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Limb sparing in osteosarcoma of the extremity treated by neoadjuvant chemotherapy. Fifteen-year experience at the Rizzoli Institute

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In recent years the number of patients with osteosarcoma of the extremity treated by limb salvage (LS) has been constantly increasing. For instance, in five neoadjuvant studies carried out at our Institute between the years 1983 and 1995, the rate of limb salvage increased from the 72% in the first study (1983-1986) to 95% in the last study (1993-1995).

This increased number of LS is necessarily associated with an increased risk of inadequate surgical margins, and we know that in the cases when osteosarcoma has been treated by surgery alone, inadequate surgical margins have been followed by local recurrences in more than 50% of patients. Therefore, the main question remains whether limb salvage procedures are really safe. Or, in other words, are we entitled to reduce surgical margins, relying on adjuvant chemotherapy for local control?

To answer these questions, we evaluated 533 patients primary high grade central osteosarcoma of the extremity, up to 40 years of age, without evidence of metastases on diagnosis, treated at our Institute by neoadjuvant chemotherapy between the years 1983 and 1994. Chemotherapy was performed according to five different protocols used successively. Surgery was a limb salvage procedure in 83%, an amputation in 12%, and a rotation-plasty in 5% of patients.

At a median follow-up of 7.5 years (2.5-13), 322 patients (61%) remained continuously free of disease, 205 relapsed, and 5 died for chemotherapy related toxicity.

The results achieved in these five studies were quite different, with a 3-year disease free survival (DFS) ranging between 50% and 80%, according to the chemotherapy protocol used.

Thirty-one (15%) of patients who relapsed had a local recurrence (LR). The rate of LR in all the 527 evaluable patients was 5.9%. The median time to local recurrence was 21 months (5-76 mos), and in 3 patients (10%) LR appeared more than 4.5 years after surgery.

The rate of LR were found to be unrelated to site, volume, and histotype of the tumor, hospital of biopsy performance, route of cisplatin (CDP) infusion (i.v. or i.a.), and the presence/absence of pathological fractures. According to the type of surgery, in patients treated by LS, the rate of LR was twice that seen in patients treated by amputation or rotation-plasty (28/438 - 6.3% vs. 3/89 - 3.3%). This difference, however, is not statistically significant, probably due to the small number of amputated patients.

The rate of LR was found to be related to:

a) surgical margins;

b) histologic response to chemotherapy.

According to the surgical margins, the rate of LR was found to be higher in patients with inadequate surgical margins (marginal, intralesional or contaminated) than in patients with adequate surgical margins (radical or wide): 14/467 - 3% vs. 17/60 - 28%. This difference is highly significant ($p<0.0001$).

According to the histologic response to chemotherapy, the percentage of LR was significantly higher in poor responders (necrosis less than 90%) than in good responders (90% or more tumor necro-

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sis): 18/185 (9.7%) vs. 13/342 (3.8%). However, no differences were found between patients with total necrosis and those with necrosis between 90-99%. It is important to stress that LRs were also observed in 4 patients with total necrosis.

Even though both, surgical margins and necrosis, are important factors influencing the LR, surgical margins seem to be more important. In fact, as regards patients with inadequate surgical margins, the rate of LR was also very high in those who had a good histologic response to chemotherapy (7/34 - 20.5%) while for patients with adequate surgical margins the rate of local recurrence was relatively low (8/159 - 5%), also in those with a poor response.

According to different studies, the highest rate of LR was registered in the last one, reporting the highest number of LS (96%) performed, while the lowest rate of LR was observed in the second study also using the protocol that gave the highest rate of 3-year disease-free survival (80%). It is interesting to note that that the second study was the only one in which no local recurrences were observed in patients with adequate surgical margins. This data could mean that a more effective chemotherapy - besides reducing the rate of systemic relapse - probably also improves local control.

In all but one case, local recurrences were associated with metastases. In 19 cases metastases followed LR; in 6 cases the two events were concurrent, and in 5 cases LR followed the appearance of metastases.

Bone metastases as the first site of systemic recurrence we found to be significantly more frequent in patients with LR than in those without LR: 10/30 (33.3%) vs. 17/176 (6.9%); $p< 0.0003$. Such different behaviour of metastatic spread could indicate a different biology of the tumours which recur locally.

The outcome after relapse in those patients who experienced LR was as follows: one patient is alive and free of disease 15 months after the treatment for LR; 30 patients are dead or alive with uncontrolled disease. This postrelapse outcome is significantly worse than the one in patients who relapsed with metastases only. In fact, the rate of patients who are free of disease 1-5 years after the last treatment is 28% for the 174 patients who relapsed with metastases alone, and only 3% for the 30 patients who also had local recurrence ($p = 0.006$). In other words, the probability of cure after relapse is only 3% for patients with local recurrence vs. more than 25% for patients who relapse only with metastases.

We conclude that in osteosarcoma of the extremity treated by neoadjuvant chemotherapy, it is possible to avoid amputation in a majority of patients, and limb-salvage procedures are relatively safe. However, when such a procedure results in inadequate surgical margins, the risk of LR is high - especially if coupled with a poor response, in spite of the adjuvant chemotherapy used. Therefore, performing a limb-salvage procedure, the evaluation of surgical margins is mandatory, because the outcome in patients who relapse with local recurrence is very poor, significantly worse than the outcome in those who relapse with metastases only.

For these reasons we believe that a LS should be planned only when the preoperative staging seems to assure the possibility of achieving adequate surgical margins. However, if at the pathologic examination of the surgical specimen, surgical margins are found to be inadequate, and immediate amputation should always be considered, especially if the histologically confirmed response to chemotherapy has been poor.