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ORIGINAL ARTICLE

Limb-sparing in patients with non-metastatic high-grade osteosarcoma

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Summary

Purpose: *To improve survival rates and functional outcome in patients with non-metastatic, high-grade osteosarcoma of the extremities, using the Scandinavian Sarcoma Group XIV neoadjuvant chemotherapy protocol.*

Patients and methods: *The analysis included 37 patients treated during the period 2000-2005. Age range was 8 to 65 year (median 23). Seven (7/37) patients were excluded from the study. The remaining 30 patients received 2 cycles of preoperative chemotherapy (high dose methotrexate, cisplatin and doxorubicin). Surgery was carried out in the 9th week. Twenty-seven (90%) patients had limb-salvage operation and in the remaining 3 amputation was performed. Based on the histopathological assessment of the removed tumor patients were classified in two groups (regarding good or poor response to chemotherapy). All 30 patients received 3 courses of postoperative chemotherapy with the same regimen. Patients with poor response received 3 more cycles of chemotherapy with high dose ifosfamide. Follow-up was 2-8 years (mean 52 months).*

Results: *Histopathological assessment showed poor response to neoadjuvant chemotherapy in 57% of the patients but no significant difference in 3-year survival between the 2 groups was noted. Three-year survival of the patients with local recurrence was 40 vs. 88% of those without local recurrence (p=0.013). Three-year survival of the patients with distant metastases was 20 vs. 92% of those without distant metastases (p=0.0002). Three-year overall survival (OS) was 80% and disease-free survival (DFS) 60% for all 30 patients.*

Conclusion: *Neoadjuvant chemotherapy in patients with high-grade osteosarcoma of the extremities gives the opportunity for limb-sparing operation and at the same time improves survival rates.*

Key words: limb-sparing, neoadjuvant chemotherapy, osteosarcoma

Introduction

Osteosarcoma is a very rare malignant bone tumor with an incidence of 4-6 cases in 1.000.000 inhabitants and appears mostly in young and active population aged 10-30 years [1]. Amputations and disarticulations as dominant treatment for malignant bone tumors in the beginning of 20th century are rarely and very selectively used today. Despite aggressive and radical surgery, 5-year survival was low (10-20%) [2,3]. Introducing new sophisticated diagnostic methods (CT and MRI) gave the possibility of precise anatomic definition of the tumors and the borders of infiltration into the surrounding tissues [4,5]. After 1980, improvement of chemotherapeutic protocols with neoadjuvant chemotherapy, better preoperative planning and modern reconstructive options after resection of osteosarcoma led to better survival rates of the patients with limb-sparing procedures [6-9]. Better planning of the biopsy and the definite operative procedure, and fostering better patient selection for specific treatment strategies, can decrease the risk of tumor spread into the surrounding tissues and lower the risk of distant metastases [10]. Currently, 80-85% of the patients with osteosarcoma on the extremities can be safely treated with wide resection and limb preservation [11]. Multidisciplinary approach to diagnosis and treatment, combination chemotherapy and a number of options for reconstruc-

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tion after osteosarcoma resection (especially in chemotherapy-sensitive tumors) have increased long-term survival rates from 60 to 80% [12-14].

The aim of this study was to improve treatment results of patients with non-metastatic high-grade osteosarcoma of the limbs, using neoadjuvant chemotherapy and limb-sparing surgery.

Patients and methods

In the period from 2000-2005, 37 patients with high-grade, extremity-localized osteosarcoma, were treated with neoadjuvant chemotherapy and surgery at the University Clinic for Orthopedic Surgery and Institute of Radiology and Oncology in Skopje.

Inclusion criteria

The selection of patients for study inclusion was based on the following criteria:

Histopathologically proven high-grade osteosarcoma (grade III or IV); primary localization on the extremities, with no evidence of lung or other metastases; patient age between 8 and 65 years; normal hepatic and renal function; leukocyte count over 3.0×10^9/L and platelet count over 100×10^9/L; neoadjuvant chemotherapy was introduced not longer than 1 month after histological diagnosis of osteosarcoma.

Exclusion criteria

Patients with central localization of osteosarcoma (e.g. pelvis, vertebra); evidence of lymphatic or haematogenous metastases at the time of diagnosis; patients under 8 years or older than 65 years; pregnant or a nursing woman.

Diagnosis was made by clinical examination, plain x-rays, CT, MRI and histopathologically with open biopsy. Staging was done with Tc 99m bone scan, chest x-rays and CT of the disease region. For preoperative planning, MRI and arteriography were carried out. After completion of the chemotherapy protocol, clinical and radiographic evaluation of the patients was done every 3 months in the first 3 years and twice a year thereafter.

Twenty-one (57%), patients were male and 16 (43%) female. The median patient age was 23 years (range 8-63). In 5 (14%) patients, osteosarcoma was localized in the upper extremities: 4 (11%) in the humerus and 1 (3%) in the ulna. In 32 (86%) patients, osteosarcoma was localized in the lower extremities: 16 (43%) in the distal femur, 4 (11%) in the proximal femur, 10 (27%) in the proximal tibia and 2 (5%) in foot. According to the exclusion criteria, 7/37 patients were excluded from the study owing to lung metastases or pelvic localization. Ninety percent of the patients (27/30) were treated with limb-sparing surgery, while the remaining 3 were treated with ablative surgery (Table 1).

All patients were administered to the Scandinavian Sarcoma Group XIV neoadjuvant chemotherapy protocol (SSG XIV). Patients received 2 cycles of preoperative chemotherapy (high dose methotrexate 1200 mg/m^2, cisplatin 45 mg/m^2/day ×2 days and doxorubicin 75 mg/m^2; Figure 1).

Surgical resection of the osteosarcoma was made 9 weeks after the beginning of neoadjuvant chemotherapy (Figure 1). Disease extent, anatomical location of the tumor and the patients' age were taken into account to define the most appropriate surgical procedure. We followed 4 basic principles of limb-sparing procedures: 1) there should be higher likelihood for less local recurrence and better survival than amputation; 2) the procedure or treatment of its complications should not delay adjuvant therapy; 3) reconstruction should be enduring and not associated with large number of local complications requiring secondary procedures and frequent hospitalizations; 4) function of the limb should not approach the one obtained by amputation, although body image, patients' preference and lifestyle might influence the decision [15]. After resection, detailed histopathological assessment of the specimen was done to determine the extent of necrosis of the tumor tissue. Considering the percentage of necrotic tumor tissue, patients were classified into two groups. The first group was with good response to chemotherapy (>90% necrosis of the tumor). The second group was with poor response to chemotherapy (>10% viable tumor). Regarding good or poor response of the tumor to chemotherapy, patients followed different branches of the protocol (Figure 1). All 30 patients received 3 courses of postoperative chemotherapy (the same as preoperative). Patients with poor response received 3 more cycles of chemotherapy with high dose ifosfamide (2000 mg/m^2/day ×5 days plus mesna) every 3 weeks.

Histopathological assessment of the specimen did not give only the extent of tumor necrosis, but information on tumor-free margins, too. Intralesional resections or marginal resections were unacceptable (Table 2) [16]. For the patients who could not satisfy the principles of limb preservation, ablative surgery was taken into consideration. For those patients disarticulation of the hip or shoulder griddle, femoral or below the knee, humeral or other amputations were more appropriate [17]. When tumor-free margins were obtained, a large skeletal defect was often present, requiring reconstruction of a bone, muscles, other soft tissues, and skin.

Table 1. Clinical data of patients with high-grade osteosarcoma of the extremities, treated with chemotherapy and surgery

Patient No.	*Age (years)*	*Gender (m/f)*	*Complications*	*Recurrence (months)*	*Metastases (months)*	*Follow-up (months)*	*Deceased (months)*	*Response to chemotherapy*	*MSTSS %*
Patients with limb preservation									
1	25	m	0	0	22	30	30	P	83.3
2	13	m	haematoma	0	20	25	0	P	60.0
3	23	m	transient paresis	0	0	46	0	P	56.0
4	16	f	0	0	0	41	0	G	56.7
5	15	f	infection	0	63	68	68	P	46.7
6	14	m	0	0	0	56	0	G	70.0
7	13	m	0	0	0	41	0	G	83.3
8	16	f	seroma	0	0	60	0	G	73.3
9	17	f	skin necrosis	6	15	25	25	P	86.7
10	54	f	0	0	0	43	0	P	56.7
11	14	f	0	0	0	100	0	G	63.3
12	63	m	0	0	0	101	0	G	96.7
13	17	m	loosening	0	0	60	0	P	66.7
14	16	m	0	0	0	64	0	G	96.7
15	20	f	0	0	51	54	54	P	80.0
16	20	f	0	0	0	40	0	G	73.3
17	23	m	0	4	0	42	0	P	33.3
18	39	f	skin necrosis	53	0	66	0	P	83.3
19	14	m	0	0	0	101	0	G	70.0
20	8	m	0	0	0	33	0	P	73.3
21	44	f	haematoma	0	0	53	0	P	90.0
22	14	m	0	0	35	40	40	P	83.3
23	44	f	0	0	0	70	0	G	63.3
24	15	f	0	0	0	100	0	G	93.3
25	15	m	loosening	2	19	27	27	P	76.7
26	24	f	infection	18	0	28	0	G	56.7
27	34	m	0	31	0	32	0	P	33.3
Patients with amputations									
28	24	m	0	0	0	34	0	G	40.0
29	13	m	seroma	0	0	25	0	P	46.7
30	15	m	seroma	35	43	45	0	P	36.7

m: male, f: female
G: good response after neoadjuvant chemotherapy (necrosis >90% of the tumor); P: poor response after neoadjuvant chemotherapy (>10% viable tumor).
MSTSS: Musculoskeletal Tumor Society score

Patients' age, tumor location and extent of resection narrowed the list of appropriate surgical alternatives.

Several options for limb-sparing procedures were available:

a) resection arthrodesis and other techniques with special indications (Figure 2 a, b) [17-19].
b) modular or special expanding endoprostheses (Figure 2 c, d) [3,4,12,14].
c) cortico-spongious or bulk allograft (Figure 2 e, f) [8,13,18-20].

Musculoskeletal Tumor Society score (MSTSS), based on the Enekings' system for functional evaluation of reconstructive procedures, was used to determine the functional results [21]. This scoring system evaluates pain, function, patient's emotional acceptance (pertinent to a patient as a whole) and specific factors for evaluating upper limb (range of motion, manual dexterity and lifting ability) or lower limb (need of support with orthopedic accessories, ability to walk and gait). For each of 6 factors, values from 0 to 5 are assigned, with total of 30 (or 100% function of the limb). For each factor, values 1, 3 and 5 are equated with criteria levels of achievement or performance. Intermediate values of 2 or 4 are assigned, based on the examiner's judgment, when achievement or performance falls between the specified values. It is recommended results to be reported numerically in percentage of normal function (last column in Table 1).

The cumulative prospective of 3-year OS was calculated from the day of diagnosis until death using the method of Kaplan-Meier [22]. The statistical significance of the differences between the survival curves was evaluated using log-rank test and the generalized Wilcoxon test, with the criteria of probability being less than 0.05.

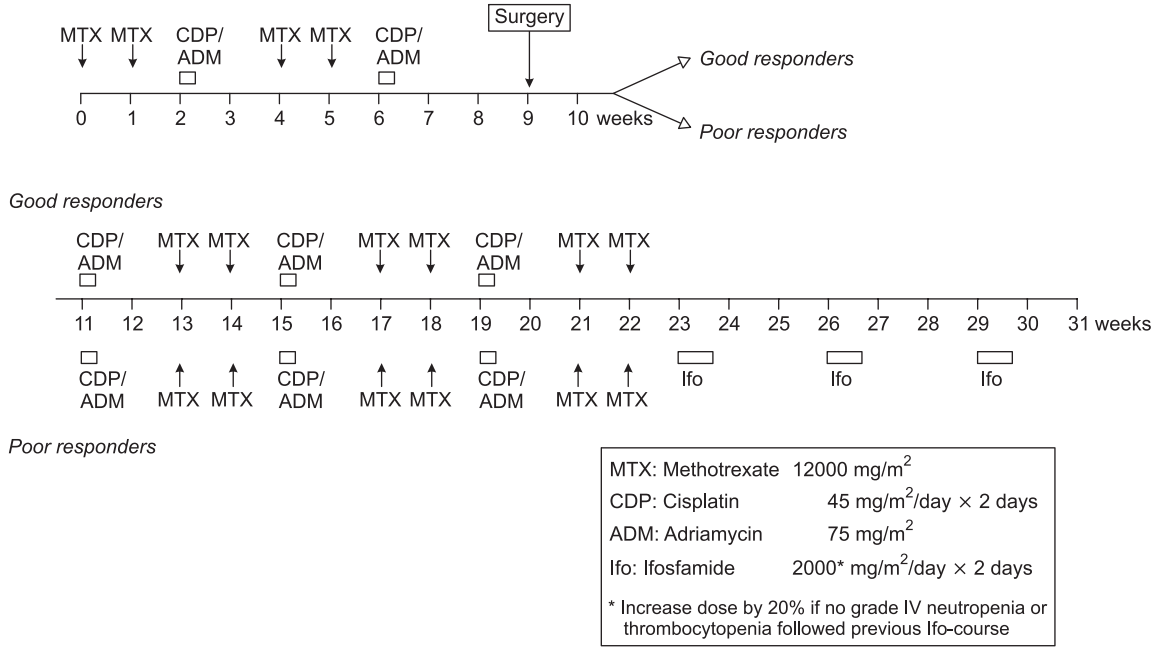

Figure 1. Scandinavian Sarcoma Group protocol (SSG XIV) for the treatment of osteosarcoma.

Table 2. Enneking's surgical resection margins

Margins of resection	*Explanation*
Radical resection	Resection of the whole anatomical compartment
Wide borders of resection	Resection of the tumor with 1 to 1.5 cm of surrounding tissue
Marginal borders of resection	Resection is at the vicinity of the tumor, but pseudocapsule is not disrupted
Intratumoral resection	Excision is made through tumor pseudocapsule, (no tumor sterility and radicality achieved)

DFS was calculated from the day of diagnosis of osteosarcoma until the first adverse event (if any) or until the most recent follow-up examination. Follow-up was 2-8 years (median 36 months). Results were updated in December 2007.

Results

After preoperative chemotherapy, clinical and radiographic tumor response was observed in 26/30 (87%) patients. Of the remaining 4 patients 3 showed no significant difference and one had radiographic progression. Histopathological assessment showed poor response to neoadjuvant chemotherapy in 57% (17/30) of the patients. In the group of patients with poor response, 75% survived 36 months, and in the group with good response 100% of the patients survived 36 months (Figure 3). Statistical analysis showed no significant difference in survival between the groups (log-rank test, p=0.06).

Twenty-seven (90%) patients with good response were subjected to limb-sparing operation and 3 (10%) to ablative surgery (Table 2). Limb-salvage was done with resection arthrodesis in 37% (10/27) of the patients, resection without reconstruction of the bone in 15% (4/27), reconstruction with bulk cortico-spongious graft in 33% (9/27) and with special endoprosthetic replacement in 15% (4/27). All 3 patients with primary ablative surgery were male. In this group, 2 patients had femoral amputations and 1 disarticulation of the hip. Five patients (5/30; 16.7%) developed local recurrence between 2 and 36 months after surgery. In the group of patients with local recurrence 40% survived 36 months, and in the group without local recurrence 88% of the patients survived 36 months (Figure 4). Statistical analysis showed high significance (log-rank test, p=0.013).

Five patients (5/30; 16.7%) developed lung me-

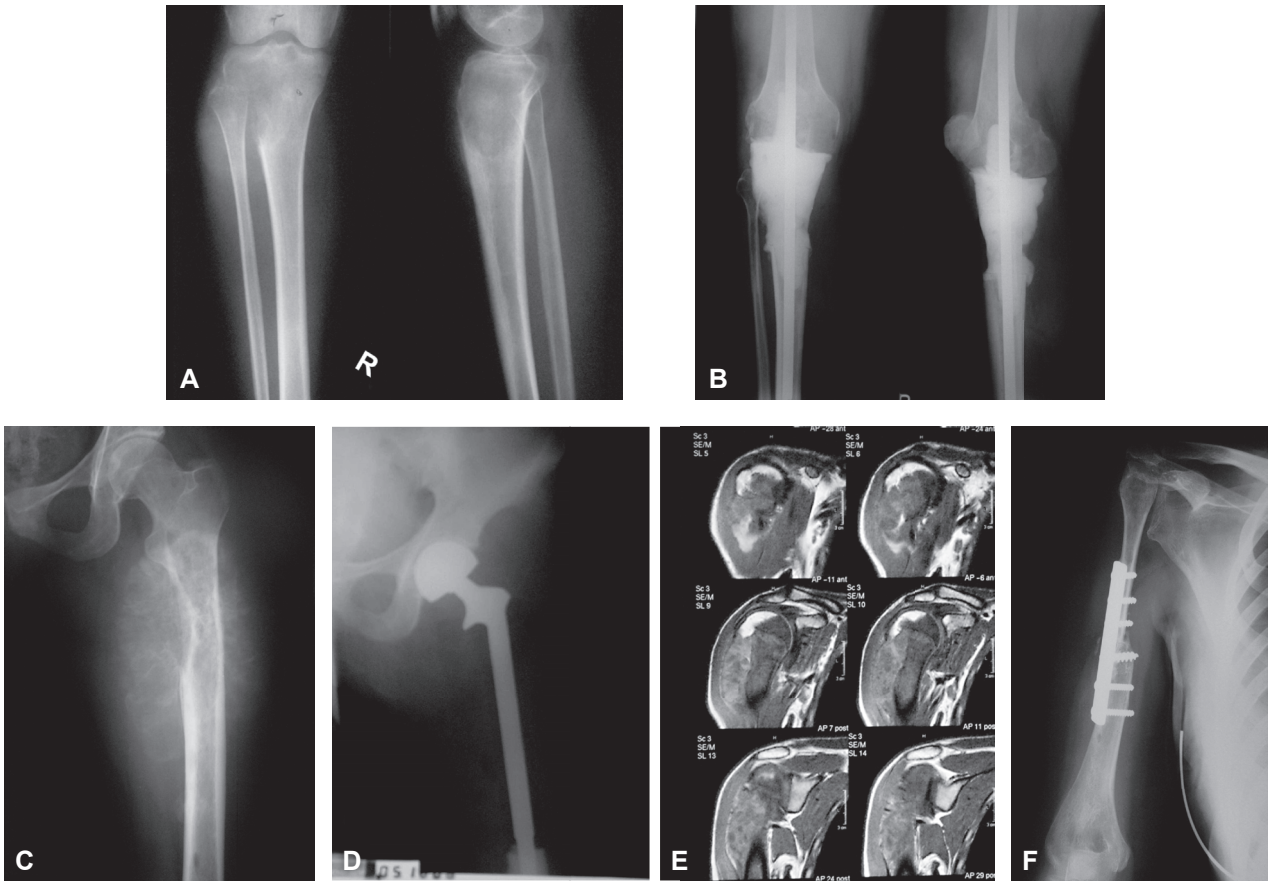

Figure 2. Various surgical options for limb-salvage operation: **A, B:** x-ray of a patient with resection arthrodesis (temporary or first stage procedure); **C, D:** x-ray of proximal femur reconstruction with special endoprosthesis (Link); **E, F:** MRI and x-ray of proximal humerus osteosarcoma reconstructed with vascularized cortico-spongious graft (fibula) and osteosynthesis.

tastases between 15 and 36 months after the surgical treatment. Only 20% survived 36 months in this group compared to the group of patients without metastases, where 92% of the patients survived 36 months (Figure 5). Statistical analysis showed high significance (log-rank test, p=0.0002).

In our study, 3-year OS was 80% (Figure 6) and 3-year DFS 60% (18/30 patients), with no significant statistical difference between good and/or poor responders (log-rank test, p=0.06).

Nine (30%) patients experienced relapse. Two of them (22%) are disease-free after resection of the local recurrence, 4 (44%) are alive with uncontrolled disease,

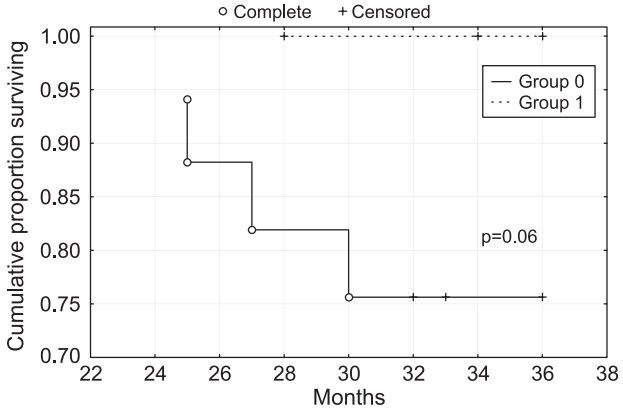

Figure 3. Cumulative 3-year survival according to response to neoadjuvant chemotherapy. Group 0: patients with poor response, Group 1: patients with good response.

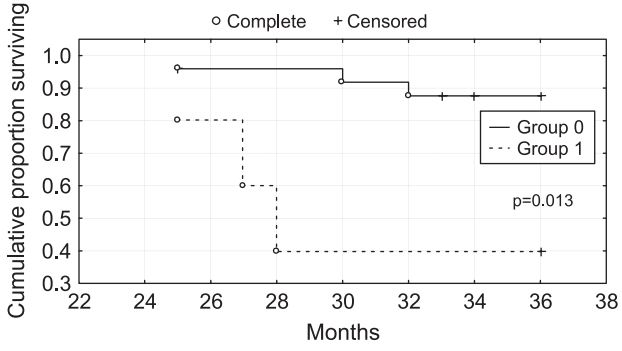

Figure 4. Cumulative 3-year survival according to local recurrence. Group 0: patients without local recurrence, Group 1: patients with local recurrence.

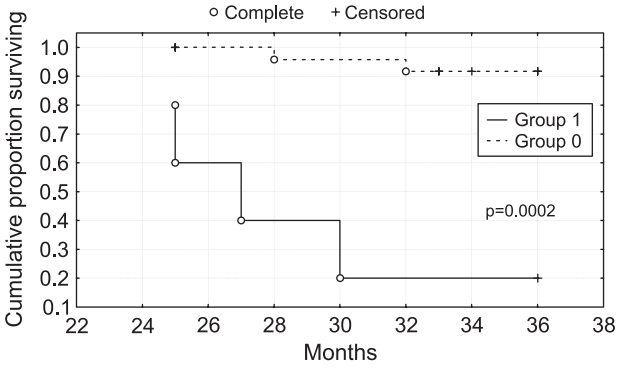

Figure 5. Cumulative proportion of surviving according to distant metastases. Group 0: patients without metastases, Group 1: patients with metastases.

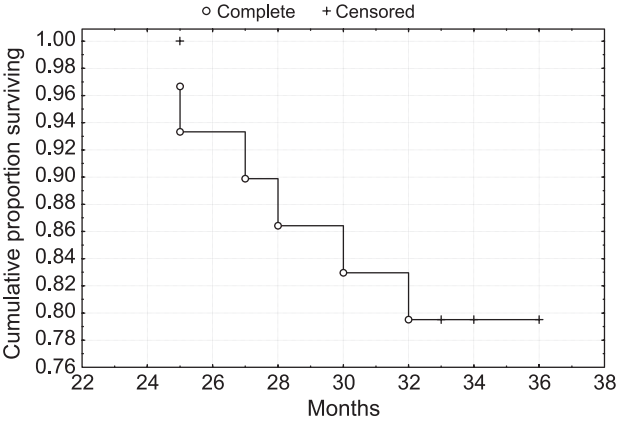

Figure 6. 3-year overall survival.

and 3 (33%) died. Only in 1 patient resection of a lung metastasis was performed. The mean survival time of this group of patients was 32 months (range 4-68).

Several postoperative complications were observed in 40% (12/30) of the patients, including 1 transient nerve palsy, 3 prolonged seromas, 2 postoperative hematomas, 2 skin necroses, 2 loosenings of the implanted materials, 1 deep and 1 superficial soft tissue infection. In 11% (3/27) of the patients with limb-sparing surgery, complications or further local recurrence led to secondary ablative surgery.

Functional results (MSTS score) of the operated limbs were evaluated after rehabilitation. Examination showed approximately 65% function of the spared upper limbs and 76% function of the spared lower limbs. Mean functional score of the amputated limbs was 41% and was lower for obvious reasons (Table 2).

Discussion

Amputations, once a dominant treatment for malignant bone tumors, are rarely and very selectively used now. Most patients with extremity-localized osteosarcoma are candidates for limb-sparing procedures because of the effective chemotherapeutic agents and regimens, the improved imaging modalities, and advances in reconstructive surgery. Various options for skeletal reconstructions include modular endoprostheses, osteoarticular or bulk allografts, arthrodeses, expandable endoprostheses, rotationplasty and limb-lengthening techniques. Two primary goals always must be considered: survival rates should be no worse than those associated with an amputation and the reconstructed limb must provide satisfactory function [6,11-14,21].

However, surgical treatment associated with a limb-sparing operation is also associated with significant complications and requires extensive rehabilitation [11]. Before consideration of limb preservation, the patient needs to be appropriately staged and assessed through a multidisciplinary approach [16]. Some elements of the disease may warrant concern, including relative contraindications to such procedures. The main risk of limb-salvage procedures is that complications, sometimes, may cause delay of chemotherapy [10].

During the past few decades neoadjuvant chemotherapy has made dramatic advances in the treatment of non-metastatic osteosarcoma of the extremities [6]. Multidrug neoadjuvant chemotherapy, popularized for patients with osteosarcoma by Rosen in the late 1970s, is usually initiated as appropriate after histopathological diagnosis and staging. Neoadjuvant chemotherapy dramatically improves long-term survival rates in patients with osteosarcoma sensitive to chemotherapy [2,5-7,9]. The Scandinavian Sarcoma Group XIV chemotherapy protocol equalizes survival rates between good and poor responders [3,6,7,15]. Patients considered operable at diagnosis or following neoadjuvant chemotherapy (9 weeks after the beginning of chemotherapy) must undergo wide margins resection of the osteosarcoma. As reported in the literature, response to neoadjuvant chemotherapy consists generally in the reduction of tumor size (usually due more to the decrease of the surrounding inflammatory tissue rather than to an actual reduction of the tumor), remission of pain, and increased density of the lesion on plain x-rays [6,11,14,18]. In the present study patients with poor response received 3 more cycles of chemotherapy with high dose ifosfamide (2000 mg/m^2/day × 5 days in each cycle). If basic principles of limb-sparing surgery and tumor sterility and radicality are not to be achieved, amputation is better choice than a limb preservation by any cost [2,8,23].

Three-year OS of the patients in our study was 80%. Histopathological assessment showed poor response to neoadjuvant chemotherapy in 57% of the patients, but there was no significant difference in 3-year

OS between the groups (due to administration of high dose ifosfamide postoperatively for poor responders). In our study, 3-year DFS was 60% (18/30 patients). Functional results (MSTS score) after rehabilitation, showed approximately 65% function of the spared upper limbs and 76% function of the spared lower limbs, which are comparable to the results published in the literature.

Conclusion

Applying neoadjuvant chemotherapy followed by limb-salvage surgery calls for responsible, trained and highly engaged medical staff. Using high dose ifosfamide for poor responders in postoperative chemotherapy improves the results and OS of these patients. If treatment and management principles of high-grade osteosarcoma are followed, limb-sparing with 60-80% survival rates could be achieved. Our preliminary results are promising and encouraging.

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