Impact of Two Cycles of Preoperative Chemotherapy With Intraarterial Cisplatin and Intravenous Doxorubicin on the Choice of Surgical Procedure for High-Grade Bone Sarcomas of the Extremities

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The authors assessed the impact of two cycles of preoperative chemotherapy (POCT) with intraarterial cisplatin (120 mg/m²) and continuous intravenous doxorubicin hydrochloride (Adriamycin; 20 mg/m²/day × 3 days) on the decision to perform a limb-sparing procedure (LSP) or amputation in 22 patients with high-grade bone sarcomas of the extremities. The tumor types were osteosarcoma (17), malignant fibrous histiocytoma (three), leiomyosarcoma (one), and malignant schwannoma (one). Surgical stages were II A (three), II B (17), and IIIB (two). The prechemotherapy surgical options chosen were 12 amputations (55% of patients) and ten LSPs (45%). The initial decisions to amputate were based on a combination of the following: improper biopsy (five cases), large tumors (ten), and those with neurovascular encroachment (six), and pathological fracture (one). Following chemotherapy, 18 LSPs (81%) and four amputations (19%) were performed. Nine of 12 patients (75%) initially deemed unresectable were converted to LSP. The median tumor response (necrosis; range, 0%–100%) was 70%; ten of 22 specimens had necrosis >95%. Median tumor necrosis for the patients treated by amputation and LSPs was 45% and 88%, respectively. Following surgery, all patients received four additional cycles of cisplatin and doxorubicin. The median follow-up period is 30 months; six patients have developed metastatic disease, with a median disease-free interval of 16.6 months. The rate of local tumor control is 95% (21 of 22 patients). The authors conclude that (1) two cycles of POCT significantly increase the percentage of patients with high-grade bone sarcomas of the extremities who can be safely treated with a LSP, (2) a response to POCT has a strong influence on the surgical decision-making process, and (3) primary amputations are not recommended before a trial of POCT.

Postoperative adjuvant chemotherapy, in conjunction with surgery, has altered the outcome of patients with osteosarcomas. Elimination of systemic micrometastases appears to be an important mechanism in the success of this form of therapy.
Two recent developments in management of bone tumors have been preoperative (neoadjuvant) chemotherapy and shorter overall lengths of adjuvant treatment. Preoperative chemotherapy (POCT) was first administered in the early days of limb-sparing surgery, during the mid-1970s, when the waiting period for a custom-made prosthesis ranged from two to three months. Surgeons learned that POCT could reduce tumor size, cause tumor necrosis, and allow in vivo sensitivity testing. In addition, the role of POCT in conversion of unresectable tumors to those amenable to limb-salvage procedures was also investigated.

This study had two primary objectives: (1) to evaluate the impact of a short course (two cycles) of POCT on the surgical decision to perform a limb-sparing procedure (LSP) versus amputation, and (2) to evaluate the impact of a short duration (six cycles) of adjuvant chemotherapy on relapse-free and overall patient survival. This report describes the impact of POCT on the choice of surgical procedure; a subsequent report (awaiting longer follow-up intervals) will address the latter question.

MATERIALS AND METHODS

Twenty-two patients with high-grade sarcomas of the extremities, including the shoulder and pelvis, participated in the study. There were 11 males and 11 females. The median age was 19.5 years (range, seven to 69 years). The histologic diagnoses were osteosarcoma (17), malignant fibrous histiocytoma (3), leiomyosarcoma (1), and malignant schwannoma (1). The surgical stages (Musculoskeletal Tumor Society) were IIA (3), IIB (17), and IIIB (2). Staging studies to determine resectability included bone scans, plain roentgenographs, biplane arteriograms, computed tomography (CT) and/or magnetic resonance imaging (MRI) of the extremity, and chest CT.

STUDY DESIGN AND TREATMENT REGIMEN

Preoperative chemotherapy consisted of two cycles of intraarterial cisplatin (DDP) over four hours and continuous intravenous doxorubicin hydrochloride (Adriamycin [ADR]; dosage, DDP = 120 mg/m² and ADR = 120 mg/m² · day⁻¹ × 3 days). Postoperatively, four cycles of DDP and ADR were given intravenously. The regimens were not altered on the basis of histologic tumor response (necrosis). Before POCT and after completion of the initial staging studies, a preliminary surgical decision (amputation or LSP) was recorded for each patient. Following POCT, all tumors were restaged, and a second, and final, surgical decision was made based upon the same criteria that had been used for the preliminary decision.

ANGIOGRAPHIC TECHNIQUE

Intravenous prehydration was started eight hours before cisplatin therapy. Catheterization, with 5 French in adults and 4 French in children, was done via the femoral route using the standard Seldinger technique. Catheters were placed in the major vessels of the extremities: the common femoral, subclavian, and iliac arteries for distal femoral, proximal humeral, and pelvic tumors respectively. The superficial femoral artery was utilized for proximal tibial tumors. Selective catheterization was not performed. An arteriogram was performed and necessary adjustments of the catheter were made. The catheter was then attached to an arterial infusion pump, and the patient was adequately heparinized to prolong partial thromboplastin time to 1.5 to two times the normal. Mannitol (12.5 g) was given intravenously 15 minutes before cisplatin.

SURGICAL CONSIDERATIONS

The decision to proceed with a limb-sparing procedure was based on six key criteria: (1) The major neurovascular bundle should be free of tumor. (2) Wide resection with a normal cuff of tissue in all directions should be possible. (3) In bloc removal of potential sites of contamination, including biopsy sites, must be feasible. (4) Bone must be resectable 5 cm to 6 cm beyond the level indicated by preoperative imaging studies. (5) The adjacent joint and capsule must be resectable (distal femoral tumors were treated by an intraarticular procedure, whereas all proximal humeral resections were extraarticular). (6) Adequate muscle must be present for both motor power and coverage of the prosthetic implant.

The contraindications to limb-sparing resection used in this protocol were as follows: (1) major neurovascular involvement, (2) inappropriate biopsy sites with extensive soft-tissue contamination, (3) pathologic fracture, (4) large tumor size or absence of adequate muscle groups to allow a functional extremity, and (5) local infection. These contraindications were recorded for each pa-
tient (Table 1). Immature skeletal age was not considered a contraindication.

PATHOLOGIC EVALUATION

The gross specimen was evaluated to determine the final surgical margin. Tumor necrosis was determined by the grid method. The percent tumor necrosis was recorded. "Good" and "poor" respondents were defined as greater than and less than 90% tumor necrosis respectively.

ANALYSIS

There were four possible options with respect to the preliminary and final surgical decision: LSP-to-LSP, LSP-to-amputation, amputation-to-amputation, and amputation-to-LSP. The relationship of the initial and final surgical decisions were evaluated and compared to the degree of tumor necrosis and to the various surgical groups. Rates of local recurrence and disease-free survival were determined.

RESULTS

TYPE OF SURGICAL PROCEDURES

Initial surgical decision (Table 1). Before POCT, 12 amputations and ten LSPs were chosen, representing a 45% limb-sparing rate. The initial decisions to perform amputation were based on one or a combination of the following considerations: poor biopsy with resultant contamination (5 patients), a large tumor (10 patients), a large tumor with neurovascular encroachment in which there was deemed no safe margin (7 patients), and pathologic fracture (1 patient).

Definitive surgical decision. The definitive procedures performed following POCT were 18 LSPs and four amputations, representing an 81% limb-sparing rate. The types of procedures performed are presented in Table 2.

Relationship of pre-versus post-POCT decision (Fig. 1). Nine of 12 patients (75%) initially deemed unresectable were converted to a limb-sparing procedure; the remaining three patients received amputations. Nine of ten patients deemed initially resectable received a LSP; the remaining patient had local tumor progression with a secondary fracture and required a high above-knee amputation.

Relationship of type of surgery to tumor necrosis (Table 1). All procedures accomplished a wide excision. The overall median necrosis was 70% (range, 0-100%). Ten of the 22 patients had greater than 95% necrosis. There was no difference in necrosis rate between the osteosarcoma (17) and nonosteosarcoma patients (5). The median necrosis for the patients treated by LSP and amputation were 88% and 45%, respectively. The median necrosis of the LSP-to-LSP (9 patients) and the amputation-to-LSP (9 patients) groups was 75% and 95% respectively. All

| Table 1. Criteria for Amputation Versus Resection Relationship to Percent Tumor Necrosis (N = 22) |
|---|---|---|---|---|---|
| Type of Surgery | No. Patients | BX | NV | FX | Path. FX | Size | Median Tumor Necrosis |
| LSP-LSP | 9 | — | — | — | — | — | 75% |
| LSP-A | 9 | 4 | 5 | — | — | 7 | 95% |
| Total LSPs | 18 | | | | | | 88% |
| Amputation | 4 | 1 | 2 | 1 | 1 | 2 | 35% |
| A-A | 1 | — | — | — | — | — | 50% |
| Total A | 4 | | | | | | 45% |
| Overall total | 22 | 5 | 7 | 2 | 10 | | 70% |

LSP, limb sparing; A, amputation. BX, poor biopsy with extensive contamination; NV, neurovascular involvement; Path. FX, pathologic fracture; Size, large tumor size.
TABLE 2. Types of Surgical Procedures Performed After Two Cycles of POCT

<table>
<thead>
<tr>
<th>Types of Surgical Procedures Performed (N = 22)</th>
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<tbody>
<tr>
<td>Limb-sparing surgery (18)</td>
</tr>
<tr>
<td>Segmental replacement (custom or modular)</td>
</tr>
<tr>
<td>Expandable replacement</td>
</tr>
<tr>
<td>Resection alone</td>
</tr>
<tr>
<td>Saddle (pelvic) prosthesis</td>
</tr>
<tr>
<td>Proximal femoral prosthesis</td>
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<tr>
<td>Neer prosthesis</td>
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<tr>
<td>Allograft</td>
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nine patients in the LSP-to-LSP group had some response; the minimum response was 50%, and in four patients response was greater than 95% necrosis.

TUMOR STATUS AND TUMOR NECROSIS

The median follow-up period is 30 months. Two patients were initially diagnosed with metastatic disease (Stage III). Six of the remaining 20 patients (five osteosarcoma, one malignant schwannoma), without signs of metastases initially, have developed metastatic disease. The disease-free interval to pulmonary metastasis was 16.6 months. The median tumor necrosis of the primary specimen of these patients was 45%. Four of the five osteosarcoma patients had less than 90% necrosis. There has been one relapse among the six good respondents and two relapses among the nine poor respondents with osteosarcoma.

Overall local tumor control was 95% (21 patients). One patient developed a local recurrence following a limb-sparing procedure for a Stage IIIB proximal femoral sarcoma and required a secondary hemipelvectomy. The primary specimen showed 95% tumor necrosis.

COMPICATIONS

Deep muscle (myocutaneous) necrosis occurred in two patients. Neither required surgical debridement. Two patients developed arterial thrombosis (one before surgery and one intraoperatively); both required embolectomies. One patient developed an infection secondary to an infected subclavian line following a distal femoral prosthetic replacement, necessitating an above-knee amputation.

DISCUSSION

The primary purpose of this prospective study was to determine the impact of preoperative chemotherapy on the choice of surgical procedure, as measured by the number of limb-sparing procedures versus amputations performed.
The criteria of patient selection for LSP are based upon careful evaluation of clinical and radiographic parameters. In this study the initial (i.e., before POCT) surgical decision was LSP for 45% of the 22 patients. This percentage in itself is higher than that reported in studies that have involved postoperative adjuvant therapy alone; it reflects, in part, the authors' positive institutional experience with LSP. Following POCT, the LSP rate rose to 81%. Nine of 12 patients who initially were judged to need an amputation were converted to a LSP. Only one patient became ineligible for limb sparing during POCT because of tumor progression.

The major preoperative factors necessitating an amputation were a poorly performed biopsy with significant local contamination of the soft tissue, adjacent joint or (both), and proximity of tumor to the neurovascular bundle. Tumor size in itself is usually not a contraindication; it affects the choice of surgery only in the sense that larger tumors tend to displace the major vessels or require a large amount of muscle to be resected and thereby reduce the function of the extremity. The neurovascular structures were displaced in some of our patients; however, they were not involved or infiltrated by tumor. Thus, a good response safely permits the widening of the margin along the vessels, either by shrinking the tumor or by destroying presumed local micrometastatic disease in the reactive zone of the tumor.

This study showed that the tumor necrosis of LSP patients was almost double that of patients who received amputations (88% versus 45% respectively). Interestingly, the amputation-to-LSP patients also had a greater necrosis (95% versus 75%) than did the initial LSP patients, although both groups had a higher rate than the patients who required amputation. The same degree of tumor necrosis was observed for both osteosarcoma and tumors other than osteosarcoma.

Almost all patients treated by a LSP had a tumor necrosis of greater than 50%, whereas those undergoing amputation had less than 50% response rate. Thus LSP can be performed safely if tumor necrosis is greater than 50%. This is different than the often quoted 90%, which relates to the reported improved likelihood of survival rather than to increased local tumor control. The authors recommend reserving amputation for those patients who do not respond clinically to POCT. Most patients, they noted, with greater than 60% tumor necrosis have a successful LSP. The low local failure rate of 5% observed in the current study indicates that a short course of POCT is effective in eradicating microscopic tumor nodules which, if left untreated, would lead to the development of a local recurrence (Fig. 2).

Unfortunately, attempts to ascertain tumor necrosis before surgery have been unsuccessful. Preoperative biopsies are fraught with the danger of unrepresentative sampling errors. Preoperative scanning studies, if reliable, would be of greater utility. The authors have found that the postulated regional tumor effect of neoadjuvant chemotherapy can be visualized on the angiographic study where increased arterial concentration of the chemotherapeutic agent results in increased drug concentration to the local/regional tumor area, which may eradicate local skip lesions as well as the major tumor, thus permitting a safe local procedure to be performed.

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Surgical decision. The definitive procedures performed following POCT were four amputations, representing sparing rate. The types of procedures are presented in Table 2. Of pre-versus post-POCT decision, nine of 12 patients (75%) initially unresectable were converted to amputations; the remaining eight patients received amputations. Nine of the 12 patients (75%) initially deemed initially resectable received a limb-sparing procedure. The remaining patient had local recurrence with a secondary fracture and was treated with a high above-knee amputation.

Table 2. Proportion of procedure types in relation to tumor necrosis.

<table>
<thead>
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<th>Size</th>
<th>Median Tumor Necrosis</th>
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<tbody>
<tr>
<td>7</td>
<td>79%</td>
</tr>
<tr>
<td>2</td>
<td>35%</td>
</tr>
<tr>
<td>1</td>
<td>50%</td>
</tr>
<tr>
<td>10</td>
<td>70%</td>
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</table>

All procedures accomplished complete excision. The overall median 70% (range, 0-100%). Ten of the had greater than 95% necrosis. No difference in necrosis rate between 7a (17) and nonosteotomists. The median necrosis rates treated by LSP and amputation were 45%, respectively. The medians of the LSP-to-LSP (9 patients) amputation-to-LSP (9 patients) were 75% and 95% respectively. All medicolegally safe margin (7 patients), and neurovascular involvement; 22)

Figs. 3A-3F. A 16-year-old patient with a distal femoral osteosarcoma. (A) Plain anterioposterior (AP) roentgenogram prior to POCT. (B) Lateral plain roentgenogram prior to POCT. (C) Plain AP roentgenogram following POCT. (D) Lateral roentgenogram following POCT. Note the smooth margins of the new bone and the reossification (arrows) of several small tumor nodules along the medial aspect. (E) CT of the distal femur prior to POCT. (F) CT of the distal femur following POCT. Following POCT there is marked rimming (arrows) of the extraosseous component, which indicates a good tumor response, even though the size did not significantly decrease. This patient initially was considered for amputation but was treated with a limb-sparing procedure instead. The gross specimen showed >90% tumor necrosis.
Figs. 4A and 4B. MRI and gross specimen of a large distal femoral osteosarcoma. (A) MRI following POCT demonstrates a large soft-tissue component with evidence (black line, arrows) of new rimming bone. (B) The gross specimen shows marked tumor necrosis (>90%). This patient was converted to a limb-sparing procedure.
oral osteosarcoma. (A) MRI following (black line, arrows) of new rimming (0%). This patient was converted to a

FIG. 5. Low-power photomicrograph of an osteosarcoma demonstrating a typical pattern of complete tumor necrosis following POCT. There is malignant osteoid with empty lacunae and the stroma has been replaced by a reparative fibrovascular tissue. There is no evidence of viable tumor cells. (Stain, hematoxylin and eosin; original magnification, ×50).

able and reproducible, would help resolve this dilemma; however, the value and reliability of radiographic signs are far from settled. Data from the M.D. Anderson group suggest that angiograms may provide helpful information; however, these authors recommend using other studies and clinical criteria as well.

Plain roentgen rays and CT indicators of response include an increase in calcification, a decrease in, and better, definition of the soft-tissue component, and remodeling of the cortex (Figs. 3 and 4).

Angiographic signs of necrosis include a reduction in vascular blush and possibly in tumor size. Some authors have reported that the correlation of CT and plain film with necrosis found at pathology is poorer than the correlation of angiography and histologic findings with necrosis. Other authors have incorporated a combination of clinical indicators such as a reduction of pain, size, temperature, and range of motion into their definition of response. The authors were unable to place full confidence in any single modality; however, in most cases, the combination of clinical and radiologic studies gave a good, although not completely quantifiable, assessment of the expected tumor response.

The authors' data suggest that one can probably convert an amputation to a LSP provided that there is no obvious tumor progression and radiographic studies indicate some regression (e.g., decreased vascularity and increased rimming seen on CT, plain roentgenography, or MR; Figs. 3–5). Such a decision was made for 75% of the patients in this study, who had initially been designated for treatment by amputation. The authors do not recommend excluding any patient from a trial of POCT, although an infected biopsy
site (rare) or gross displaced fracture (unusual) may require a primary amputation. Pathologic fracture was a contraindication for LSP in this study. In selected cases where healing occurs following POCT, it may, however, be possible to attempt resection. This would have to be a subjective decision taken by a surgeon and based on experience.

In summary, this study suggests the following: (1) A short course (2 cycles) of POCT is safe and permits a significant amputation-to-LSP conversion. (2) Tumor necrosis of 50% or greater correlates with successful LSP. (3) Most patients with high-grade osteosarcoma of the extremities: Twenty years' experience at the Instituto Orthopedico Rizzoli. Cancer 45:229. 1981.

In the 1980s, clinical orthopaedic surgeons performed limb-salvage procedures with increasing frequency, and randomized controlled trials comparing amputation to limb-salvage treatment were performed. These studies demonstrated that limb salvage was equivalent to amputation in terms of local recurrence and survival. The results of these trials were reported in the medical literature, providing evidence that limb-salvage surgery was a viable treatment option for patients with osteosarcoma.

In conclusion, limb-salvage surgery is a viable treatment option for patients with osteosarcoma and should be considered in appropriate cases. The decision to perform limb salvage should be made on an individualized basis, taking into account the patient's wishes, the tumor characteristics, and the surgeon's expertise.

REFERENCES