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LONG-TERM FOLLOW-UP AFTER NEO-ADJUVANT CHEMOPTHERAPY AND SURGERY IN 29 PATIENTS WITH HIGH-GRADE NON-METASTATIC OSTEOSARCOMA OF EXTREMITIES

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Abstract

Objectives. Currently, 80-85% of patients with osteosarcoma on the extremities can be safely treated with wide resection and limb preservation.

Background. Neo-adjuvant chemotherapy and a number of options for reconstruction after osteosarcoma resection (especially in chemotherapy-sensitive tumors) have increased long-term survival rates.

Methods. From the group of 47 patients with high-grade osteosarcoma, 8/47 patients were excluded, owing to lung metastases at first presentation or pelvic localization. Another 10/39 patients were excluded from the study due to primary indication for ablative surgery. Seventy-five percents of the patients (29/39) were treated with limb-sparing surgery. The mean age was 23.4 ± 14.5 years (range 8-63). Mean follow-up was 49.9 ± 23.1 months (range 23-108). All patients received neo-adjuvant chemotherapy protocol according to the Scandinavian Sarcoma Group XIV. After neo-adjuvant chemotherapy a clinical and radiological response of the tumor has been observed.

Results. Response to neo-adjuvant chemotherapy was good in 16/29 patients (55.2%). Local recurrence appeared in 17/29 patients (58.6%). Lung metastases appeared in 18/29 patients or 62.1%. Mean survival time of the patients was 53 months, and 10% of the examinees survived longer than 105 months. Up-to-date 10/29 patients (34.5%) are disease or event-free.

Conclusion. There was significant different overall survival time in our study between the groups of patients with a good response to neo-adjuvant chemotherapy compared to the group of patients with a bad response (p=0.0002). Furthermore, overall survival time in our group of patients was shorter than the time reported in the literature.

Key words: neo-adjuvant chemotherapy, limb-sparing surgery, 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 the young and active population aged 10- 30 years [1]. Before 1970, amputation was the primary treatment for high-grade osteosarcoma and 80% of patients died of lung metastatic disease. Despite aggressive and radical surgery, 5-year survival was low (10-20%) [2].

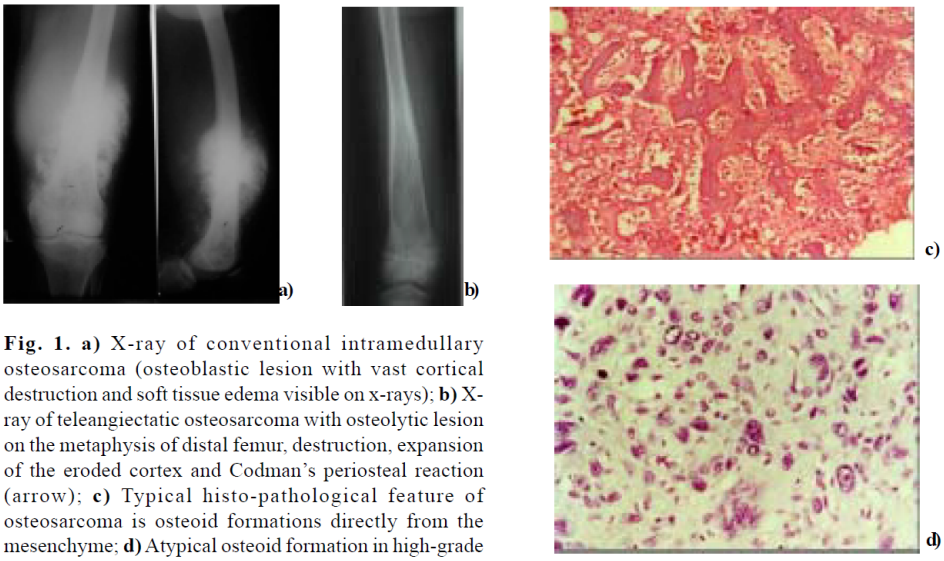


Fig. 1. a) X-ray of conventional intramedullary osteosarcoma (osteoblastic lesion with vast cortical destruction and soft tissue edema visible on x-rays); **b)** X-ray of teleangiectatic osteosarcoma with osteolytic lesion on the metaphysis of distal femur, destruction, expansion of the eroded cortex and Codman's periosteal reaction (arrow); **c)** Typical histo-pathological feature of osteosarcoma is osteoid formations directly from the mesenchyme; **d)** Atypical osteoid formation in high-grade anaplastic osteosarcoma typifies the diagnosis.

After 1980, improvement of chemotherapeutic protocols with neo-adjuvant chemotherapy, better preoperative planning and modern reconstructive options after resection of osteosarcoma led to better survival rates of patients with limb-sparing procedures [3, 4, 5].

A multidisciplinary approach to diagnosis and treatment, combination chemotherapy and a number of options for reconstruction after osteosarcoma resection (especially in chemotherapy-sensitive tumors) have increased long-term survival rates from 60 to 80%. Amputations, once a dominant treatment for malignant bone tumors, now are rarely and very selectively used. 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. Application of neo-adjuvant chemotherapy improves survival rates and functional outcome in patients with non-metastatic, high-grade osteosarcoma of the extremities [6].

Before consideration of limb preservation, the patient needs to be appropriately staged and assessed through a multidisciplinary approach. 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 a delay of chemotherapy [7].

Depending on cytological or histopathological features of the tumor matrix or tumor cells, osteosarcomas are divided into two groups. In the first group there are patients with *low-grade osteosarcoma* and surgery alone has the primary role of treatment. In the second group there are patients with *high-grade osteosarcoma* (Fig. 1). In this group of patients "sandwich therapy" is strongly preferred (neo-adjuvant chemotherapy - surgery - adjuvant chemotherapy) [3, 8, 9].

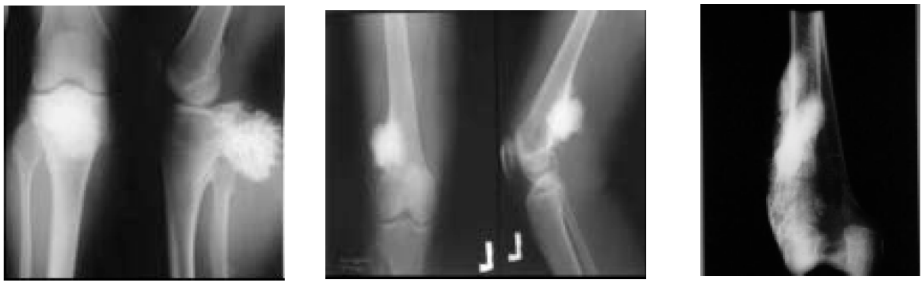
Considering the localization of the osteosarcoma in the diameter of the bone, it can be central (or conventional) or peripheral (periostal, juxtracortical or parosteal). The conventional type of osteosarcoma is most often seen in every day practice. There are rare variants of osteosarcoma such as: small-cell, giant cell-rich and teleangiectatic osteosarcoma, which can be differential diagnostic and treatment problem [10, 11].

Surface osteosarcomas (periostal, parosteal or juxtracortical) arise on the outer surface of the long bone metaphysis, sparing the medullar canal (Fig. 2a). The peak incidence is in the second and third decade, affecting more females than males. These osteosarcomas are considered to have their low-grade and high-grade variants [12, 13].

Material and methods

Following the "wave of modern" poly-chemotherapy, in the period of 2005-2013, a prospective study was done. In this period, 47 patients with high-grade osteosarcoma were treated [13].

According to the exclusion criteria, 8/47 patients were excluded, owing to lung metastases at first presentation or pelvic localization. Another 10/39 patients were excluded from the study due to primary indication for ablative surgery (amputation or disarticulation). Seventy-five percent of the patients (29/39) were treated with limb-sparing surgery (Table 1). Fourteen (48%) patients were male and 15 (52%) were female. The mean age was 23.4 ± 14.5 years (range 8-63). Mean follow-up was 49.9 ± 23.1 months (range 23-108).



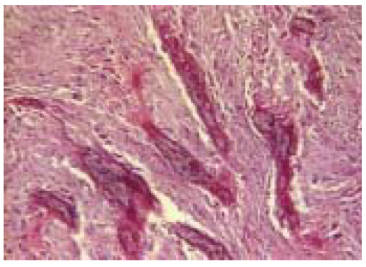


Fig. 2. a) Frontal and lateral x-ray of the periosteal osteosarcoma of right distal femur; **b)** X-ray in frontal and lateral view of parosteal osteosarcoma of the proximal tibia; **c)** Frontal and lateral x-ray of high-grade surface osteosarcoma on the right distal femur; **d)** Parosteal osteosarcoma showing parallel osteoid trabeculae embedded in fibroblastic stroma (HE, x100).

All patients received the Scandinavian Sarcoma Group XIV neo-adjuvant chemotherapy protocol (SSG XIV). Patients received 2 cycles of preoperative chemotherapy (high dose methotrexate of 1200 mg/m^2, cisplatin 45 mg/m^2/day ×2 days, and doxorubicin 75 mg/m^2), (Fig. 3).

After resection, a detailed histopathological assessment of the specimen was done to determine the extent of necrosis of the tumor tissue. Histopathological assessment of the specimen did not only identify the extent of tumor necrosis, but gave information on tumor-free margins, too. Considering the percentage of necrotic tumor tissue, patients were classified into two groups. The first group experienced a good response to chemotherapy (>90% necrosis of the tumor). The second group had a poor response to chemotherapy (>10% viable tumor).

Regarding a good or poor response of the tumor to chemotherapy, patients were assigned to different branches of the protocol (Fig. 3). All 29 patients received 3 courses of postoperative chemotherapy (the same as preoperative). Patients with a poor response received 3 more cycles of chemotherapy with high dose of ifosfamide (2000 mg/m^2/ day ×5 days plus Mesna) every 3 weeks (Fig. 3).

We have analyzed the following parameters (Table 1) of the clinical and radiological data after neo-adjuvant chemotherapy:
-age,
-gender,
-time of follow-up,

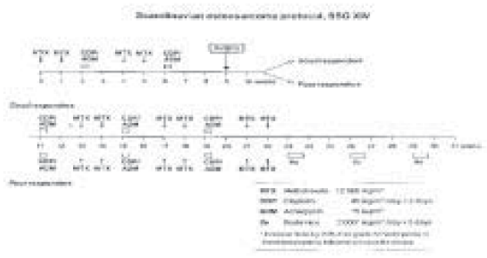


Fig. 3. Scandinavian Sarcoma Group Protocol XIV

-necrosis of the resected tumor after neo-adjuvant chemotherapy (poor or good response),
-decrease of pain,
-reduction of tumor diameter,
-tumor pseudo-capsule seen on MRI,
-sclerosis seen on radiographs or CT,
-local recurrence and metastases.

Most commonly used imaging techniques were: plain-film radiographs (as "gold" standard), Tc-99m bone scintigraphy, CT of the affected site or of the lungs and CT or conventional angiography [9]. Positron emission tomography (PET-scan) and Thallium scintigraphy have not been used.

Plain-film radiographs in two orthogonal plains showed mixed osteosclerotic and osteolytic tumor, affecting the metaphysis of the bone (Fig. 4). The destruction in some cases was so advanced that

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

Patie. No.	*Age (y.)*	*Gender (m.)*	*Follow-up*	*Response to neoad. chemoth.*	*Decrease of pain*	*Decrease in diameter*	*Pseudo-capsule*	*Sclerosis*	*Recurrence (m.)*	*Metastases (m.)*	*Deceased after (m.)*
1	25	M	30	P	0	1	0	0	0	22	30
2	13	M	32	P	1	1	1	0	0	27	32
3	23	M	50	G	1	1	U	1	0	29	-
4	16	F	44	P	1	1	1	1	0	38	44
5	15	F	68	G	1	1	1	1	50	57	68
6	14	M	51	G	1	1	1	1	0	0	-
7	8	F	50	G	1	1	1	1	29	43	50
8	13	M	45	G	1	1	1	1	0	0	-
9	16	F	54	P	1	1	1	1	0	36	54
10	17	F	23	P	0	0	0	0	6	12	23
11	54	F	38	P	1	1	U	1	0	0	38
12	14	F	107	G	1	1	1	1	0	0	-
13	63	M	106	G	1	1	1	1	96	100	106
14	17	M	67	P	1	0	1	1	54	60	67
15	16	M	59	G	1	1	1	0	0	0	-
16	20	F	54	P	1	1	1	0	0	46	54
17	20	F	47	G	1	1	1	1	0	0	-
18	16	M	10	P	0	0	0	0	2	4	10
19	39	F	61	P	1	0	1	1	53	57	61
20	14	M	26	P	0	0	0	0	19	19	26
21	8	M	40	G	1	1	1	0	0	0	-
22	44	F	59	G	1	1	U	1	0	0	-
23	14	M	40	G	1	1	1	1	0	30	40
24	44	F	35	P	0	1	0	0	21	28	35
25	15	F	108	G	1	1	1	0	0	0	-
26	15	M	27	P	0	0	0	0	2	11	27
27	48	F	43	G	1	1	1	1	0	0	-
28	24	F	33	G	1	1	1	1	18	0	-
29	34	M	51	G	1	1	0	1	35	45	51

M: *male;* **F**: *female;* **G**: *good response after neo-adjuvant chemotherapy (necrosis >90% of the tumor);* **P**: *poor response after neo-adjuvant chemotherapy (>10% viable tumor);* **U** *-unknown or missing data;* **1**-*yes;* **0**-*no or none.*

pathological fractures or complete bone erosion were present (Fig. 4b). There was a typical periostal reaction due to aggressive expansion of the tumor, forming hairy, sun-ray or velvet-like specula of neoplastic bone. In some cases "Codman's triangles" (arrows on Fig. 4a) were present**.** Plain-film radiographs were used in correlation with bone scintigraphy and CT to detect local recurrence or bone and lung metastases. Additional data for diagnosis and decision-making process was obtained using a "computer assisted diagnosis" in analysis of the x-rays [14, 15].

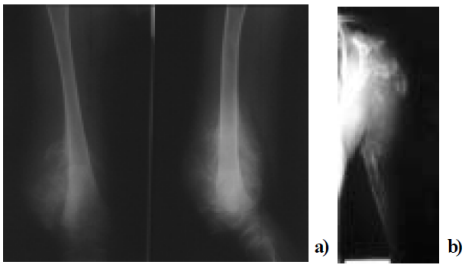


Fig. 4. a) X-ray in two orthogonal planes of typical mixed sclerotic and lytic osteosarcoma of the distal femur. Tumor has penetrated bone and formed a soft tissue mass with Codman's triangles. **b)** Frontal plane X-ray of osteosarcoma causing pathological fracture on proximal humerus with small, confluent cloud-like densities, destroying the bone completely.

Computer tomography (CT) scan of the affected extremity was useful in visualization of the intra and extra-osseous extent of the tumor, especially when extensive necrosis and surrounding edema were present. High-definition CT scans obtained a three dimensional view of the tumor in relation to adjacent neurovascular structures, especially when contrast medium was used (Fig. 4). All patients with osteosarcoma underwent CT scanning of the chest and lungs for detection of pulmonary metastases. After surgery, in patients with non-metastatic osteosarcoma, CT scans of the lung were repeated every three to six months in the following two years [6].

Obtaining an MRI prior to surgical resection permitted accurate planning of the osteotomy and gross tumor excision for achieving a "wide" surgical margin. Skip metastases on MRI were easily detectable in the same bone or in the adjacent joint. MRI studies (which are inferior to high-definition CT scans) for lung metastases detection were not regularly done [5].

Biopsy and staging. Biopsy was the key step in the diagnosis and treatment of osteosarcoma. Improperly performed biopsy could compromise the treatment plan. It was mandatory to place the biopsy in the line of definite surgical approach for osteosarcoma resection. A large needle biopsy (core biopsy) sometimes was preferable, because it was less invasive, with lower risk for skin necrosis, infection and pathological fracture. If no representative osteosarcoma tissue was obtained, an open biopsy was done.

One must state that obtaining an accurate histopathological diagnosis of the tumor (especially of osteosarcoma) may be a very delicate task. Osteosarcoma can be divided into high-grade or low-grade variants, depending on cellularity, pleomorphism, anaplasia and number of mitoses [10, 16, 17].

1This fact and the data for presence or absence of osteosarcoma metastases were enough to do the Enneking's surgical staging [18].

Treatment. A multidisciplinary approach was obligatory in the diagnosis and treatment of osteosarcoma. To achieve high standards in treatment specialized radiologists, pathologists, orthopedic, vascular and other surgeons (specialized in oncologic surgery), pediatric oncologists, specialized physical therapist and often social workers were needed [6]. High-grade osteosarcoma patients without clinically detectable lung metastases **were presumed to have micrometastases**. In these patients the treatment consisted of preoperative (neo-adjuvant) chemotherapy, wide or radical surgical resection and postoperative (adjuvant) chemotherapy i.e. "sandwich therapy". Parosteal osteosarcoma or low-grade intra-medullar osteosarcoma patients were treated with wide or radical surgical resection alone. Chemotherapy was reserved only for cases with high-grade malignant transformation. These cases were treated with preoperative (neo-adjuvant) chemotherapy similar to that used for conventional osteosarcomas [4, 19, 20, 21].

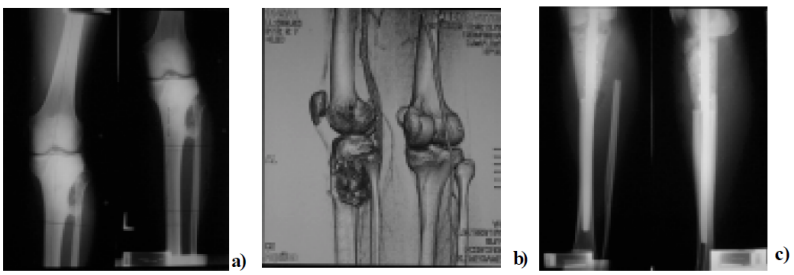


Fig. 5. a) X-ray of the proximal tibia osteosarcoma; **b)** CT angiography of the osteosarcoma, with visualization of the arteries; **c)** X-ray after modified Campanacci resection arthrodesis of the knee.

Surgery. The two primary surgical options were tumor resection with limb-salvage, and amputation. Surgical margins in excision included resection of tumor, pseudo capsule, and a cuff of normal tissue en block. Meticulous preoperative planning before biopsy and definitive surgery ensured better results. The limb-salvage surgery for osteosarcoma patients was possible due to the use of preoperative (neo-adjuvant) chemotherapy and to advancement in musculoskeletal imaging, prosthetic implant design and surgical technique (Fig. 5). During surgical treatment basic principles of limb-salvage procedures were kept in mind [22, 23, 24].

When "negative" tumor margins were obtained, a large skeletal defect was often present, requiring reconstruction of the bone, muscles, other soft tissues, and the skin. Patient age, tumor location and extent of resection determined the appropriate surgical alternatives.

Several options for limb-sparing were available: resection arthrodesis and other similar techniques with special indications (Fig. 7c), modular or special expanding endoprostheses (Fig. 5), cortico-spongious or bulk auto graft. For ablative surgery patients, disarticulation of the hip or shoulder griddle, rotationplasty, femoral or below knee, humeral or other amputations were far more appropriate [25].

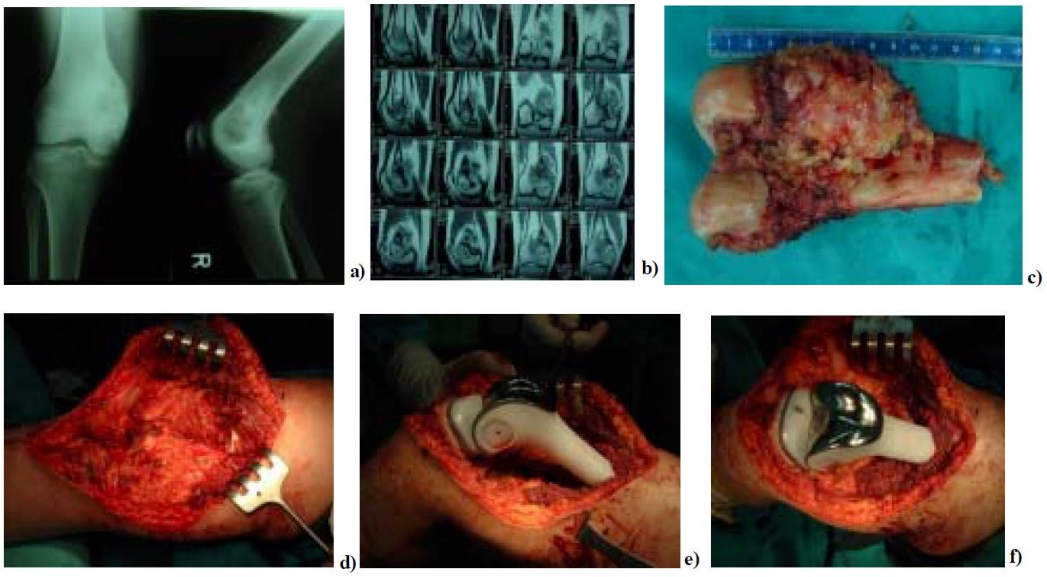


Fig. 6. a) x-ray of high-grade chondroblastic osteosarcoma of right distal femur in a girl aged 17; **b)** anterior and lateral MRI view of the lesion; **c)** photo of the resected tumor; **d)** tumor site ready for reconstruction; **e, f)** reconstructed right femur and knee (Link modular endoprosthesis).

There were a few relative contraindications taken into consideration for limb-salvage surgery: wrong site or ill-planed biopsy; massive encasement of neurovascular bundles; extensive tumour involvement in soft tissue, muscles or skin; complex or complicated (i.e. with infection) pathological fractures; expected inequalities of the extremities more than 8 cm; and exceptionally poor effect of the neo-adjuvant chemotherapy.

In the process of decision making for limb-salvage surgery versus amputation the "rule of three" was very helpful. For extremity survival the bone (1), nerves (2), blood vessels (3), and muscle and skin (4) were necessary to be preserved. If osteosarcoma involved one or two of the former structures, limb preserving was possible. If any three of the former were involved, amputation was taken into consideration [5, 24].

Postoperative follow-up. After chemotherapy, patients were closely followed by the orthopedic surgeon and the oncologist. The patients were monitored for local recurrence, distant or systemic metastases and complications related to reconstruction of the extremity. CT scanning of the chest, plain film radiographs of the reconstructed extremity and meticulous physical examinations were recommended every three months for the first two years and at least every six months from the second year through the fifth year, and subsequently on a yearly basis. Also, annual bone scintigraphy is mandatory for the first two years after completion of the chemotherapy [5, 9].

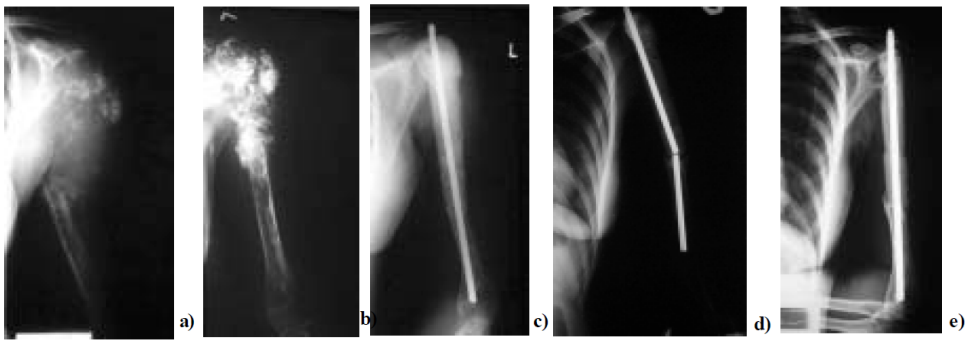


Fig. 7. a) Fourteen-yearold female osteosarcoma patient with pathological fracture of the left proximal humerus at the first presentation. The patient had preoperative (neo-adjuvant) chemotherapy with Swedish Sarcoma Protocol XIV. **b)** Excellent response (>90% tumor necrosis) with sclerosation after neo-adjuvant chemotherapy (arrow shows the site of pseudo-healing of the pathological fracture). **c)** Radiograph of the humerus after wide resection of the osteosarcoma, and first stage reconstruction of the bone with intramedullary rod and bone cement. **d)** "Stress-fracture" of the intramedular rod 6 years after the treatment. **e)** Considering the financial possibilities, reconstruction with new intramedular rod was sufficient for the patient's function.

Results

Various effects of neo-adjuvant therapy, such as: remission of pain, reduction of the size of the tumor, sclerosation, pseudo capsule formation, decreasing of neo-vascularisation, tumor necrosis and decrease of the elevated alkaline phosphathase and lactate dehydrogenase levels were recorded. After neo-adjuvant chemotherapy, a clinical and radiological response of the tumor has been observed. There was reduction, or more often complete remission of pain.

This was usually followed by decrease or normalization of serum alkaline phosphathase and lactate dehydrogenase levels (if elevated). An increased density on plain radiographs (Fig. 7b) with decreased vascularity on the angiograms was associated/was noticed.

Clinical and radiographic reduction in tumor size was observed in more than half of the patients. This was more due to a decrease of the surrounding inflammatory and reactive tissue than to an actual reduction in tumor size. Neo-adjuvant chemotherapy in some patients decreased the size of the primary tumor (Fig. 7) by reducing its neo-vascularity and promoting tumor demarcation from surrounding tissue with pseudo-capsule (Fig 7b).

Response to neo-adjuvant chemotherapy was good (more than 90% necrosis of the tumor) in 16/29 patients (55.2%). The examinees with a good response to neo-adjuvant therapy had significantly longer overall survival time than the patients with a poor response (Fig. 8).

Ten percents of the patients with poor response survived for more than 65 months (Fig. 9), while 58% of the patients with a good response survived for more than 100 months (Log-Rank test=3.74 p=0.0002).

Local recurrence appeared in 17/29 patients (58.6%). The examineås without local relapse had significantly longer overall survival time than the examined

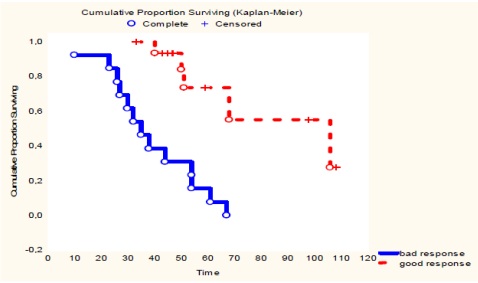


Fig. 8. Neo-adjuvant chemotherapy response in correlation with survival in patients treated with SSG XIV chemotherapy protocol.

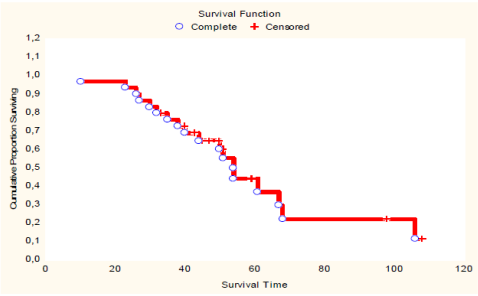


Fig. 9. Disease and event free survival time of the patients with extremity localized high-grade osteosarcoma treated with SSG XIV neo-adjuvant chemotherapy protocol and surgery (10% of the examinees survived longer than 105 months).

patients with relapse. Ten percents of the patients with relapse survived more than 100 months, while 48% of the examined with no local relapse were alive even after 100 months (Log-Rank test p=0.0002). Most of the tumor relapses were seen in the patients by 22 months after surgery. The 3 patients with early local recurrences had secondary extirpation of the relapsed tumor and one of them had to be amputated.

Lung metastases appeared in 18/29 patients or 62.1%. The examinees with metastases had significantly shorter overall survival time than the metastasis-free patients. Four percents of the examined patients with metastases survived longer than 100 months, while 90% of the examined with no metastases were alive even after 100 months (Log-Rank test p=0.0002).

Plain radiograph or CT-scan sclerosis of the tumor after neo-adjuvant chemotherapy was seen in 18/29 patients (62.1%). Pseudo-capsule was seen in 19/29 patients (65.5%), but in 3/29 (10.3%) MRI imaging showed inconclusive data. Cystic necrosis on MRI scans after neo-adjuvant chemotherapy was seen in 14/29 patients (48.3%). Inconclusive results for cystic necrosis were found in 3 and data was missing for 1 patient.

Up-to-date mean survival time of the patients was 53 months (4.4 years), and 10% of the examinees survived longer than 105 months (8.7 years) as presented in Figure 9. Disease and event-free are 10/29 (34.5%) of the patients.

Discussion

Prior to the introduction of chemotherapy, when amputation was the primary treatment for patients with osteosarcoma, the predicted long-term survival was 15-20%. Dismal survival rates were presumably attributable to pulmonary metastatic disease, whether clinically obvious or occult [8]. Survival rates dramatically increased during 1970's and 1980's with the pioneer work of Rosen and Jaffe. Currently, long-term survival rates are 60% to 70% for patients with localized osteosarcoma and for extremity localized up to 80% [26]. Despite the use of modern neo-adjuvant chemotherapy the 10-year survival rates decline significantly to 20% in patients with clinically detectable metastases [27]. Most of the patients ultimately die because of respiratory failure caused by the metastatic burden [9, 13, 25]. Excluding high-grade surface osteosarcoma, which has similar prognosis to that of conventional osteosarcoma, the surface (parosteal and periostal) osteosarcoma variants have the best prognosis of all. The 10-year survival rates for this group of patients are up to 85% [5, 12, 25]. The site of the lesion has prognostic importance. Best survival rates are expected in patients with appendicular localization of the osteosarcoma. Central localization (as pelvis, ribs and vertebrae) are less common sites of osteosarcoma, but with the poorest prognosis. Osteosarcoma of the jaws is associated with an especially good prognosis, whereas some osteosarcoma involving the scull has a very poor prognosis [11, 28]. Badly planned and ill preformed biopsy can complicate the final surgery and may decrease survival rates due to local spreading or risk for early metastatic disease [16, 17].

The overall treatment results in high-grade osteosarcoma are less impressive than widely presumed. Whereas classical osteosarcoma survival has indeed increased, in other subgroups, comprising more than 40% of the entire osteosarcoma population , the prognosis has been modestly improved. Today still more than half of an unselected osteosarcoma population eventualy succumbs to the disease, despite the current multimodal primary tretatment as well as second-line chemotherapy and surgical metastatectomies [4, 25, 27].

Neo-adjuvant chemotherapy enables limb-sparing in majority of patients with extremity localised osteosarcoma. During the past 20 years dramatic advances have been made in the treatment of non-metastatic osteosarcoma in terms of cure rate and quality of life for survivors. These advances are mainly due to the development of effective adjuvant and neo-adjuvant chemotherapeutic regimens. Reports on the progress and controversis in the treatment of osteosarcoma occurred with respect to the construct, expirimental design and interpretation of the many important studies which led to these remarkable results [22].

The survival rate of patients can be as high as 60%-75% when both the primary tumor and the solitary lung metastasis are adequately resected [3, 27]. The rate of surgical site recurrence is 4% to 16% for both limb-salvage and amputations. However, surgical treatment associated with a limb-sparing operation is also associated with a significant number of complications and requires extensive rehabilitation. Complications following limb-salvage reconstructions include wound complications, infections, mechanical failure, and nonunion. The main risk of limb-salvage procedures is that complications sometimes may cause a delay of chemotherapy. The reported incidence of complications with limb-salvage surgical techniques is 4% to 38% [5, 20, 29, 30].

The evaluation variables influencing systemic and local recurrence and final outcome are extremely important in defining risk-adapted treatments for patients with nonmetastatic osteosarcoma of the extremity. Upon multivariate analysis, age d" 14 years, high serum levels of alkaline phosphatase, tumor volume >200 mL, a dual-drug regimen chemotherapy, inadequate surgical margins, and poor histologic response to treatment maintained independent prognostic values on the outcome of nonmetastatic osteosarcoma of the extremities. These factors must be considered when deciding risk-adapted treatments for osteosarcoma patients. [22, 28, 30] Amputation remains the indicated treatment when these factors are taken into concideration or tumor resection to disease-free margins leaves a nonfunctional limb [5, 8].

Conclusion

With advances in neo-adjuvant chemotherapy, radiographic imaging, and reconstructive surgery, most patients with osteosarcoma now can be offered limb-sparing treatment. As reported in literature, if treatment and management principles of high-grade osteosarcoma

with neo-adjuvant therapy are followed, long-term 60-80% overall survival rates could be easily achieved.

Our results are slightly different from those published in the literature. In our study, there was significantly different overall survival time between the groups of patients with a good response to neo-adjuvant chemotherapy compared to the group of patients with a bad response (p=0.0002). Furthermore, overall survival time in our group of patients was shorter than the time reported in the literature. Up-to-date mean survival time of the patients was 53 months (4.4 years), and 10% of the examinees survived longer than 105 months (8.7 years). Up-to-date 10/29 patients (34.5%) are disease and event-free.

The key factor for increased survival rates was introduction of modern protocol with neo-adjuvant chemotherapy. In spite of the recorded differences in the results reported in the literature, the treatment regimen with neo-adjuvant chemotherapy is promising and encouraging.

References

1. Price CH, Jeffree GM. Incidence of bone sarcoma in SW England, 1946-74, in relation to age, sex, tumour site and histology. Br J Cancer 1977; 36 (4):511–22.
2. Rosen G. Pre-operative (neo-adjuvant) chemotherapy for osteogenic sarcoma: a ten year experience. Orthopedics 1985; 8:659.
3. Bacci G, Picci P, Ferrari S, Ruggieri P, Casadei R, Tienghi A, et al. Primary chemotherapy and delayed surgery for non-metastatic osteosarcoma of the extremities. Cancer 1993; 72 (11): 3227-38.
4. Bruland OS, Pihl A. On the current management of osteosarcoma. A critical evaluation and a proposal for modified treatment surgery. Eur J Cancer 1999; 33: 1725-31.
5. Di Caprio MR, Friedlander GE. Malignant Bone Tumours: Limb Sparing Versus Amputation. J Am Acad Ort Surg 2003; 11(1): 125-9.
6. Wittig JC, Bickels J, Priebat D, Jelinek J, Kellar-Graney K, Shmookler B, et al. Osteosarcoma: A Multidisciplinary Approach to Diagnosis and Treatment. Am Fam Physician 2002; 65 (6): 1123-32.
7. Saeter G, Bruland OS, Follerås G, Boysen M, Høie J. Extremity and non-extremity high-grade osteosarcoma, Acta Oncol 1996; 35: 129-34.
8. Enneking WF. Osteosarcoma (editorial comment). Clin Orthop Rel Research 1975; 111: 2-4.
9. Messerschmitt PJ, Garcia RM, Abdul-Karim FW, Greenfield EM, Getty PJ. Osteosarcoma. J Am Acad Ort Surg 2009; 17: 515-27.
10. Fletcher CDM, Unni KK, et al. Classification of tumours. Pathology and genetics of tumours of soft tissue and bone. Lyon: IARC Press; 2002.
11. Unni KK. Osteosarcoma of bone. J Orthop Sci 1998; 3:287-94.
12. Samardziski M, Zafiroski G, Tolevska C, Konstadinova-Kunovska S, Vasilevska V. Parosteal osteosarcoma. Bratisl Lek Listy 2009; 110: 240-4.
13. Samardziski M, Zafiroski G, Tolevska C, Zafirova-Ivanovska B, Kostadinova-Kunovska S, Kalicanin-Markovska M. Limb-sparing in patients with non-metastatic high-grade osteosarcoma. J BUON 2009; 14: 63-9.
14. Lodwick GS, Haun CL, Smith WE, Keller RF, Robertson ED. Computer diagnosis of primary bone tumours, a preliminary report. J Bone Joint Surg Am 1963; 80:273-5.
15. Samardziski M, Zafiroski G, Janevska V, Miladinova D, Popeska Z. Computer assisted diagnosis of benign bone tumors. Radiol Oncol 2004; 38: 165-9.
16. Mankin HJ, Lange AT, Spanier SS. The Hazards of biopsy in patients with malignant primary bone and soft-tissue tumours. J Bone Joint Surg Am 1982; 6: 1121-7.
17. Campanacci M. Errors in the diagnosis and treatment of the musculoskeletal tumors: What must not be done. Chir Organi Mov 1999; 84: 1-17.
18. Enneking WF, Spanier SS, Goodman MA. A surgical staging of musculoskeletal sarcomas. J Bone Joint Surg (Am) 1980; 62: 1027-30.
19. Jaffe N, Raymond AK, et al. Analysis of efficacy of the intra-arterial cis-Diammine-dichlorplatinum-II and high dose methotrexate with citrovorum factor rescue in the treatment of primary osteosarcoma. Reg Cancer Treat 1985; 2: 157-63.
20. Bacci G, Picci P. Analysis of factors influencing treatment options in osteosarcoma. Review. Forum 1994; 4 (1): 52-64.
21. Bacci G, Ferrari S, Tienghi A, Bertoni F, Mercuri M, Longhi A, et al. A comparison of methods of loco-regional chemotherapy combined with systemic chemotherapy as neo-adjuvant treatment of osteosarcoma of the extremity. Eur J Surg Oncol 2001; 27: 98-104.
22. Bacci G, Longhi A, Versari M, Mercuri M, Briccoli A, Picci P. Prognostic factors for osteosarcoma of the extremity treated with neo-adjuvant chemotherapy: 15-Year experience in 789 patients treated at a single institution. Cancer 2006; 106(5): 1154-61.
23. Longhi A, Errani C, De Paolis M, Mercuri M, Bacci G. Primary bone osteosarcoma in the pediatric age: State of the art. Cancer Treat Rev 2006; 32: 423-36.
24. González-Herranz P, Burgos-Flores J, Ocete-Guzmán JG, López-Mondejar JA, Amaya S. The management of limb-length discrepancies in children after treatment of osteosarcoma and Ewing's sarcoma. J Ped Orthop 1995; 15: 561-65.
25. Bacci G, Rocca M, Salone M, Balladelli A, Ferrari S, Palmerini E, et al. High-grade osteosarcoma of the extremities with lung metastases at presentation: Treatment with neo-adjuvant chemotherapy and simultaneous resection of primary and metastatic lesions. J Surg Oncol 2008; 98: 415-20.
26. Meyers PA, Schwartz CL, Krailo MD, Healey JH, Bernstein ML, Betcher D, et al. Osteosarcoma: The addition of muramyl tripeptide to chemotherapy improves overall survival. A report from Children's Oncology Group. J Clin Oncol 2008; 26: 633-8.

27. Yonemoto T, Tatezaki S, Ishii T, Satoh T, Kimura H, Iwai N, et al. Prognosis of osteosarcoma with pulmonary metastases at initial presentation is not dismal. Clin Orth Rel Res 1997; 349: 194-9.
28. Yu XC, Wang W. Multivariate analysis of factors influencing on preoperative chemotherapy response for osteosarcoma. Cancer Res Prev Treat 2009; 36 (10): 863-8.
29. Kotz R, Dominkus M, Zettl T, Ritschl P, Windhager R, Gadner H, et al. Advances in bone tumor treatment in 30 years with respect to survival and limb salvage. A single institution experience. Intern Othoped 2002; 26: 197-206.
30. Pochanugool L, Subhadharaphandou T, Dhanachai M, Hathirat P, Sangthawan D, Pirabul R, et al. Prognostic factors among 130 patients with osteosarcoma. Clin Orthop Rel Res 1997; 345: 206-14.