The Role of Radiotherapy in Oseosarcoma

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Abstract A survey of the literature shows that the experience with radiotherapy (RT) in the local treatment of osteosarcoma (OS) is limited. This is due to various reasons: OS is a rare tumor and surgery is the treatment of choice with high local control rate, and uncertainty exists in regard to the efficacy and tolerance of radiotherapy. Publications on this topic were analyzed and will be reviewed. Furthermore, experience from the Cooperative Osteosarkomstudiengruppe (COSS)-Registry, including 100 patients (pts) treated using radiotherapy for OS, was analyzed.

The COSS-registry includes a total of 175 pts (5% of all pts) with histologically proven OS irradiated over the period of 1980–2007. 100 pts were eligible for analysis. The median age was 18 (3–66) years. Indication for RT was a primary tumor in 66, a local recurrence in 11, and metastases in 23 pts. 94 pts got external photontherapy; 2 pts, proton therapy; 2 pts, neutron therapy; and 2 pts, intraoperative RT. In addition, a group of 17 pts received bone-targeted radionuclide therapy by samarium-153-EDTMP-therapy alone or in combination with external RT. The median dose for external RT was 55.8 Gy (30–120). All the pts received chemotherapy in accordance with different COSS-protocols.

The median follow-up was 1.5 (0.2–23) years. Survival and local control rates at 5 years were calculated, and univariate and multivariate analyses performed. 41 pts are alive, 59 pts died. The overall survival rate after biopsy was 41% at 5 years, while the overall survival rates after RT for the whole group, for treatment of primary tumors, local recurrence, and metastases were 36%, 55%, 15%, and 0% respectively.

In 41 cases, local control was achieved, whereas local progression or local recurrence occurred in 59 cases, with a median time to local recurrence of 0.5 (0.1–4) years after RT. 15 pts were nonresponders to radiotherapy. Local control for the whole group was 30%. Local control rates for combined surgery and RT were significantly better than those for RT alone (48% vs. 22%, $p = 0.002$). Local control for treatment of primary tumors, local recurrence, and metastases were 40%, 17%,

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and 0% respectively. Local control for pts given an addition of samarium-153-EDTMP was poor, though not statistically significant . A dose of over 60 Gy had no significant effect on local control. Prognostic factors for survival were indication for RT, RT plus surgery vs. RT alone and tumor location. Prognostic factors for local control were indication for RT, and RT plus surgery vs. RT alone.

For the majority of pts, surgery remains the local treatment of choice. Radiotherapy is an important option as local treatment of unresectable tumors, following intralesional resection, or as palliation of symptomatic metastases. Survival prognosis of such pts, however, is poor. Despite the fact that many of these pts will eventually die, they may benefit in terms of prolonged survival and prolonged local control. The combination of surgery, radiotherapy, and chemotherapy can be curative. The consistent use of full-dose chemotherapy is of importance for the response to radiotherapy. Prognostic factors for survival are indication for RT, RT plus surgery vs. RT alone and tumor location. Prognostic factors for local control are indication for RT, and RT plus surgery vs. RT alone.

Introduction

A combination of neoadjuvant chemotherapy, surgery and postoperative chemotherapy is the standard treatment for pts with OS. Complete resection with clear margins is the gold standard in the local therapy.[1–4] The majority of pts are currently treated using limb salvage procedures.[1,2,5,6] However, limb salvage is not feasible in OS-pts with advanced extremity or axial tumors. In such cases, gross tumor resection may not be possible, and when achievable, the resection margins are close or positive.

The COSS group performed a multivariate analysis of 1,702 pts with OS. Histological response to neoadjuvant chemotherapy (>90% necrosis) and surgical remission were the main prognostic factors.[7] Picci et al.[8] reported that local recurrence after limb-salvage surgery is associated with less than wide surgical margins, a suboptimal response to chemotherapy , and complications from the biopsy procedure . Ozaki et al.[9] reported a local recurrence rate of 70% for 67 pts with pelvic OS. They also reported that a recurrence developed in 31 of 50 pts (62%) who underwent resection, and 16 (94%) of 17, who did not. Pts with spinal lesions also have a poor prognosis. Of 22 pts with spinal lesions treated by COSS, 15 pts (68%) experienced a local failure.[10] In head and neck OS, a local recurrence rate of approximately 50% has been reported, with the mandible as the most favorable site, followed by the maxilla, and then the extragnathic sites.[11] Single modality, nonoperative options have not been reliably effective in controlling the primary tumor.[12–14]

Historically, in the prechemotherapy era, Cade[15] used a strategy of high-dose radiotherapy and delayed amputation. Gaitan-Yanguas[16] showed a dose-response relationship with no lesions controlled at doses of 30 Gy, and all lesions controlled with doses of >90 Gy. Machak et al.[17] reported on a series of pts with extremity lesions who refused amputation and received neoadjuvant chemotherapy and radiotherapy. Local control was related to response after induction chemotherapy. All the 11 pts with

a good response to neoadjuvant chemotherapy achieved local control after radiotherapy. The calculated local progression-free survival among nonresponders was 31% at 3 years, and 0% at 5 years. DeLaney et al.[18] reported on 41 pts with OS who were either not resected or were excised with close or positive margins and who underwent RT with external beam photons and/or protons at the Massachusetts General Hospital. Local control rates, according to the extent of resection, were 78.4% for gross total resection, 77.8% for subtotal resection, and 40% for biopsy only. The use of a bone-seeking radioisotope, samarium153ethylene diamine tetramethylene phosphonate (EDTMP), can provide additional radiation to osteoblastic OS.[19–22]

Publications reporting on the experience with radiation for local treatment of OS were analyzed and will be discussed. In addition, data from the COSS-Registry of 100 pts with radiotherapy for OS were analyzed.

Material/Methods

Since 1980, most OS pts from Germany, Austria, and Switzerland have been treated on protocols of the Cooperative Osteosarcoma Study Group (COSS). A uniform concept of preoperative and postoperative chemotherapy in combination with aggressive surgery has formed the basis of all consecutive neoadjuvant study protocols since 1980.[7] Registration was never limited to the typical young pts with localized limb tumors; rather, all pts with osteosarcoma were eligible. In addition to the pediatric population, many adults with OS were also registered.

The COSS-registry includes over 3,500 pts with histologically proven OS. A total of 175 pts (5%) were identified to have been externally irradiated over the period of 1980 – 2007. Inadequate follow-up concerning survival and/or local control, missing radiotherapy details or histologies other than OS were exclusion criteria for the analysis. After exclusion based on these criteria, 100 pts (2.9%) were eligible. Table 1 lists the patient characteristics. The median age was 18 (3–66) years, 57 pts were below 20 years and 43 pts, above 20 years of age. Indication for RT was a primary tumor in 66, a local recurrence in 11, and metastases in 23 pts. A total 65 pts were irradiated with curative, and 35 pts with palliative, intent. The anatomical sites of irradiated tumors or metastases were as follows : pelvis, 33; lower extremity, 29; spine, 13; head and neck, 13; thoracic sites, 10; and upper extremity, 2. The median follow-up was 1.5 (0.2–23) years after radiotherapy. Survival and local control rates at 5 years were calculated, and univariate and multivariate analyses performed.

Radiotherapy

Early COSS-Protocols did not include recommendations regarding radiotherapy; EURO.B.O.S.S. and EURAMOS-1 were the first protocols to do so.

Table 1 Patient characteristics

Indications for radiotherapy	
Primary tumor	66
Local recurrence	11
Metastasis	23
Age	
Median age	18 (3–66) years
<20 years	57
≥20 years	43
<40 years	86
≥40 years	14
Localisation of the treated tumors	
Pelvis	33
Spine	13
Thoracic sites	10
Head and neck	13
Lower extremity	29
Upper extremity	2

Radiotherapy was performed in 35 pts as preoperative (9), postoperative (24), or intraoperative (2) radiotherapy. The majority of pts (65) were treated with radiotherapy after biopsy, or for unresectable tumors or metastases in combination with chemotherapy.

Table 2 shows details of the RT. Ninety-four pts received linear accelerator-based external photon therapy. Special techniques were used in 6 pts (2 pts, Proton therapy; 2 pts, neutron therapy; and 2 pts, intraoperative RT). A group of 17 pts received high-dose samarium-153-EDTMP therapy for large and unresectable primary or recurrent tumors and/or metastases, alone or in combination with external RT,[23,24] some of them with high doses and stem cell rescue. Eight pts had bone metastases and nine pts, an advanced OS of the pelvis. For the treatment of hematopoetic toxicity, cryopreserved hematopoetic progenitor cells were used. The median dose for external RT was 55.8 Gy (30–120); for preoperative RT, 50 Gy (30–68) ; postoperative RT, 54 Gy (36–72); for RT without surgery, 56 Gy (30–75,6); for primary RT, 59.7 Gy (20–120); for local recurrence, 50.4 Gy (30–70); and for metastases, 45 Gy (30–66). Complications were not analyzed.

Chemotherapy

Chemotherapy was given to all pts according to the COSS protocol active at the time of enrollment. All protocols included high-dose methotrexate at 12 g/m^2 per course with leucovorin rescue. In addition, doxorubicin 60–90 mg/m^2 per course, cisplatin 90–150 mg/m^2 per course, ifosfamide 6–10 g/m^2 per course, and bleomycin, cyclophosphamide, and dactinomycin were used in varying combinations. For the

Table 2 Radiotherapy (RT) characteristics

Treatment modalities	Patients
Preop RT	9
Postop RT	24
Intraop RT	2
RT/RCHTH	65
Radiotherapy	
External RT with photons	94
IMRT	3
Stereotactic RT	1
Neutrontherapy	2
Protontherapy	2
Intraoperative RT	2
Additionally Hyperthermia	2
Dose of radiotherapy	Gy
Median dose for external RT	55.8 (30–75.6)
Median dose for primary RT	59.7 (20–120)
Median dose for local recurrence	50.4 (30–70)
Median dose for metastases	45 (30–66)
Median dose preoperative RT	50 (30–68)
Median dose postoperative RT	54 (36–72)
Intraoperative RT	20
Extra corporal RT	120
Neutrons	12, 16
Total dose of irradiation	
<60 Gy	59 patients
≥60 Gy	41 patients

treatment of primary tumors, the duration of chemotherapy ranged from 24 to 38 weeks.[7] Therapy of relapse was not standardized; however, most protocols included general recommendations.[25] Surgical removal of all detectable tumor foci was recommended whenever feasible. The decision to use second-line chemotherapy and the choice of drugs were left to the discretion of the treating physician. Since 1990, COSS has suggested carboplatin and etoposide, if chemotherapy is considered.

Assessment of Response

For pts with assessable, unresected or partially resected disease, local control was defined as durable stabilization or regression of tumor demonstrable on cross-sectional imaging with CT or MRI. Local failure in these pts was defined as tumor growth on cross-sectional imaging and was invariably accompanied by progression of local symptoms. For pts whose disease had been grossly resected, local control was defined as the absence of tumor regrowth demonstrable on cross-sectional imaging with CT or MRI.
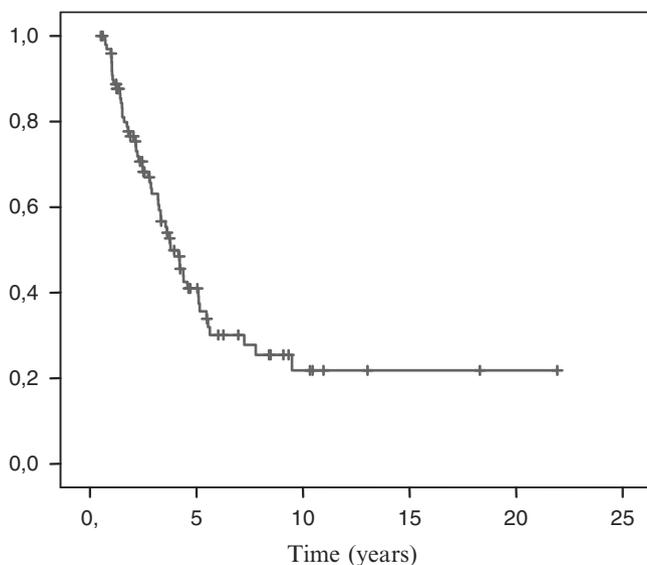
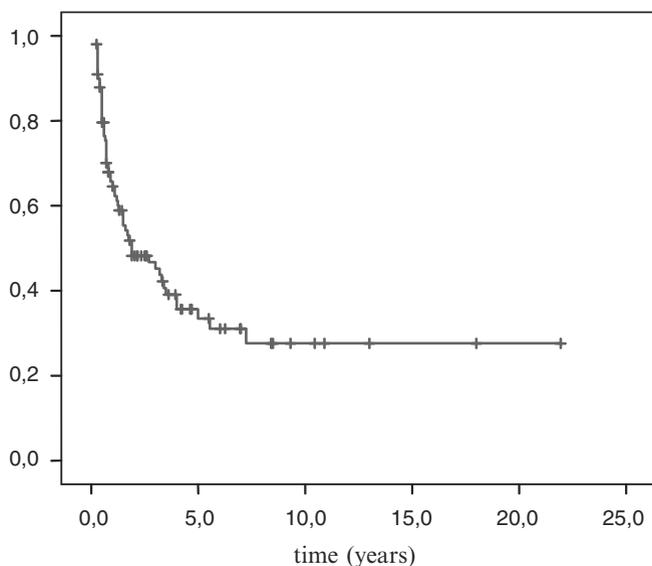**Fig. 1** Cumulative overall survival for all patients ($n = 100$)

Statistical Analysis

An analysis of the overall survival and local control rates was performed using the Kaplan–Meier method.[26] The log-rank test was used to compare the survival curves.[27] Multivariate analyses of overall survival and local control were completed using the Cox proportional hazards model.[28] The overall survival rate was calculated for all the pts from the time of biopsy (Fig. 1). All other overall survival and local control rates were calculated from the end of radiotherapy. Only four variables (dose <60 Gy vs. ≥60 Gy, RT plus surgery vs. RT alone as local treatment, tumor location extremity vs. axial tumors, and indication for RT primary tumor and local recurrence vs. metastases) that resulted in a significant value in univariate analysis were included in the multivariate models.

Results

Survival

The overall survival rate after biopsy was 41% at 5 years (Fig. 1). At the last follow-up, 41 pts were alive, 59 pts had died. The overall survival rate after RT for the whole group was 36% at 5 years (Fig. 2). The results for the overall survival rates are demonstrated in Table 3. There is a highly significant difference in survival between treatment with RT plus surgery and that with RT alone (62%
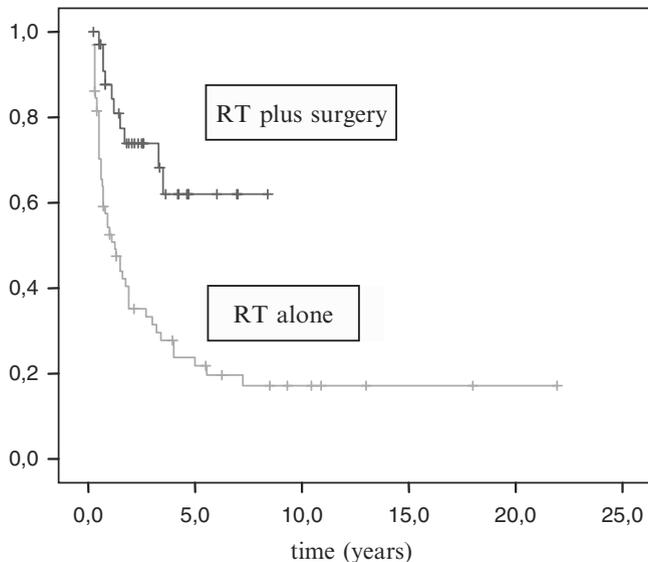
**Fig. 2** Cumulative survival for all patients after RT

Table 3 Results for overall survival (OS)

Group	Patients *n*	OS at 5 years (%)	OS at 10 years (%)	*p*
Localization				
Extremity tumors	31	43	37	0.057
Axial tumors	69	28	–	
Indication				
Primary	66	48	39	<0.0001
Local recurrence	11	13	–	
Metastasis	23	–	–	
Local treatment				
RT plus surgery	35	63	–	<0.0001
RT alone	65	22	18	
Modality				
Only external RT	83	38	30	0.191
Additional 153-Sam	17	15	–	
RT dose				
<60 Gy	59	27	22	0.145
≥60 Gy	41	41	35	
Age				
<20 years	57	41	41	0.761
≥20 years	43	31	22	

vs. 26%, $p<0,0001$, Fig. 3). The overall survival rates for the treatment of primary tumors, local recurrences, and metastases were 55%, 15%, and 0% (Fig. 4) respectively. Pts with extremity tumors had a better chance of survival

Fig. 3 Cumulative survival for patients after RT plus surgery vs. RT alone ($p < 0.0001$)
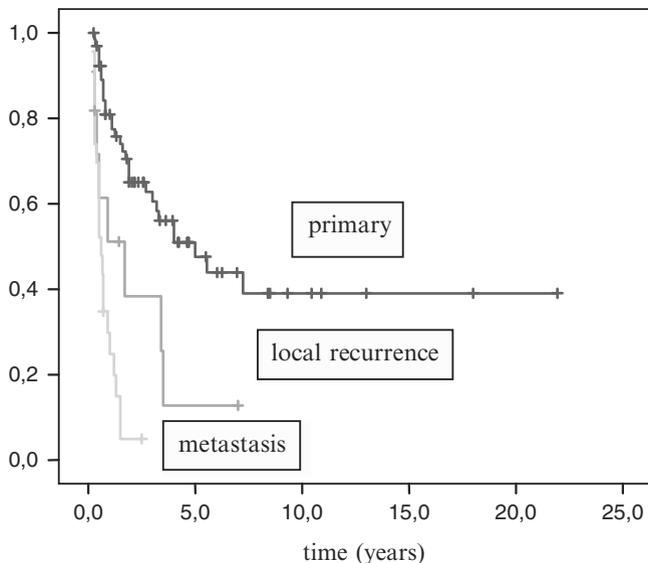
Fig. 4 Cumulative survival for different indications (primary, local recurrence, metastasis)

than pts with axial tumors (55% vs. 29%, $p = 0.016$). The survival rate for pts with additionally administered samarium-153-EDTMP in comparison to that of other pts was not significantly different (42% vs. 15%, $p = 0.137$). Age had no significant influence on survival.

Table 4 Results for local control (LC)

Group	Patients n	LC at 5 years (%)	LC at 10 years (%)	p
Localization				
Extremity tumors	31	35	35	0.156
Axial tumors	69	27	–	
Indication				
Primary	66	39	39	<0.0001
Local recurrence	11	18	–	
Metastasis	23	–	–	
Local treatment				
RT plus surgery	35	48	–	0.002
RT alone	65	22	22	
Modality				
Only external RT	83	34	34	0.127
Additional ^{153}Sam	17	10	–	
RT dose				
<60 Gy	59	30	30	0.790
≥60 Gy	41	32	32	
Age				
<20 years	57	33	33	0.516
≥20 years	43	28	28	

Local Control

The results for the local control rates are shown in Table 4. In 41 cases, local control could be achieved; in 59 cases, a local progression or local recurrence occurred with a median time to local failure of 0.5 (0.1–4) years after RT. Fifteen pts were nonresponders to radiotherapy. The local control rate for the whole group was 30% at 5 years (Fig. 5). The local control rate for combined surgery and RT was significantly superior to that of RT alone (48% vs. 22%, $p=0.002$, Fig. 6). The local control rates for treatment of primary tumors, local recurrence, and metastases were 40%, 17%, and 0% respectively (Fig. 7). Local control for pts who received additional samarium-153-EDTMP-therapy was worse than for those with only external RT; however, the difference was not significant. A dose of over 60 Gy had no significant effect on local control.

Prognostic Factors

The prognostic factors for survival were indication for RT, RT plus surgery vs. RT alone and tumor location of the irradiated tumor site (Table 5).The prognostic factors for local control were indication for RT, and RT plus surgery vs. RT alone (Table 6).
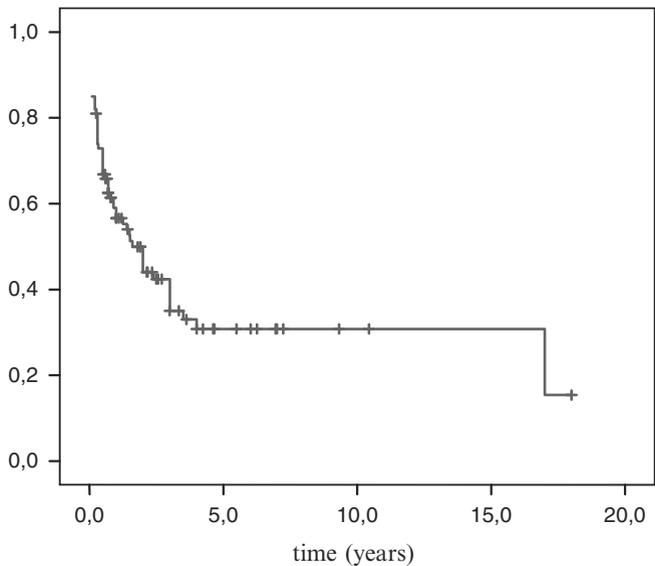
Fig. 5 Cumulative local control for all patients ($n = 100$)
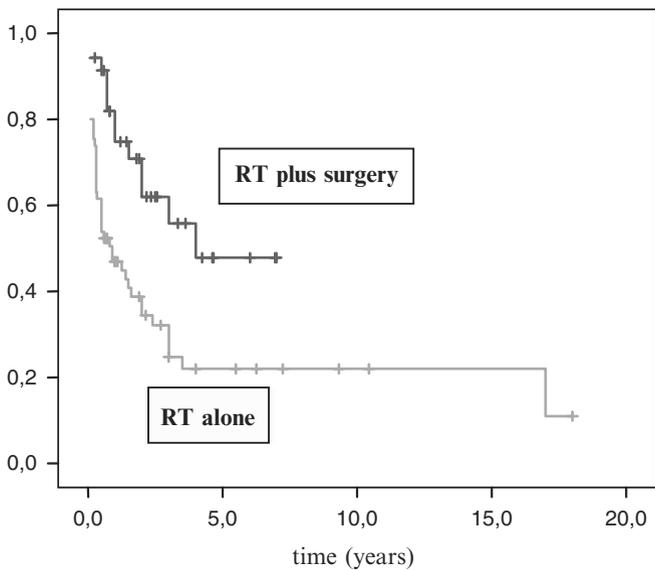
Fig. 6 Cumulative local control for patients after RT plus surgery vs. RT alone ($p = 0.002$)
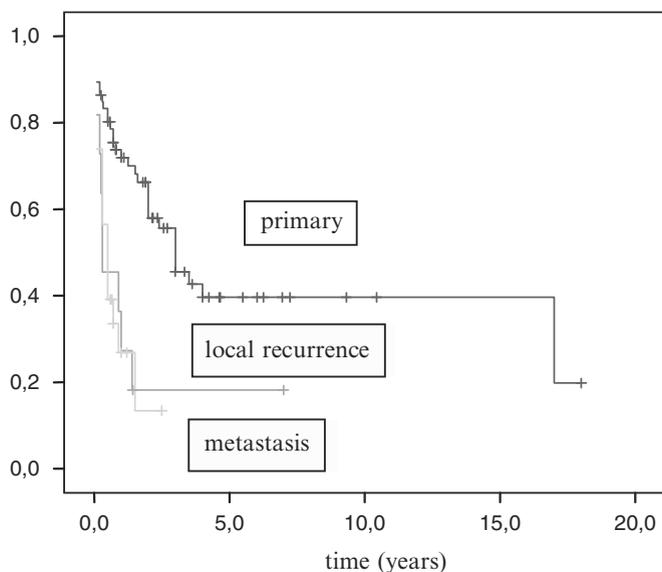
Fig. 7 Cumulative local control for different indications (primary, local recurrence, metastasis)

Table 5 Multivariate analysis of prognostic factors for overall survival

Factor		Hazard ratio(95% confidence intervall)	*p*-value
RT modality	RT + surgery	1	
	RT alone	5.149 (2.4–10.8)	<0.0001
RT indication	Primary	1	
	Local recurrence	3.738 (1.6–8.5)	0.002
	Metastasis	5.252 (2.6–10.3)	<0.0001
Tumor location	Axial	1	
	Extremity	0.542 (0.28–1.0)	0.058
Dose	<60 Gy	1	
	≥60 Gy	0.708 (0.4–1.2)	0.231

Discussion

The combination of neoadjuvant and adjuvant chemotherapy with complete resection of the primary tumor with clear margins is the standard treatment for pts with OS.[1-4,8] A high percentage of pts are currently being treated using limb salvage

Table 6 Multivariate analysis of prognostic factors for local control

Factor		Hazard ratio(95% confidence interval)	p-value
RT modality	RT+surgery	1	
	RT alone	2.743 (1.4–5.28)	<0.003
RT indication	Primary	1	
	Local recurrence	3.353 (1.5–7.3)	0.003
	Metastasis	2.98 (1.4–5.9)	0.002
Tumor location	Axial	1	
	Extremity	0.628 (0.3–1.1)	0.139
Dose	<60 Gy	1	
	≥60 Gy	1.12 (0.6–1.9)	0.686

procedures.[1,2,5,6] Local control of the primary or recurrent tumor is of great importance for cure.[7,25] Although limb salvage surgery can be done in many pts with OS, some pts have extremely challenging extremity or axial tumors, and complete resection is difficult to achieve. In these cases, gross tumor resection may not be possible, and when achievable, the resection margins are close or positive.

In pts with surgery as local treatment, the definition of histopathological remission is possible. In radiotherapy for gross tumor after biopsy or partial resection of the tumor, an alternative definition is necessary. Local control has to be defined as durable stabilization or regression of tumor demonstrable on cross-sectional imaging with CT or MRI (see above). Because of the osteoblastic stroma in OS, tumors may not necessarily shrink, even if a response occurs. Local failure in these pts has to be defined as tumor growth on cross-sectional imaging. It was invariably accompanied by progression of local symptoms. For pts whose disease had been grossly resected, local control has to be defined as the absence of tumor regrowth demonstrable on cross-sectional imaging with CT or MRI.

The limited success of radiotherapy in the past has been attributed to a suggested low cellular radiosensitivity of OS tumor cells. However, Larsen et al.[29] had demonstrated that the parameters of the radiation cell survival curves (α and β) of three OS cell lines, are in the same order as those of most nonsarcoma cell lines derived from tumors known to be clinically radiocurable. Another paper showed that the doses required by these OS cell lines to achieve 50% survival (D50%) were much lower than the D50% of a human melanoma line, known to be radioresistant.[30] However, tumor radiocurability is determined by various radiobiological factors such as cellular radiosensitivity, tumor hypoxia, reoxygenation, tumor size, repair, and proliferation rate. In clinical reality, the efficacy of radiotherapy is often limited by large tumor size and a significant proportion of hypoxic cells.[31] In addition, tumor location may prohibit the safe delivery of adequate radiation doses.

Radiotherapy as single modality has not been reliably effective in controlling the primary tumor.[12–14] Cade[15] advocated a strategy – "a holding action"; giving high-dose

radiotherapy to relieve local pain. He then restricted delayed amputation to pts without evidence of lung metastases during subsequent follow-up.

Ozaki et al.[9] reported for the COSS, a local recurrence rate of 70% for 67 pts with pelvic OS. Recurrence developed in 31 out of 50 (62%) pts who underwent resection, and 16 (94%) out of 17 pts who did not. Out of 30 pts with intralesional surgery, or no surgery, 11 pts took radiotherapy and had better overall survival compared with 19 pts who went without radiotherapy ($p = 0.0033$). The Cox proportional hazard model revealed that existence of primary metastasis, intralesional surgery, or no surgery, and no local radiotherapy were by themselves poor prognostic factors. Pts with spinal lesions also have a poor prognosis. Of 22 pts treated by the Cooperative Osteosarcoma Study Group, 15 (68%) experienced a local failure.[10] Sundaresan et al.[32] described that some OS of the spine respond to radiotherapy.

The publication by Machak et al.[17] reported a local control rate at 5 years of 56% in 31 extremity OS pts who were treated with external beam radiotherapy to a median dose of 60 Gy, and neoadjuvant chemotherapy. Among pts with a good imaging and good biochemical (as assessed by normalization of alkaline phosphatase) response, no local failure was observed. Caceres et al.[33] noted a high response rate among pts with limb OS treated by chemotherapy and 60 Gy of RT. In 80% of those pts, biopsies after treatment were negative. DeLaney et al.[18] reported on 41 pts with OS that were either not resected or were excised with close or positive margins and who underwent RT with external beam photons and/or protons at the Massachusetts General Hospital. The survival rates in DeLaney's series and in ours are similar. In the Boston Series, the actuarial survival at 5 years according to the extent of surgery was 74.4% for gross total resection; 74.1% for subtotal resection; and 25% for biopsy only. The local control rate at 5 years according to the extent of resection was 78.4% for gross total resection; 77.8% for subtotal resection; and 40% for biopsy only, compared with 48% for pts with surgery and radiotherapy and 22% for those with radiotherapy alone in our series. Both, the poor overall survival and local control rates support the need for multidisciplinary local treatment for further improvement in treatment results.

A clear dose-response relationship could not be demonstrated in the analysis of DeLaney or in ours This might have been an effect of limited size and heterogeneity of the populations. In the series of Machak et al.[17] and our own series, long-term local control after RT doses of 60 Gy and chemotherapy could be demonstrated. Gaitan-Yanguas[16] showed a dose-response relationship with no lesions controlled at doses of 30 Gy, and all lesions controlled with doses of >90 Gy. Lombardi et al.[34] used hypofractionated, accelerated radiotherapy to overcome the intrinsic radioresistance of OS.

New techniques allowing local dose escalation are emerging. Several series utilized intraoperative radiotherapy to increase the dose and spare later reactions.[35–38] Hong et al.[36] described extracorporeal irradiation (ECI) in the management of 16 pts with primary malignant bone tumors, four of them with OS. After en bloc resection, a single dose of 50 Gy was delivered to the bone segment extra corporeally. At a median follow-up of 19.5 months, there were no cases of local recurrence or graft

failure. One patient required amputation due to chronic osteomyelitis. Oya et al.[37] reported 39 pts with OS of the extremities, who were treated with high-dose intraoperative radiotherapy. The irradiation field included the tumor plus an adequately wide margin, and excluded the major vessels and nerves. A dose of 45–80 Gy was delivered with electrons or X-rays. The cause-specific and relapse-free 5-year survival rate was 50% and 43%, respectively. Distant metastases developed in 23 pts; 19 died and 4 were alive for >10 years. Nine local recurrences were found 4–29 months after IORT. Functional status was examined in 21 pts; four of them needed nonnarcotic analgesics, and 17 (81%) were free of pain. Five pts had a minor to moderate functional deficit, and 16 had only cosmetic alterations without a functional deficit. Hence, IORT may be a treatment option in specialized centers.

With modern radiation techniques, higher radiation doses can be delivered with fewer side effects. Highly conformal RT techniques such as intensity modulated RT (IMRT), image-guided radiotherapy (IGRT), proton therapy, and heavy ion therapy are suitable techniques.[18,39–42] The availability of these techniques has encouraged radiation oncologists to treat OS with doses of ≥70 Gy. In a Japanese series of 15 pts with unresectable OS treated with carbon ion therapy the actuarial survival rate was 45%.[42] However, because of limited experience and follow-up, no definite conclusions can be drawn about these high radiation doses.

A local recurrence has a worse prognosis in comparison to primary tumors. The overall survival and local control at 5 years in DeLaney's[18] series (overall survival 78,8% vs. 54%; $p < 0.05$, and local control 73.8% vs. 48%; $p < 0.05$) and our series (overall survival 55% vs. 15%, $p < 0.0001$, and local local control 40% vs. 17%, $p < 0.0001$) were better for patients with radiotherapy for primary tumor.

Preoperative radiotherapy was reported by several groups.[43–45] Chambers et al.[43] reported on 33 pts with preoperative RT and resection for craniofacial OS. They reported an overall survival rate of 73% at 5 years.[43] Dincsbas et al.[45] analyzed 64 pts with neoadjuvant and adjuvant chemotherapy, preoperative RT in 44 cases, and limb sparing surgery. The median follow-up was 44 months. at which the tumor necrosis rate was ≥90% in 87% of the pts. The 5-year local control and overall survival rates were 97.5% and 48.4% respectively. The authors concluded that preoperative RT, when combined with chemotherapy, may facilitate the chance of extremity-sparing surgery with good local control .

Neutron therapy was used in some centers on the basis of an assumedly improved radiobiological effectiveness of neutrons. Two pts were treated with neutrons in the COSS-series. Other small series have been reported,[46] but on their basis alone, no definitive conclusions can be made. Neutrons are available only in a very limited number of centers worldwide.

Prophylactic lung irradiation (PLI) without effective adjuvant and neoadjuvant chemotherapy was used three decades ago.[47] Currently there is no indication for PLI, because effective chemotherapeutic agents are used nowadays in the treatment protocols.[47,48]

The use of a bone-seeking radioisotope, samarium-153-EDTMP, can provide additional radiation to disseminated skeletal metastases and osteoblastic OS.[19–23,49–53] Several series have shown that provision of high-dose samarium-153-EDTMP and

peripheral blood stem cells to pts with favorable imaging results can deliver an additional 40 to 200 Gy of radiation to lesions of osteoblastic OS.[22,52] In our series The overall survival and local control rates for pts with external beam radiotherapy and samarium-153-EDTMP were worse than those for pts with external beam radiotherapy only. This can be explained by the fact that all the pts receiving samarium-153-EDTMP-therapy had advanced local tumors and/or multiple metastases. Over and above that, the differences in overall survival and local control were not significant. Further studies aiming to define the exact role of this multimodal concept are warranted.

Chemotherapy is of great importance for the efficacy of radiation as local treatment.[54] Intra-arterial chemotherapy for OS was introduced in the Eighties.[55–57] Estrada-Aguilar et al.[57] reported on five pts treated with intra-arterial cisplatin and concurrent radiotherapy for nonresectable OS. Long-term local control was achieved in all the pts. Two pts were long-term survivors with no evidence of local or systemic relapse 56 and 77 months after therapy.[57] Radiosensitizers have also been used. Martinez et al.[58] reported on intra-arterial infusion of the radiosensitizer 5′-bromodesoxyuridine (BUdR) combined with hypofractionated irradiation and chemotherapy for primary treatment of OS. Nine pts were treated; local control was achieved in seven cases, and four pts survived 6–10.5 years after irradiation.

Chemotherapy was given to 85% of the pts in DeLaney's series and to all the pts in Machak's and our own series.[17,18] Local control was related to response after induction chemotherapy. All 11 pts with a good response to neoadjuvant chemotherapy achieved local control after radiotherapy. The calculated local progression-free survival among nonresponders was 31% at 3 years and 0% at 5 years.[17]

DeLaney et al.[18] analyzed 14 pts for chemotherapy response. Six pts had a good histological or imaging response, and 8 pts had either moderate or poor response. Of those with a good response, none developed local failure, but for those with a moderate or poor response, the local control rate was only 35.7% ($p < 0,05$). Mahajan et al.[53] analyzed 39 high-risk, metastatic, and/or recurrent pts treated with a combination of external beam radiotherapy to 119 sites in combination with different chemotherapeutic drugs, most commonly ifosfamide or methotrexate; 11 pts also received samarium-153-EDTMP-therapy. Objective and potentially durable responses were documented using PET-CT and bone scans. Improvement was demonstrated in 72%, of the pts, stable disease in 25% and progression in 3%.

In most cases chemotherapy can be continued during radiotherapy, but enhancement of radiation toxicity is likely to occur with several agents, and the combination of chemotherapy and radiation may result in severely acute and late side effects. This is of particular concern when the spinal cord is within the treatment volume. High-dose methotrexate should be avoided during radiotherapy. Adriamycin (doxorubicin) should be avoided because of enhanced intestinal toxicity and increased skin toxicity. Concurrent ifosfamide should be avoided if a significant volume of the bladder is in the radiation field. The nucleoside analog gemcitabine can be used as a radiation enhancer in OS.[53,59,60] Given as a radiation enhancer one day after samarium-153-EDTMP infusion, additional efficacy has been observed in some pts.[53,59,60]

Conclusions

For the majority of osteosarcomas, surgery remains the local treatment of choice. Radiotherapy is an important option as local treatment of unresectable tumors, following intralesional resection, or as palliation of symptomatic metastases. The probability of long-term survival, however, is low. Despite the fact that many of the pts will eventually die of their disease, they may benefit in terms of prolonged survival and prolonged local control. The combination of surgery, radiotherapy, and chemotherapy can be curative. The consistent use of full-dose chemotherapy is of importance for the response to radiotherapy. In the COSS series, prognostic factors for survival are an indication for RT, RT plus surgery vs. RT alone and tumor location. Prognostic factors for local control are an indication for RT, and RT plus surgery vs. RT alone.

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