherapy regimen, when this is looked at using ECG-gated radionuclide scans.

Our new protocol, therefore, is comparing the exact chemotherapy regimen I mentioned today with a chemotherapy regimen which limits the total doxorubicin dose to 350 mg per meter squared, a limit at which little clinical or subclinical cardiomyopathy would be expected. This prospective trial is in progress, and we have entered about 35 patients in this trial to the present time.

Another very reasonable trial would be to see if the radiation therapy could be eliminated. That will probably be our next trial.