Surgical procedure and local recurrence in 223 patients treated 1982–1997 according to two osteosarcoma chemotherapy protocols

The Scandinavian Sarcoma Group experience

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In the present multicenter study from the Scandinavian Sarcoma Group, local recurrence was analyzed regarding a change in the chemotherapy protocol and an increasing number of limb–salvage procedures 1982–97. Surgery was performed at 13 hospitals in Scandinavia. We analyzed the data of 223 patients with non–metastatic, high–grade osteosarcoma of the extremities, treated according to the SSG II and VIII protocols. The rate of limb–salvage surgery was 0.3 in SSG II, as compared to 0.6 in SSG VIII. The local recurrence rates of the limb–salvage patients were 10 % (SSG II) and 11 % (SSG VIII), as compared to 4% and 2 %, respectively, among the amputated patients. We found no significant difference in outcome i.e., in local recurrence and survival rate despite an increased rate of good responders in SSG VIII, as compared to SSG II. It may be shown that the continuously increasing use of limb–salvage surgery is associated with a higher rate of local recurrence than with ablative surgery, despite better chemotherapy.

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The second multicenter study in the Scandinavian Sarcoma Group (SSG) focused on neoadjuvant chemotherapy in high–grade osteosarcoma (OS). The use of this SSG II protocol started in 1982 and continued actively through the 1980s. During this period, amputation was still, at least in Scandinavia, regarded as the safest surgical procedure and was therefore most commonly chosen for OS patients. Because of poor tumor response, the SSG II protocol was changed to a more aggressive chemotherapy protocol, SSG VIII, from April 1990 to May 1997. At the same time as SSG VIII started, many Scandinavian orthopedic oncology surgeons had increased their knowledge, skill and use of limb–salvage surgery. With the SSG VIII protocol, the projected 5–year metastases–free survival and overall survival rates increased by 5% compared to SSG II (Saeter et al. page 74 this issue).

In the present study, we analyzed local recurrence in relation to the change in chemotherapy protocol from SSG II to VIII and an increasing rate of limb–salvage procedures.

Patients and methods

246 patients, treated according to the SSG II protocol (114) and SSG VIII protocol (132), were reported to the SSG Register from 1982–1997. Follow–up, including data on local recurrence, metastases and death from disease, was continuously reported. Re-evaluation of histology, including malignancy grade and tumor response to chemotherapy, was performed by the SSG Pathology Board. The effect of chemotherapy was assessed on a 4–grade scale, ranging from no effect (grade 1) to complete tumor necrosis (grade 4). Grades 3–4, corresponding to > 90% tumor necrosis, were regarded as a good chemotherapy response. Type of surgical procedure was recorded as limb–salvage (including 2 patients with rotationplasty) or amputation. The analysis also included surgical stage and margin, according to Enneking, as assessed from surgical and pathological reports. The surgical margin was classified as compartmental, wide, marginal, intralesional or contaminated wide/marginal margin.

In this study, 7 patients from the SSG II and 16 from the SSG VIII protocol were excluded from the analysis. The reasons for exclusion were: Stage IB OS

Table 1. Participating hospitals and number of patients

Center	n
Norway	
Norwegian Radiumhospital, Oslo	43
University Hospital, Bergen	15
University Hospital, Trondheim	7
University Hospital, Tromsö[a]	2
Sweden	
Karolinska Hospital, Stockholm[a]	36
University Hospital, Lund	27
Sahlgren Hospital, Gothenburg	24
University Hospital, Umeå	12
University Hospital, Linköping	7
Finland	
University Hospital, Helsinki	46
University Hospital, Tampere[a]	3
University Hospital, Turku[a]	1
Total	223

[a] Only SSG VIII

(3 patients), Stage IIIB OS (5), reclassification to Ewing's sarcoma (1) and MFH (1), tumor located in the mandible (1), no surgery (1), no preoperative chemotherapy (1), no information about surgical margin, surgical procedure, stage and/or follow–up (10). Hence, 223 patients with extremity, nonmetastatic, high–grade OS, treated according to SSG II and VIII, were analyzed. Surgery was performed at 5 hospitals in Sweden, 4 in Norway and 3 in Finland (Table 1). Table 2 shows the clinical features of the patients.

Results

The rate of local excision, i.e., limb–salvage surgery, was 0.27 in SSG II, compared to 0.57 in SSG VIII (Table 3). The rate increased from 0.26 in 1982–1985 to 0.71 in 1994–1997. The margin was assessed as wide or better in 90% of all cases in SSG II and 87% in SSG VIII. There were no intralesional margins. Good response to preoperative chemotherapy (grades 3–4) was seen in only 19% of patients treated according to the SSG II protocol, as compared to 54% of patients treated according to the SSG VIII protocol.

Local recurrence occurred in 14 of 223 patients (6%), i.e., in 6 of 107 SSG II patients (6%) and 8 of 117 SSG VIII patients (7%). Mean time from surgery to local recurrence was 18 (2–47) months. The 14 patients with such recurrence showed no difference in age or tumor location, compared to those without local recurrence. Margin was assessed as wide in 11 of these 14 patients—5/6 in SSG II and 6/8 in SSG VIII. Analysis of tumor response showed that it was good (grades 3–4) in 3 of the 14 recurrent cases—0/6 in SSG II and 3/8 in SSG VIII. In the limb–salvage

Table 2. Patient characteristics according to chemotherapy protocol

	SSG II n=107	SSG VIII n=116
Age range (years)	6–36	2–41
Age median	16	16
Male	68%	62%
Tumor site		
Distal femur	58%	52%
Proximal tibia	24%	26%
Humerus	13%	13%
Other	5%	9%
Stage IIB	96%	94%

Table 3. Surgery and outcome according to chemotherapy protocol

	SSG II n=107	SSG VIII n=116
Surgery		
Limb–salvage	27%	57%
Wide or better margin	90%	87%
Marginal/contaminated margin	10%	13%
Intralesional margin	0%	0%
Outcome		
Grade 3–4 tumor response	19%	54%
Local recurrence	6 (6%)	8 (7%)
Local recurrence/limb–salvage	3/29	7/66
Wide margin *and* local recurrence	5	6
Grade 3–4 tumor response *and* local recurrence	0	3
5–year metastases–free survival	56%[a]	61%[b]

[a] Saeter et al. 1991
[b] See page 75 this issue

group of 95 patients, there were 10 local recurrences (11%), as compared to 4 such recurrences in the amputation–group of 128 patients (3%). The recurrence rate, in relation to chemotherapy protocol and limb–salvage is shown in Table 3. Of the 14 patients with a local recurrence, 10 had died of the disease (5 each in SSG II and SSG VIII), 1 was alive with disease and 3 had no sign of disease (11, 1 and 0.5 years after surgery for local recurrence).

Discussion

In the present study of two treatment strategies with regard to chemotherapy and type of surgery, we found no significant difference in outcome i.e., in local recurrence and survival. The only clear difference was that between patients undergoing limb–salvage and ablative surgery. This difference could not be ex-

plained by type of chemotherapy. Thus, the local recurrence rates of the limb–salvage patients were 10% (SSG II) and 11% (SSG VIII), as compared to 4% and 2%, respectively, among the amputated patients. These findings are comparable to those from other trials, such as the multicenter COSS study (Winkler et al. 1991) and that by Glasser and Lane (1991). However, a lower local recurrence rate (5–7%) after limb–salvage surgery has been reported by other orthopedic oncology centers, such as the Royal Orthopaedic Hospital and the Rizzoli Institute (Carter et al. 1991, Picci et al. 1997).

Considering the similar rate of wide procedures in the two chemotherapy groups, we expected a significant improvement in local control and survival after initiation of the new SSG VIII protocol. This assumption was, indeed, supported by the higher rate of good responders in SSG VIII, as compared to SSG II. However, the local recurrence rate was the same in both groups. Moreover, the projected 5–year metastases–free survival of the SSG VIII patients was only slightly higher than that of the SSG II patients.

The reasons for failure to improve local tumor control in the SSG VIII group, despite a higher incidence of good responders, are obscure. One explanation may be due to overlooking of skip lesions and another reason the type of surgery. Presumably, limb–salvage procedures entail an increased risk of omitting such lesions in the surgical specimen. In fact, such a case undergoing wide local excision was recently reported by the Rizzoli Institute (Picci et al. 1997).

Another explanation deals with the quality of surgical margins defined as wide. Regrettably, there is no clear–cut distinction between wide and marginal surgery. According to Enneking, a wide surgical margin is achieved by "an intracompartmental en bloc dissection with a cuff of normal tissue" (Enneking et al. 1980). However, the thickness of this cuff of normal tissue has yet to be defined. According to our definition during the 1980s, based on that of Enneking, we regarded an osteotomy > 4 cm from the tumor boundaries and excision of > 2 cm of healthy soft tissue in all planes around the tumor as a wide procedure. After starting more effective preoperative chemotherapy in the 1990s, in terms of tumor necrosis, we often noticed a dense, calcified periosteum–like tissue around the tumor, as described by the Rizzoli Institute (personal communication). In such cases, we regarded an osteotomy > 1 cm from the tumor and an excision of > 0.5 cm of healthy tissue as a wide procedure. This change in the definition of a wide margin, prompted by more effective chemotherapy and presumed to permit more limb–salvage procedures, may well explain the failure to achieve better local control in the SSG VIII patients. Notably, none of the patients in this study underwent intralesional surgery. Nonetheless, it is obvious that limb–salvage procedures entail narrower margins, especially in tumors around the knee, close to nerves and vessels (Picci et al. 1997). There seems to be an urgent need for a clearer distinction between wide and marginal procedures. So far, there is no consensus in this matter which, indeed, may influence the comparison of results from various centers.

The fact that this study failed to show a clear relation between surgical margin and local recurrence, since 6 local recurrences occurred after wide excision in the SSG VIII study, may be due to the limitations of the per– and postoperative assessments of surgical margin. Thus, some surgical reports tended to describe reconstructive and technical matters more thoroughly than the surgical margins. Moreover, it was obvious from some pathology reports that the postoperative assessment of surgical margin was not always based on the method recommended by Enneking of describing the "quality" of the margin. Thus, in some cases we had to deduce the quality of the surgical margin from a vague description. This is one of the weaknesses of multicenter studies, which are difficult to overcome. In contrast, reports from a single institution (Picci et al. 1993, 1997, Bacci et al. 1998) have, indeed, shown a relation between surgical margin and local recurrence. Thus the assessments of surgical margin, no matter how accurate, should be based on clear–cut definitions. Today, regrettably, there are still no criteria for distinguisling between wide and marginal procedures.

With increased experience of limb–salvage surgery, hopefully with a better tumor response, using the new ISG/SSG I protocol introduced in 1997, local tumor control should improve, despite an increasing rate of limb–salvage surgery. However, the optimal ratio of limb–salvage to ablative procedures in OS remains to be defined. It seems that the continuously increasing use of limb–salvage surgery is associated with a higher rate of local recurrence than with ablative surgery, despite better chemotherapy.

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