

# Limb-Salvage Treatment versus Amputation for Osteosarcoma of the Distal End of the Femur\*

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**ABSTRACT:** A retrospective multi-institutional study of 227 patients with osteosarcoma of the distal end of the femur was done to compare rates of local recurrence, metastasis, and survival. Three cohorts of patients who had had either a limb-sparing procedure, an above-the-knee amputation, or disarticulation of the hip were compared. The results revealed prevalences of eight of seventy-three, nine of 115, and zero of thirty-nine as to local recurrence; forty-three of seventy-three, sixty-five of 115, and twenty-one of thirty-nine as to metastasis; and thirty-three of seventy-three, forty-eight of 115, and eighteen of thirty-nine as to death. Of the seventeen patients who had a local recurrence, sixteen died. In the limb-salvage group, eighteen patients required amputation, because of local recurrence in eight and other local complications in ten. The Kaplan-Meier estimates of the percentage of patients who survived and the percentage of patients without recurrent disease showed no difference among the three surgical groups (Mantel-Cox test statistic:  $p = 0.8$ ) after a median length of follow-up of five and one-half years. Various covariant adjusted estimates yielded similar results. For the entire group of patients, the rate of continuously disease-free survival was 42 per cent, and the over-all rate of survival was 55 per cent at five years. It appears that, compared with above-the-knee amputation or disarticulation of the hip, the use of a limb-salvage procedure for osteosarcoma of the distal end of the femur did not shorten the disease-free interval or compromise long-term survival.

In the last ten years, there has been increasing interest in limb-salvage surgery for osteosarcoma. When this procedure is compared with amputation, it raises the following three concerns that are the subject of the present study: the incidence and consequences of local recurrence, the length of the disease-free interval, and the rate of long-term survival. While there are other important concerns (for in-

stance, the immediate and delayed morbidity after a limb-saving procedure, the function of the preserved limb, and the possible psychosocial benefits of preservation of a limb), they are not touched on in this report of a multi-institutional collaborative investigation.

## Methods

In August 1982, an extensive questionnaire was sent to all members of the Musculoskeletal Tumor Society. They were asked to register all patients who were less than thirty years old and who were diagnosed, between July 1, 1975, and June 30, 1980, as having a high-grade conventional osteosarcoma that originated in the distal metaphysis of the femur<sup>5,7</sup>. To be eligible, a patient must have been treated at the member institution by an above-the-knee amputation, disarticulation of the hip, or a limb-sparing surgical procedure. A patient was excluded from the study if a metastasis was clinically evident at the time of diagnosis; if the patient was more than twenty-nine years old; or if the patient had a tumor that was diagnosed as parosteal or periosteal osteosarcoma, low-grade osteosarcoma of the intramedullary canal, osteosarcoma complicating Paget disease, or radiation-induced sarcoma. Patients with multicentric or telangiectatic osteosarcoma or malignant fibrous histiocytoma also were specifically excluded.

The data that were recorded in the questionnaire included the age, sex, and race of the patient; the size of the tumor, as measured on a conventional radiograph; the imaging techniques that were used to screen for metastases preoperatively; and the surgical stage, as described by Enneking et al.<sup>7</sup>. The type of chemotherapeutic or radiotherapeutic adjuvant treatment before surgery, if any, and the nature of the definitive surgical procedure were also recorded. If a limb-salvage procedure had been performed, the physician was asked to note whether it was intra-articular or extra-articular. Complications, secondary procedures (including amputation), and adjuvant chemotherapy or radiotherapy after surgery were also listed.

In the original 1982 questionnaire and again in a subsequent assessment in September 1984, the results at follow-up for each patient were recorded. On both occasions, the importance of supplying the result for all eligible patients was stressed. Additional cases of patients who met the criteria already cited but who were overlooked on the first questionnaire were submitted, and they were included in

\* No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article. No funds were received in support of this study.

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TABLE I

Institution	Number of Patients			
	Total	Limb-Salvage Surgery	Above-the-Knee Amputation	Disarticulation of the Hip
University of Chicago Medical Center, Chicago, Illinois	6	0	0	6
University of Florida Medical Center, Gainesville, Florida	25	8	1	16
Columbia-Presbyterian Hospital, New York, N.Y.	5	4	1	0
University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania	2	0	0	2
Memorial-Sloan Kettering Cancer Institute, New York, N.Y.	9	5	1	3
Roswell Park Memorial Institute, Buffalo, New York	3	0	3	0
University of Minnesota School of Medicine, St. Paul and Minneapolis, Minnesota	3	0	1	2
University of Iowa Hospitals, Iowa City, Iowa	5	0	5	0
University of California-San Francisco, San Francisco, California	5	0	3	2
Kaiser Permanente-Oakland, Oakland, California	5	1	4	0
Massachusetts General Hospital, Boston, Massachusetts	7	2	5	0
University of Wisconsin, Madison, Wisconsin	10	2	5	3
University of California-Los Angeles Hospital, Los Angeles, California	29	19	9	1
Istituto Ortopedico Rizzoli, Bologna, Italy	33	5	28	0
Lenox Hill Hospital-Hospital for Joint Diseases, New York, N.Y.	7	3	4	0
University of Kansas, Kansas City, Kansas	5	5	0	0
Milwaukee Children's Hospital, Milwaukee, Wisconsin	2	0	2	0
Sahlgren Hospital, Göteborg, Sweden	2	0	1	1
William Beaumont Hospital, Royal Oak, Michigan	1	0	1	0
University of Kentucky Medical Center, Lexington, Kentucky	1	0	0	1
Mayo Clinic, Rochester, Minnesota	24	2	22	0
Rush Presbyterian-St. Luke's Medical Center, Chicago, Illinois	2	0	2	0
University Hospital in Lund, Lund, Sweden	3	0	3	0
Columbus Children's Medical Center, Columbus, Ohio	3	2	0	1
Children's Hospital National Medical Center, Washington, D.C.	2	0	1	1
Children's Hospital, Boston, Massachusetts	28	15	13	0
Total	227	73	115	39

the study. The local recurrences and metastases were tabulated according to site and date of recognition. Surgical resection of pulmonary metastases, if it had been done; the status of the disease at the last clinical evaluation; and the date of death were also recorded.

Three variables as to outcome were considered: length

of time to recognition of a local recurrence, length of time to recognition of metastasis, and length of time to death. Time was measured from the date of definitive surgery, which usually coincided with or closely followed the date of biopsy. Kaplan-Meier estimates<sup>8</sup> were calculated for the three variables in each surgical group.

### Material

Two hundred and forty-eight cases of patients from twenty-six institutions were submitted for study, and after careful assessment twenty-one were declared ineligible, leaving 227 cases for analysis (Table I). The reasons for excluding the twenty-one patients were: the diagnosis was made before July 1, 1975, or after June 30, 1980 (twelve patients); a variant of osteosarcoma was present (four patients); the patient was more than twenty-nine years old at the time of diagnosis (two patients); and metastasis was present at the time of diagnosis (three patients).

The mean age of the 227 patients was 15.7 years. Twenty-five patients were in the first decade of life; 174, in the second; and twenty-eight, in the third. One hundred and twenty-four patients were male and 103, female. One hundred and ninety-four were classified as white; twenty-eight, as black; and five, as Oriental. The size of the tumor was less than five centimeters in twenty-five patients, five to ten centimeters in 120, eleven to fifteen centimeters in sixty-two, and more than fifteen centimeters in twelve patients. In eight patients the size was not recorded.

For thirty-one patients, only conventional radiographs of the lungs were used to evaluate the pulmonary parenchyma for metastasis at the time of diagnosis. In addition to conventional radiography, the remaining 196 patients had either conventional or computed tomography of the lungs, or both, to detect pulmonary metastasis. For 154 patients, bone scintigraphy was employed to detect occult metastasis to bone at the time of diagnosis. The stage of the osteosarcoma<sup>7</sup> in 213 patients was IIB (that is, high-grade

and extracompartmental), and in only fourteen patients was it stage IIA (that is, high-grade and intracompartmental). Before the definitive surgical procedure, thirty patients received systemic intravenous chemotherapy, twenty-six patients underwent local radiation therapy and intra-arterial chemotherapy, and one patient had local radiation therapy only. The remaining 170 patients received no adjuvant therapy before surgery.

Seventy-three patients had had a limb-salvage surgical procedure; 115, an above-the-knee amputation; and thirty-nine, a radical amputation (disarticulation of the hip). In all patients, no gross or histological evidence of tumor was found at the site of surgical incision. Of the seventy-three patients who had had a limb-salvage procedure, thirty-five had had a surgical margin that traversed the knee joint and thirty-eight, a resection that included the knee joint. In forty-one patients, the limb was reconstructed with a segmental metal prosthesis; in nine, with an allograft-metal composite; in eight, with an allograft alone; and in one, with an autoclaved bone-metal composite. Arthrodesis of the knee had been done with autografts in twelve patients. Two patients had had a rotationplasty<sup>9</sup>. Eighteen of the seventy-three patients who had undergone a limb-salvage procedure ultimately had an amputation, because of local recurrence in eight and complications with the wound in ten patients.

Several regimens of postoperative chemotherapy were administered to 203 patients, with either Adriamycin (doxorubicin) or methotrexate serving as the main drug in all of the programs. In addition, nine of the 203 patients also underwent prophylactic whole-lung radiation therapy. Only

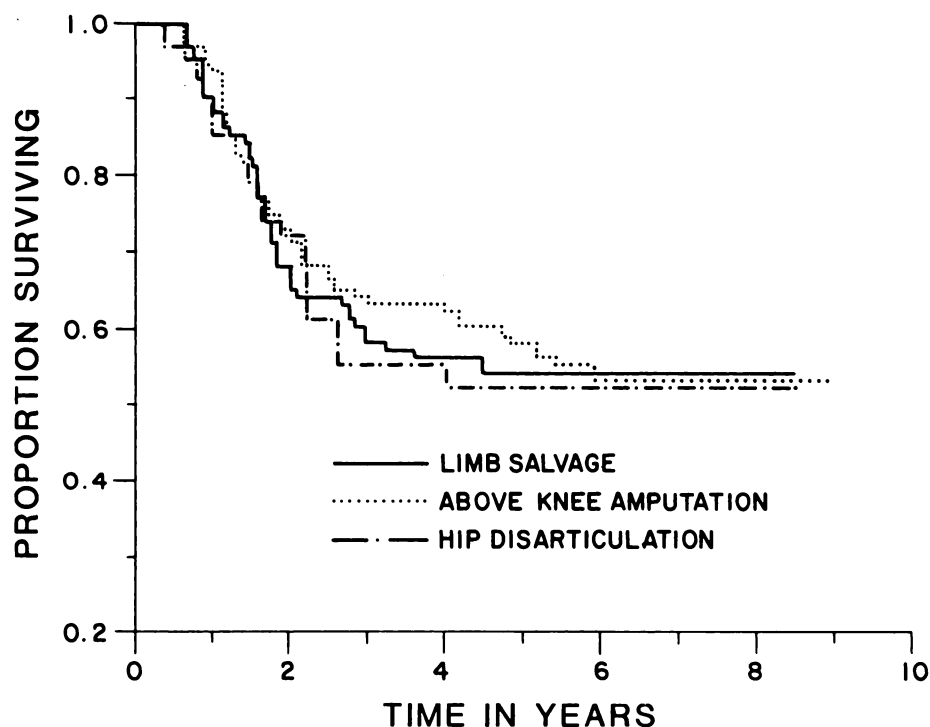


FIG. 1

Kaplan-Meier analysis of length of survival of 227 patients with high-grade osteosarcoma of the distal end of the femur who were treated by one of three different surgical procedures.

twenty-four patients did not receive any chemotherapy after surgery.

### Results

There was a local recurrence of tumor in eight of the seventy-three patients who had had a limb-salvage procedure, in nine of the 115 patients who had had an above-the-knee amputation, and in none of the thirty-nine patients who had had a disarticulation of the hip. The exact sites of recurrence were not recorded, but of the seventeen patients with recurrence, only one survived, and this patient had the recurrence in the stump of the limb that had undergone an above-the-knee amputation. In the other sixteen patients, metastasis and local recurrence were discovered simultaneously in five patients, metastasis was detected one to three months before discovery of the local recurrence in seven patients, and local recurrence was detected one to three months before observation of metastasis in four patients.

Most metastases were detected initially in the pulmonary parenchyma, but they were found initially in another osseous site in six patients and in the ipsilateral inguinal lymph nodes in two. More than half of the patients with pulmonary metastasis underwent at least one thoracotomy. The median length of follow-up for the survivors in the entire study population was 5.54 years.

The Kaplan-Meier estimates of the proportion of patients who survived and of the proportion who did not have reappearance of the disease were remarkably similar for each of the three surgical procedures (Figs. 1, 2, and 3). For the entire study group, the rate of continuously disease-free

survival was about 40 per cent at five years, and the total rate of survival was 55 per cent at five years from the time of diagnosis. The Mantel-Cox test statistic comparing the three entire curves simultaneously resulted in *p* values that were no smaller than 0.8 under the null hypothesis of equality of survival, regardless of the type of surgery. At five years, the standard error of the difference in survival and the difference in survival without disease for the Kaplan-Meier estimates was about 0.1 when the results of disarticulation of the hip were compared with other procedures and about 0.08 when the results of limb-salvage procedures were compared with those of above-the-knee amputation. These standard errors were approximately correct for the entire one to five-year period. No two groups differed by more than one standard error.

Five patients died as an apparent result of the chemotherapy at 0.1, 0.3, 1.0, 1.0, and 4.1 years after diagnosis. One patient each died of suicide, leukemia, and breast cancer at 1.5, 3.8, and 4.8 years after diagnosis, respectively. In the reported analysis, all eight of these patients were considered lost to follow-up. The analyses were repeated with all of these special patients, in appropriate subsets, being treated as having died due to tumor. The results were that all of the estimates of survival were slightly lowered, but the relative differences between the three groups of patients remained almost identical because the eight patients were distributed among the three groups roughly in proportion to the relative sizes of the groups.

We explored the assumption that there were no important biases among the patients who underwent one of the

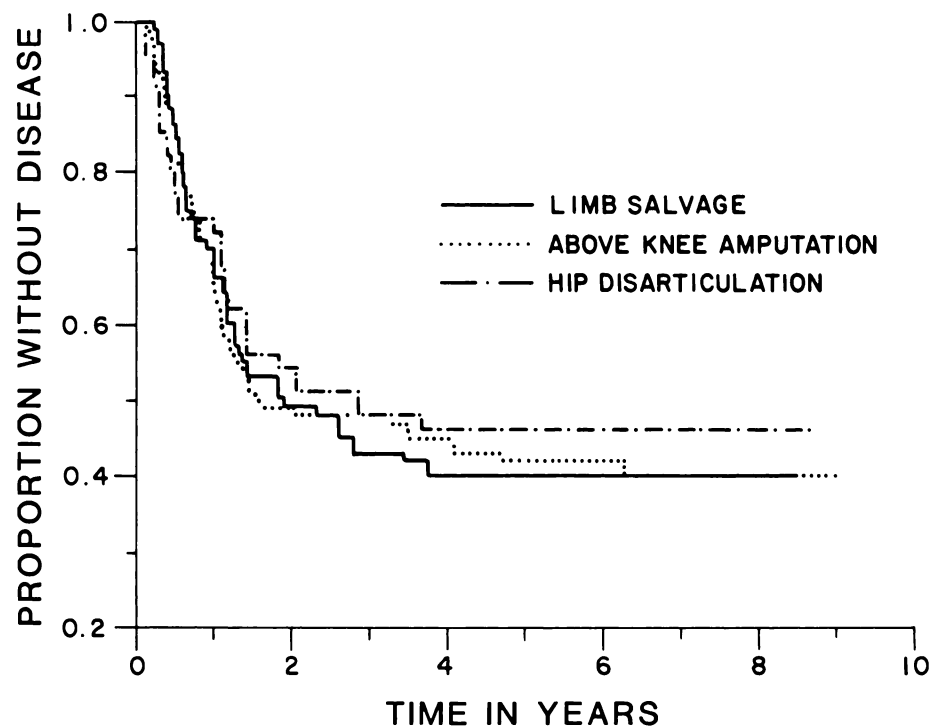


FIG. 2

Kaplan-Meier analysis of time to reappearance of disease in the 227 patients with high-grade osteosarcoma of the distal end of the femur who were treated by one of three different surgical procedures.

three different types of operation. For this purpose, we analyzed the age, race, and sex of the patients; the diameter of the tumor; the surgical stage; the type of imaging that was used to detect metastasis; and the date of surgery during the five-year interval. We found one important bias: disarticulation of the hip tended to be performed more often in black patients and in young individuals. There was no discoverable bias as to the other variables.

None of the institutions that contributed cases of patients to our study had a randomization protocol for implementation of surgical procedures. When the surgical decision was examined for each institution, it appeared that at ten institutions only one type of surgery usually was performed, whereas at ten others either a limb-salvage procedure or an above-the-knee amputation had been done and at two either an above-the-knee amputation or a disarticulation of the hip had been done. At only four institutions were all three types of surgical procedures performed, and at these four no more than two operations in the smallest surgical group were performed. At only a few of the participating institutions was there a large black population, and the bias against a limb-sparing procedure in these patients was attributed to the preference of the individual surgeon. Young age was related to the biased surgical decision against a limb-sparing procedure because of the problems with limb-length discrepancy that would ensue. There were other (unexplored) possibilities that may have biased the surgical decision: the preference of the patient and patterns of referral.

One important way in which the regimen of treatment differed among the twenty-six institutions was the type of

chemotherapy. Many different drugs were administered, in varying dosages and schedules. A few patients refused chemotherapy, and a few institutions gave no postoperative chemotherapy to most of their patients. For eighteen of the twenty-four patients who received no postoperative chemotherapy, an above-the-knee amputation had been done. Of the remaining six patients who did not receive postoperative chemotherapy, five patients had had a limb-salvage procedure and one patient had had a disarticulation of the hip. The number of patients who did not receive postoperative chemotherapy was sufficiently small so that when the analyses were repeated, excluding these twenty-four patients, the relative differences between the three surgical groups remained unchanged. Patients in the limb-salvage group generally were given chemotherapy for a short period before the definitive surgery more often than were the patients in the other two groups, because of institutional preference. Finally, because limb-salvage operations were performed more frequently in the later years of the study, patients who had a limb-salvage procedure underwent more thorough imaging for metastases than did earlier patients, possibly excluding some patients who might have been included in the early part of the study because of detection of metastases at the time of diagnosis.

In order to adjust the comparisons for the imbalances discovered in the recorded covariants in Table II, we developed Cox proportional hazard models<sup>2</sup>. Many different subsets and quantifications of the covariants were studied, and the modeling based on Cox regression analysis disclosed that, with the exception of the covariant of chemotherapy after surgery, none of the covariants appeared to be strongly

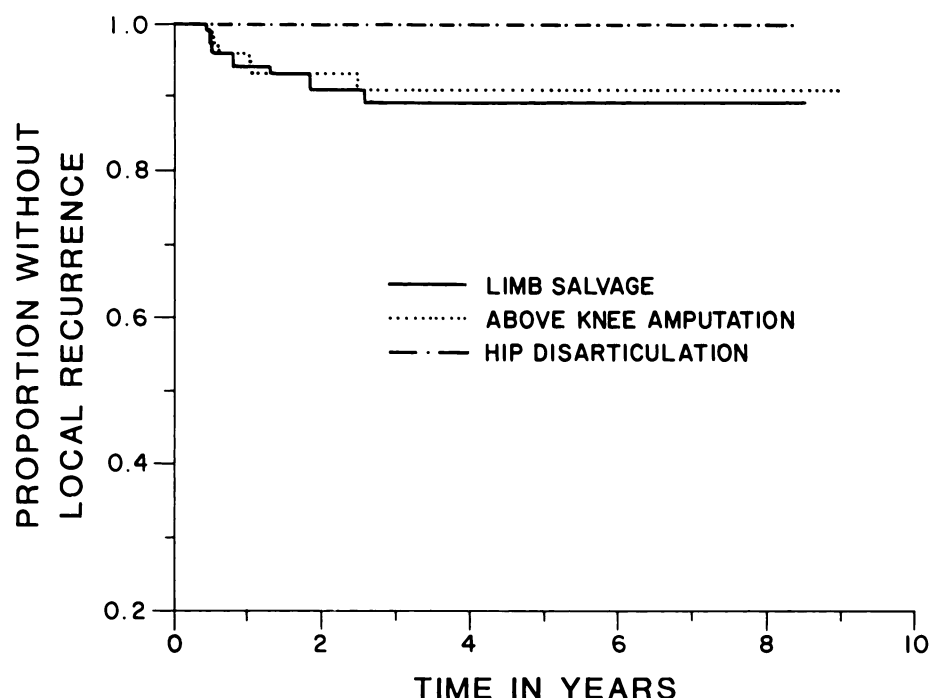


FIG. 3

Kaplan-Meier analysis of time to local recurrence in the 227 patients with high-grade osteosarcoma of the distal end of the femur who were treated by one of three different surgical procedures.

TABLE II  
COX REGRESSION MODELS

Covariant*	Possible Values	Reappearance of Disease†		Death†	
		Parameter	SE	Parameter	SE
Trt1	1 — limb-sparing surgery, 0 — otherwise	0.08	0.31	0.06	0.34
Trt2	1 — above-the-knee surgery, 0 — otherwise	0.08	0.27	-0.04	0.30
Sex	0 — male, 1 — female	-0.14	0.18	-0.06	0.20
Age	3-29 yrs.	0.02	0.02	0.01	0.02
Race	0 — white, 1 — non-white	0.18	0.26	0.45	0.28
Diameter of tumor	0 — < 5 cm, 1 — 5-10 cm, 2 — 11-15 cm, 3 — > 15 cm	0.02	0.13	-0.07	0.14
Stage	0 — IIA, 1 — IIB	0.08	0.39	0.28	0.48
Calendar time	0-5 yrs. measured from 1975 to surgery	-0.04	0.06	-0.04	0.07
Imaging technique	1 — tomography or computed tomography, 0 — neither of the above	-0.10	0.16	-0.11	0.17
Chemotherapy					
Before surgery	1 — yes, 0 — no	0.07	0.24	0.09	0.26
After surgery	1 — yes, 0 — no	-0.55	0.29	-0.63	0.30

\* Trt1 compares the results of limb-sparing surgery with those of disarticulation of the hip. Trt2 compares the results of above-the-knee amputation with those of disarticulation of the hip. Numerous other quantifications of covariants were explored, with similar results.

† A positive number means increased risk relative to disarticulation of the hip. SE = standard error. The standard errors are inflated by a small amount due to the inclusion of all of the covariants. No substantial reductions occur when the models with fewer covariants are used.

related to outcome. Even if deaths resulting from chemotherapy were treated as deaths due to disease, so that the benefit of chemotherapy would not be exaggerated, the only covariant that appeared to be related to outcome was postoperative chemotherapy. However, several points need to be made about this variable: first, it represents many different regimens, and second, it is almost completely confounded with the institutional variable, which was not modeled. As a result, values for the variable of postoperative chemotherapy (-0.55 for reappearance of disease and -0.63 for death) are difficult to interpret. Because of the difficulties in characterizing the chemotherapy as varied and as administered in the three groups, the data do not contain reliable information regarding the effects of postoperative chemotherapy. However, an important fact is that the chemotherapy, beneficial as it may have been, had no practical consequence in the comparison of the results of the three types of surgical procedures. When the Kaplan-Meier plots were repeated with the patients who did not receive chemotherapy excluded, the rates of disease-free and long-term survival of patients with an above-the-knee amputation improved slightly compared with those for patients who had undergone the other types of procedures.

### Discussion

We chose to study only osteosarcomas of the most anaplastic grade in the metaphysis of the distal end of the femur, because that site is the most common for this type of osteosarcoma in adolescents and young adults and is the most common when a limb-salvage procedure is chosen as a regimen of treatment<sup>4,10,13</sup>. We tried to minimize variability

across surgical groups by narrowly defining the disease, its anatomical site, and the age of the patient; by restricting the study to a recent, short period of time; and by including a wide variety of institutions in the United States, Italy, and Sweden. Accordingly, the number of cases of patients with osteosarcoma that were contributed by each institution is only a fraction of the number who were treated during the study period and in no way reflects the number that are presently seen or the type of surgical practice that is now employed at the contributing institutions.

One potential weakness of the study was the lack of a central review of the pathological findings<sup>3</sup>, but this was deemed unimportant because of the rigid criteria in the protocol and the special expertise of the contributing individuals and institutions, all members of the Musculoskeletal Tumor Society. Because only patients who were less than thirty years old and had a high-grade osteosarcoma were eligible, outlying varieties of osteosarcoma were appropriately eliminated, including radiographic and pathological variants<sup>5</sup>. The institutions and individuals that contributed data to this study are experienced in the treatment of malignant tumors of bone. Many of the patients were included previously in large single-institution reports or national cooperative studies with central review of the pathological findings.

It must be emphasized that, as far as the regimen of treatment is concerned, the patients were not randomized, and there may be significant bias in assignments to the three surgical groups<sup>1,11</sup>. Given the inter-institutional differences in preferences as to surgical treatment, it would surely be impossible, especially nationally, to randomize surgical treatment.

The major factor determining which type of surgical procedure would be performed on each patient appeared to be the surgeon's preference. In almost all contributing institutions, one of the procedures was used in preference to another, but in only four institutions were all three procedures used. This fact alone shows that it would not have been feasible to use a single institution for the study or to employ randomization in an effort to answer the question of which outcome can be expected from a limb-salvage operation.

Recently, investigators at the Mayo Clinic identified six characteristics of patients that were strongly related to prognosis in osteosarcoma<sup>14</sup>. We restricted our data in regard to one of these factors — anatomical location — and disregarded two others — duration of symptoms and type of cell. The other three — age and sex of the patient and diameter of the tumor — appeared not to be correlated with survival in the present group of patients even when covariants were quantified as they were in the Mayo Clinic study. In that study, an age of less than ten years was the variable that was most strongly associated with a poor prognosis. In our study, age was the most unbalanced covariant because only two very young patients had received limb-sparing surgery, fifteen had undergone an above-the-knee amputation, and eight had had disarticulation of the hip. In contrast to the Mayo Clinic study, the very young patients in our study had a rate of survival that was similar to the rate of older patients. Moreover, analyses of the cases of the patients in our study show that comparison of the length of survival among young patients who had undergone different operations did not indicate any differences in the length of the disease-free interval and the length of survival, and when patients who were less than ten years old were removed from the analysis, the estimated rates of survival remained very similar in the two groups of patients (ten to nineteen years old and twenty to twenty-nine years old) who received one of the three different surgical regimens. It appears to us that, with the possible exception of anatomical site, none of the factors in the Mayo Clinic report had any significant effect on survival. There may have been variables

that were significant, but they were not identified.

Whereas the rate of local recurrence after disarticulation of the hip in the patients in our study was zero, the rate of local recurrence in the patients who had had a limb-salvage procedure or an above-the-knee amputation was considerable (approximately 10 per cent) and very similar. One could explain the similar rates by using the concept of occult skip metastases in the ipsilateral femur, as described in 1975 by Enneking and Kagan<sup>6</sup>. All of the patients in their study who manifested this phenomenon died, and it was hypothesized that these patients had a more aggressive pattern of disease, with a poorer prognosis. The existence of skip metastases could explain the very similar rates of recurrence of tumor in the groups that had had a limb-salvage procedure or an above-the-knee amputation, as observed in our study. All but one of the patients who had a local recurrence died, and it is possible that these patients, like those of Enneking and Kagan<sup>6</sup>, had skip metastases. It is probable that more extensive surgery, such as the disarticulation of the hip that was used for the patients of Enneking and Kagan<sup>6</sup>, would not have cured them. Thus, patients with skip metastases or local recurrence may have characteristics of the disease or other factors that are as yet unidentified and that have poor prognostic implications. However, because the pattern of local recurrence in the patients in our study was not recorded, we cannot confirm that the patients with a recurrence indeed had a skip metastasis.

A remarkable result of this study was the great similarity of outcomes with all three surgical procedures, even when many different models adjusting for covariant imbalances were computed. Furthermore, the continuously disease-free survival of 40 per cent in five years and the overall rate of survival of 55 per cent at five years are quite encouraging<sup>12</sup>. Although treatment of metastasis was not a focus of the study, quite a few of the patients whose cases were studied had salvage by thoracotomy and chemotherapy after pulmonary metastasis had been detected.

NOTE: The authors would like to thank Terri J. Smith, University of Chicago, for her technical assistance in the preparation of this manuscript.

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