Osteosarcoma of the limb

AMPUTATION OR LIMB SALVAGE IN PATIENTS TREATED BY NEOADJUVANT CHEMOTHERAPY

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We have studied 560 patients with osteosarcoma of a limb, who had been treated by neoadjuvant chemotherapy, in order to analyze the incidence of local and systemic recurrence according to the type of surgery undertaken. Of these, 465 patients had a limb-salvage procedure and 95 amputation or rotationplasty.

At a median follow-up of 10.5 years there had been 225 recurrences. The five-year disease-free survival and overall survival rates were 60.7% and 68.5%, respectively, with no significant difference between patients undergoing amputation and those undergoing resection. The incidence of local recurrence was the same for patients treated by either amputation or limb salvage and correlated significantly with the margins of surgical excision and the histological response to chemotherapy. The outcome for patients with a local recurrence was significantly worse than for those who had recurrent disease with metastases only.

We conclude that limb-salvage procedures are relatively safe in osteosarcoma treated by neoadjuvant chemotherapy. They should, however, only be performed in institutions where the margins of surgical excision and the histological response to chemotherapy can be accurately assessed. If the margins are inadequate and the histological response to chemotherapy is poor an immediate amputation should be considered.

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The surgical treatment of high-grade osteosarcoma of the limb without metastasis at presentation has changed considerably in the last 20 years. Previously, amputation or disarticulation was the most common surgical procedure. Today, limb-salvage operations are often undertaken. Controversy still remains, however, regarding the safety of resection with limb salvage compared with amputation in osteosarcoma of a limb treated by neoadjuvant chemotherapy. Some studies have shown an incidence of local recurrence after limb resection of up to four times higher than that after amputation. In other studies no difference in the incidence of local recurrence has been found between patients who undergo amputation and those treated by limb salvage. Since a local recurrence in osteosarcoma carries a dismal prognosis, it is not yet clear whether the outcome of those treated by neoadjuvant chemotherapy could be compromised by limb-sparing operations.

We have therefore compared the results achieved by amputation or limb salvage in a large series of patients with osteosarcoma of a limb treated by neoadjuvant chemotherapy at a single institution.

Patients and Methods

Between March 1983 and June 1995, we entered 570 patients with osteosarcoma of the limb into five different protocols of neoadjuvant chemotherapy which were used at different times. Patients were considered to be eligible for these trials if they met the following criteria: 1) typical radiological and histological features of primary, central high-grade osteosarcoma; 2) a tumour located in the limb; 3) age under 40 years; 4) no previous history of tumour; 5) no previous treatment; and 6) no evidence of metastases at diagnosis.

Preoperative evaluation and chemotherapy. The diagnosis of osteosarcoma, established by clinical and radiological findings, was confirmed on histological specimens of tissue obtained from an open or needle biopsy, as well as from the resected specimens. All patients underwent a thorough physical examination, and laboratory tests were carried out. The primary tumour was evaluated on standard radiographs, technetium-99 methylene diphosphate (MDI) bone scans and CT. MRI has also been performed in recent
years. These investigations were repeated before surgery. Bone metastases were investigated by total body scans, whereas standard chest radiographs and CT of the chest were used to exclude lung metastases. Chemotherapy was given according to five different, successive protocols (IOR/OS-1, IOR/OS-2, IOR/OS-3a, IOR/OS-3b and IOR/OS-4) which have previously been described in detail.\textsuperscript{1,14-16}

**Surgery.** The type of surgery (amputation, limb salvage or rotationplasty) and the type of reconstruction for patients treated by limb salvage, depended on the location and extent of the tumour, the patient’s age and the desired lifestyle. The clinical and radiological response to preoperative chemotherapy was also considered. Six patients with very large tumours underwent amputation before completing the scheduled preoperative treatment because of radiological progression of the tumour. In each case, a thorough discussion of the available options between the patient, or legal guardian in the case of minors, and the surgeon, preceded the choice. No patient was refused a resection with limb salvage if they insisted on that option, although this was discouraged if adequate surgical margins could not be guaranteed. In this review, the surgical treatment was divided into two groups, amputation and limb-sparing surgery. Rotationplasties were surgically classified as amputations.

**Pathological evaluation.** We determined the surgical margins by three techniques: a) gross inspection of the specimen; b) careful dissection; and c) histological examination. The pathologist first dissected the specimen to determine the anatomical extent of the tumour. A section for preparation of a macrosection was then selected. Finally, the area of tissue to be used for routine histological examination was chosen. We defined the surgical margin as the least adequate margin of the whole specimen. According to the criteria described by Enneking, Spanier and Goodman\textsuperscript{17} we classified these margins as ‘radical’ if all the bone and muscles involved were removed as one block, ‘wide’ if the lesion, its reactive zone, and a surrounding cuff of normal tissue were taken as a single block, ‘marginal’ if the plane of dissection left microscopic disease at the margin of the wound, and ‘intralesional’ if the dissection passed within the lesion. The histological response to chemotherapy, evaluated by a previously reported method,\textsuperscript{18} was classified as ‘good’ (90% or more tumour necrosis) or ‘poor’ (less than 90% tumour necrosis).

**Follow-up.** During postoperative chemotherapy, radiography of the treated limb and of the chest were performed. Additional clinical assessments were made when indicated. After the completion of chemotherapy, patients were reviewed every two months for the first three years, and then every six months.

**Statistical analysis.** Our aim was to compare the incidence of local and systemic recurrence in patients treated by amputation and those treated by limb-sparing surgery. The overall survival was also calculated. This should be considered with caution since for many reasons the treatment after relapse was not standardised. We defined disease-free survival and local recurrence-free survival as the time from the beginning of preoperative chemotherapy until the last follow-up, or the time when metastases or local recurrence were diagnosed. We defined the overall survival time as the period from the beginning of treatment to the last follow-up or death. The probability of disease-free survival, local recurrence-free survival, and overall survival time was determined by the method of Kaplan and Meier and compared by means of the log-rank test. The Cox proportional hazards regression analysis was used for multivariate analysis. The significance was set at $p = 0.05$. The results were updated to December 2000.

**Results**

Of the 570 patients who entered the five neoadjuvant protocols, ten died for reasons unrelated to the tumour. They were chemotherapy toxicity (7), a road-traffic accident (1), pulmonary embolism (1) and suicide (1). These patients were excluded from our analysis. This left 560 in the study details of whom are given in Table I. The margins of surgical excision, the histological response to chemotherapy and the numbers treated by the various chemotherapeutic protocols are given in Table II.

**Survival.** At a mean follow-up of 10.5 years (5 to 17), 335 patients (59.8%) remained continuously free from disease; recurrence occurred in 225. Of these, metastases were present in 191, local recurrence associated with metastases in 32 and an isolated, local recurrence in two. The mean time to recurrent disease was 22.6 months (3 to 96). The

| Table I. | Details of the 560 patients with osteosarcoma of the limb who had either amputation (95) or limb salvage (465), by number and percentage |
|---|---|---|---|---|
| Number of patients | Amputation* | Limb salvage | p value |
| Gender | | | | NS\textsuperscript{†} |
| Men | 320 | 57 (60) | 263 (56.6) | |
| Women | 240 | 38 (40) | 202 (43.4) | |
| Age in years | | | | 0.02 |
| <14 | 238 | 51 (53.7) | 187 (40.2) | |
| ≥14 | 322 | 44 (46.3) | 278 (59.8) | |
| Tumour site | | | | 0.0007 |
| Femur | 306 | 58 (16,0) | 248 (53.3) | |
| Tibia | 154 | 20 (21,0) | 134 (28.8) | |
| Humerus | 63 | 7 (13,6) | 56 (12,0) | |
| Other sites | 37 | 10 (10,5) | 27 (5,8) | NS |
| Tumour size (cm\textsuperscript{3}) | | | | |
| <150 | 249 | 30 (31,6) | 219 (47,1) | |
| >150 | 311 | 65 (68,4) | 246 (52,9) | 0.007 |
| Serum alkaline phosphatase | | | | |
| Normal | 302 | 41 (43,2) | 261 (56,1) | |
| Elevated | 258 | 54 (56,8) | 204 (43,9) | 0.02 |
| Pathological fracture | | | | |
| Yes | 73 | 23 (24,2) | 50 (10,8) | |
| No | 487 | 72 (52,6) | 415 (89,2) | 0.0007 |

* including 29 rotationplasties
† not significant
The first site of metastases was the lung in 193 patients (85.8%) and the skeleton in 28 (12.5%). In the remaining four the first site was the heart in two, the central nervous system in one and the lymph nodes in one. The overall five-year disease-free survival was 60.7% although this was significantly higher for patients treated by limb salvage than for those who had ablative surgery (Table III). The five-year disease-free survival also correlated with the histological response to preoperative treatment, the serum alkaline phosphatase level at presentation, the size of the tumour and the protocol of chemotherapy given.

However, on the multivariate analysis only the type of histological response to chemotherapy (p < 0.0001; RR = 1.4; 95% CI 1.2 to 1.8) and the levels of serum alkaline phosphatase (p = 0.002; RR = 1.3; 95% CI 1.1 to 1.7) remained significant and not the type of surgery. **Local recurrences.** Of the 225 patients who had recurrent disease, 34 (15%) had a local recurrence which was confirmed by histological examination. The incidence of local recurrence for all 560 patients was 6.0% and the mean interval from surgery to local recurrence was 23.4 months (6 to 110). The incidence of local recurrence was not affected by gender, age, tumour volume or the presence of pathological fractures, but was related to the site of the tumour, the surgical margins and the histological response to chemotherapy. It was higher in lesions located in the femur than in those elsewhere. For those patients with adequate surgical margins there were no local recurrences in the 34 patients who underwent amputation with radical margins. For the 443 patients with wide margins, the incidence of local recurrence was 3.1% (14/443). This difference was not statistically significant. For the patients with inadequate surgical margins there was no significant difference in the incidence of local recurrence in those with marginal, intralesional, and contaminated margins. The incidence of local recurrence was significantly higher for those patients with a poor histological response to chemotherapy than for those who responded well. This difference was statistically significant (p = 0.01). Local recurrences were seen in five of the 98 patients who had total necrosis. With the multivariate analyses only the surgical margins (p < 0.0001; RR = 1.7; 95% CI 1.2 to 1.9) and the histological response to chemotherapy (p = 0.005; RR = 1.4; 95% CI 1.1 to 1.7) maintained their independent significance. In all but two patients, local recurrences were associated with metastases. In 19 patients the metastases followed local recurrence at a median of four months (2 to 14). In ten patients local recurrence and metastases were diagnosed at the same time and in three, local recurrence was diagnosed at a median of 12 months (4 to 18) after the diagnosis of metastases. In the 32 patients who had local and systemic recurrent disease the first sites of metastases were the lung in 19 patients (59.4%), the skeleton in 11 (34.4%) and elsewhere in two (6.2%). For the 191 patients who had further disease without local recurrence the first site of metastasis was the lung in 172 patients (90.0%), the skeleton in 17 (8.9%) and elsewhere in two (1%). The incidence of bony deposits as the first site of the metastatic spread was significantly higher in patients who had a local recurrence (34.4%) than in those who had further disease without local recurrence (8.9%).
Post-relapse treatment and outcome. Metastases were treated by metastectomy alone in 115 patients, and by metastectomy followed by further chemotherapy in 56. In the remaining 52 patients, the exact treatment was either not known (30) or no specific treatment was undertaken (22).

The treatment of local recurrences was variable. For the two patients in whom the local recurrence was not associated with metastases, and who had initially been treated by limb salvage, amputation was performed. Both patients are alive and free from disease 18 to 36 months after the recurrence. In the 19 patients in whom the local recurrence was followed by metastases, the treatment consisted of repeated resection with limb salvage in three and amputation in 15. In the remaining patient, initially treated by transmedullary amputation for a tumour in the distal femur, the local recurrence was treated by disarticulation of the hip.

In the ten patients in whom local recurrences and metastases were detected simultaneously the local recurrence was treated by palliative radiotherapy in seven, by amputation in two and by repeated resection with limb salvage in one. In these last three patients the treatment of local recurrence was combined with thoracotomy to remove lung metastases. In the three patients in whom local recurrences followed metastases the treatment of the local recurrence consisted of palliative radiotherapy. Despite treatment all patients for whom the local recurrence was associated with metastases died at a median of 31.6 months (12 to 64) after the beginning of treatment. The five-year overall survival for all the patients with recurrence was 20.8%. The outcome of patients with recurrent disease who had local recurrences was significantly worse than for the 191 patients who had metastases without local recurrence. Of these, 30 are alive and free from disease at a median of 24 months (4 to 110) after the last treatment. Two are alive with uncontrolled disease at six and 22 months and 159 died at a median of 33.6 months (9 to 132) from the beginning of treatment. The five-year survival of patients with further disease with or without local recurrence was 5.9% (2/34) and 23.6% (45/191), respectively (p < 0.03).

Comparison between amputated and resected patients. The patients who had an amputation and those with a limb salvage were similar as regards gender and anatomical location of the tumour (Table I). In the amputation group there was a significantly higher rate of patients younger than 14 years, with high serum levels of alkaline phosphatase at presentation and with a tumour volume of more than 150 ml.

The lowest rate of limb salvage was performed in patients treated with the first protocol of chemotherapy (71.4%) and the highest in patients treated with the last (95.0%).

In the 95 patients treated by amputation the surgical margins were radical in 34, wide in 58, contaminated in two and intralesional in one, whereas in the 465 patients treated by limb salvage the surgical margins were wide in 385, marginal in 54, intralesional in 28. Therefore the rate of inadequate surgical margins (marginal, intralesional or contaminated) was significantly higher in the latter group than in patients treated by ablative surgery (17% v 3.1%; p = 0.0008).

The rate of a good histological response was significantly higher in the 465 patients treated by limb salvage than in the 95 treated by ablative surgery (68% v 48.4%; p = 0.0001), but in six patients with very large lesions amputation was necessary before completing the scheduled preoperative treatment because of radiological progression of the tumour.

The rate of five-year disease-free survival with univariate analysis was higher for patients treated by limb salvage than for those treated by ablative surgery (63% v 49%; p > 0.01), but the difference was not significant. There were no differences in the site of first metastases in amputated and resected patients (lung metastases: 89.5% v 85.1%; NS) as well as in the time to relapse (19.6 months v 23.7 months; NS).

Discussion

In recent years the number of patients with osteosarcoma of the limb treated by limb salvage instead of amputation has increased. This is due to the improved efficacy of chemotherapy, which can reduce the extent of surgery required, the development of modern radiological tools such as CT and MRI and the availability of new reconstructive procedures. These can allow good functional results and offer alternatives determined by the location of the tumour, the age of the patient and the desired lifestyle.

The larger number of limb-salvage procedures which are undertaken is inevitably associated with a reduction of surgical margins. This can increase the incidence of local recurrence. Previously, in patients who did not receive associated chemotherapy, conservative surgery resulted in an incidence of local recurrence which correlated strictly with surgical margins. Even in patients treated by neoadjuvant chemotherapy, it is not yet clear whether the reduction of surgical margins is associated with an increased risk of local recurrence. The reported results for the incidence of local recurrence in patients undergoing amputation and those treated by resection and neoadjuvant chemotherapy are contradictory. In multicentre studies the incidence of local recurrence seems to be higher in patients treated by resection when compared with those treated by amputation. Conversely, in two uni-institutional studies with a smaller number of patients, the incidence of local recurrence was the same for both groups.

The results of our study, with a much larger number of patients, confirm that in those treated by neoadjuvant chemotherapy in a single institution, limb-salvage operations are relatively safe. Despite the higher percentage of inadequate surgical margins in patients undergoing limb-salvage procedures than in those who had amputation, there
was no significant difference in the incidence of local recurrence between the two groups. Disease-free survival was also unaffected. Chemotherapy, as well as its effect on microscopic disease, will also reduce the incidence of local recurrence.

Our study also confirmed that local recurrence is a serious problem in osteosarcoma of the limb. This has been reported previously by others. In our series, the outcome for patients who had a local recurrence was significantly worse than for those who had recurrent disease with only metastases. The five-year survival in the two groups was 6% and 24%, respectively (p < 0.03).

The main strength of our study is that all patients had been treated at the same institution by the same team of surgeons. The main shortcoming is that patients treated by ablative surgery or limb salvage were not randomised. The two groups are not balanced for some of the risk factors for the development of recurrent disease. For example, in the amputation group there was a significantly higher incidence of patients treated by a less effective chemotherapeutic protocol. There were more patients aged less than 14 years old, with a higher level of serum alkaline phosphatase, and more with larger tumours. Despite these disadvantages, our study suggests that limb-salvage procedures, when undertaken by experienced surgeons and including neoadjuvant chemotherapy, do not compromise the outcome of patients with osteosarcoma of the limb provided that the resection is performed with wide margins. Unless there are significant factors to preclude wide surgical margins such as extensive tumours, difficult anatomical locations or markedly displaced pathological fractures, most patients with osteosarcoma of the limbs may now be surgically treated by limb salvage. For those patients who undergo operations with inadequate surgical margins the risk of local recurrence is very high, especially when associated with a poor histological response to chemotherapy. Because of the poor outcome in patients who develop local recurrences, should a pathological examination of the resected specimen demonstrate inadequate surgical margins and an associated poor response to chemotherapy, a secondary amputation should be recommended. This may be difficult for the patient, but we believe that it is our duty to suggest this to them. It is for this reason that we consider that patients with osteosarcoma of the limb should be surgically treated in selected centres. These should be fully equipped to undertake a pathological examination of the surgical margins and to be able to make an accurate assessment of the histological response to chemotherapy.

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References