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Short Communication

Long-term outcome after polychemotherapy and intensive local radiation therapy of high-grade osteosarcoma

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ABSTRACT

Background: Current standard therapy for high-grade osteosarcoma is neoadjuvant chemotherapy and complete resection of the primary tumour. Irradiation can improve local control if complete tumour resection is not possible or refused, but data on long-term outcome are not available.

Patients and methods: We report on long-term results for overall survival, occurrence of local recurrence and metastasis, joint function and side-effects in 13 patients with high-grade osteosarcoma having been treated with a combination of local irradiation and polychemotherapy (median follow-up of 13.5 years).

Results: Ten of the 13 patients were alive 4–23 years after diagnosis. Three patients suffered local recurrence, in 2 of them tumour control and long-term survival could be achieved by secondary salvage surgery and polychemotherapy. In 5 patients pathological fractures of the irradiated bones occurred, none of them was associated with local recurrence. In 7 of the 10 long-term survivors good or fair joint function was achieved.

Conclusions: We conclude that combination of chemotherapy and intensive local irradiation can achieve long-term local control and even cure in high-grade osteosarcoma. Thus radiation therapy may represent an alternative to definite surgery in selected patients, in particular in those with good response to chemotherapy, when surgery is not feasible or refused.

1. Introduction

Osteosarcoma is the most common malignant primary bone tumour in childhood and adolescence. Current standard therapy includes neoadjuvant polychemotherapy and complete resection of the primary tumour, achieving 5-year overall survival rates of about 65%.[1]

The value of radiation therapy in osteosarcoma has not yet been resolved. Reports from the pre-chemotherapy era describe radiological and histological regressions of

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osteosarcoma after intensive irradiation, but most patients died from distant metastasis due to ineffective systemic tumour control.[2–5] Combined with effective neoadjuvant polychemotherapy, local radiotherapy performed in patients after marginal tumour resection significantly improved local tumour control and survival.[6–9]

Here we report on long-term results after intensive local radiation therapy for a group of 13 patients with high-grade osteosarcoma in whom definite surgery was not feasible or refused.

2. Patients and methods

From 1977 to 2004, following informed consent 13 patients with histologically proven osteosarcoma (5 osteoblastic, 2 chondroblastic, 2 telangiectatic, 2 giant cell, 1 fibroblastic and 1 mixed osteoblastic–chondroblastic) were treated with polychemotherapy and intensive local radiation therapy (Table 1). Local irradiation was performed because amputation was refused by 11 patients and because surgery was not feasible in 2 patients (patients #10 and 13).

In 12 patients osteosarcoma was localised, in one patient (patient #9) a solitary lung metastasis was detected at diagnosis. Osteosarcoma was diagnosed as a secondary malignancy 8 years after acute lymphoblastic leukaemia in patient #8. Histological diagnosis of high-grade osteosarcoma was confirmed by two independent pathologists for all patients.

Median follow-up was 161 months (range 50–278 months). The tumour size ranged between 71 ml and 679 ml (median 216 ml). In the majority of the patients (69%) the tumour was located in the region of the knee (distal femur: 5 and proximal tibia: 4).

Polychemotherapy was performed according to the protocols of the Co-operative Osteogenic Sarcoma Study (COSS) of the German Paediatric Oncology Group (GPOH) (COSS-77/-80/-82/-91/-96).[10–12] For most patients, pre-irradiation chemotherapy consisted of high-dose methotrexate, doxorubicin and cisplatin (patients #1 and 2: cyclophosphamide instead of cisplatin; patients #5–7: plus ifosfamid).

During radiation therapy, a median tumour dose of 60 (50–70) Gy was administered using a cobalt-60 unit (patients #1–4) or a linear accelerator (patients #5–15) with parallel opposing fields in 5 fractions per week (1.8 Gy or 2 Gy per fraction).

Assessment of the joint function after radiation therapy was performed using a scale adapted to a system for functional evaluation of the Musculoskeletal Tumour Society.[13] Date of the analysis was 1st November 2008.

3. Results

3.1. Survival and local control

In all patients the clinical response to pre-radiation chemotherapy as assessed by reduction of pain and restitution of joint function was good. In 3 patients (patients #2–4) re-biopsy followed by histological examination showed less than 1% vital tumour cells.

At the time of analysis, 10 of 13 patients were alive without evidence for disease 4 to 23 years (median 13.5 years) after

Table 1 – Patient characteristics and long-term outcome after chemotherapy and local irradiation.

Patient	Age (years)	Sex	Histology	Localisation	Tumour size (cm^3)	Stage	Radiation dose (Gy)	Local recurrence (months)	Metastasis (months)	Pathological fracture (months)	Current status/months
1	12	F	Giant-cell	Distal tibia	71	T2M0	70			17	NED/203
2	11	F	Vhondroblastic	Distal femur	216	T2M0	60			12	NED/180
3	13	M	Osteoblastic	Proximal femur	679	T2M0	50			8	NED/278
4	25	M	Telangiectatic	Distal femur	207	T2M0	60				NED/277
5	14	M	Fibroblastic	Proximal tibia	179	T2M0	60	42			NED/114
6	16	M	Osteoblastic	Distal femur	245	T2M0	60	40			NED/127
7	13	M	Telangiectatic	Distal femur	198	T2M0	60			36	NED/154
8	19	M	Osteoblastic	Distal femur	169	T2M0	55			24	DOT/104
9	16	M	Osteoblastic	Proximal tibia	361	T2M1	55				NED/140
10	13	M	Chondroblastic	Ileum	462	T2M0	62	46	47		DOD/49
11	15	F	Osteoblastic	Proximal tibia	243	T2M0	60		16		DOD/40
12	17	M	Osteoblastic–chondroblastic	Distal tibia	215	T2M0	63				NED/102
13	18	F	Giant-cell	Sacrum	624	T2M0	60				NED/50

CR: complete remission; NED: no evidence of disease; DOD: dead of disease; DOT: dead of tertiary malignancy.

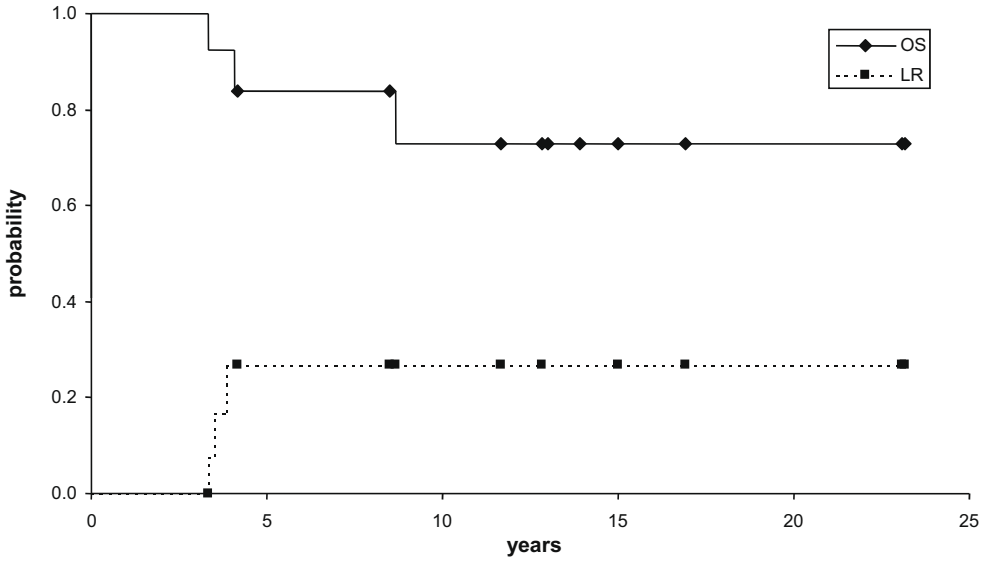

Fig. 1 – Overall survival (OS ± standard error) and cumulative incidence of local recurrence (LR ± standard error) for osteosarcoma patients after local radiation therapy.

diagnosis (overall survival 75 ± 12%, 95% confidence interval (CI): 41–91%; Fig. 1). Three patients died of metachronous pulmonary metastasis, disseminated disease following local recurrence and myelodysplastic syndrome, respectively.

Local recurrence occurred in 3 patients after 40–46 months (cumulative incidence 24 ± 4%; Fig. 1). In all 3 patients secondary chemotherapy and salvage surgery were performed (patient #5: amputation; patient #6: rotation plasty according to Borggreve[14] and patient #10: hemipelvectomy) achieving local tumour control and long-term survival in 2 of 3 patients (patients #5 and #6). Patient #10 developed distant bone metastases one month after hemipelvectomy and died from disseminated disease 2 months later.

Distant metastases occurred in 2 patients. Patient #10 developed distant bone metastases 47 months after diagnosis and died from disseminated disease 2 months later. In patient #11 multiple pulmonary metastases occurred 16 months after primary diagnosis. Despite surgical resection of the pulmonary metastases and secondary chemotherapy she died 40 months after diagnosis.

3.2. *Side-effects and functional results*

In 7 of 10 living patients the affected limb could be preserved (Table 2). One of these 7 patients (patient #13) suffered from intermittent pain in the affected limb necessitating analgesic treatment. Three of the 7 patients (patient #3, patient #7 and patient #13) reported of minor disabilities resulting in gait alterations, but none of the patients required walking supports.

Due to local recurrence followed by secondary salvage surgery, the affected limb could not be preserved in 2 patients (patient #5: mid-thigh amputation and patient #6: rotation plasty according to Borggreve). In one patient (patient #2) local recurrence was suspected, but histologically excluded after amputation.

Eight to 36 months after primary diagnosis, in 5 patients pathological fracture of the irradiated bone occurred. Four patients were treated successfully either conservatively with immobilization (patients #1 and #8) or with osteosynthesis (patients #3 and #9). None of these patients suffered local recurrence.

Table 2 – Long-term functional results after chemotherapy and local irradiation.

Patient	Function	Pain	Walking supports	Gait	Total
1	No disability	No	No	No alteration	Good
2	Amputation				
3	Minor disability	No	No	Minor alteration	Fair
4	No disability	No	No	No alteration	Good
5	Amputation				
6	Borggreve plasty				
7	Minor disability	No	No	Minor alteration	Fair
8					
9	No disability	No	No	No no alteration	Good
10					
11					
12	No disability	No	No	No alteration	Good
13	Minor disability	Intermittent	No	Minor alteration	Fair

One patient (patient #8) who suffered from osteosarcoma as secondary malignancy 8 years after acute lymphoblastic leukaemia, died of myelodysplastic syndrome 8.5 years after the diagnosis of osteosarcoma.

4. Discussion

From 1980 to 1998 only 26 of 1702 children with high-grade osteosarcoma registered within the COSS protocols received radiation therapy instead of surgical tumour resection achieving a 10-year overall survival of 31.5%.[1]

There are few reports describing effective local control after irradiation instead of tumour resection.[15–17] In the largest study group published yet, local tumour control after irradiation with 50–60 Gy was achieved in 22 of 31 patients.[18] In addition, radiotherapy performed after incomplete tumour resection, which is associated with a survival of less than 20%,[1,19] significantly improved local control and survival for this group of patients.[6–9] So, unless there is some evidence that selected patients with high-grade osteosarcoma may benefit from local radiation therapy, there are no data about long-term results after local irradiation instead of surgical tumour resection.

Our results indicate that long-term local control and even cure can be achieved by a combination of polychemotherapy and intensive local radiation therapy. If good response to chemotherapy is a prerequisite for effective irradiation remains speculative, as all patients showed good clinical response after neoadjuvant chemotherapy. Local radiation therapy can safely be administered, and functional results are predominantly good or fair. Because of the small number of patients, the survival rate calculated here, though encouraging, cannot be compared with the survival rate after standard therapy. It shows, however, that a substantial part of the patients are long-term survivors. The occurrence of slowly healing pathological fractures as well as an increased risk for the development of secondary malignancies has to be taken into consideration.

The development of new irradiation modalities that allow to precisely deliver high radiation doses to osteosarcoma lesions may further increase the efficiency of local tumour control by radiation therapy.[20,21] Treatment with radiosensitising agents (e.g. samarium) might improve tumour control by irradiation with low toxicity.[22–24]

In addition, a combination of irradiation and surgery for local treatment should be considered for tumours poorly responding to chemotherapy (pre-operative irradiation), or in case of R1- or R2-resections (post-operative irradiation).[7,25]

In conclusion, complete surgical resection undoubtedly remains the local treatment of choice in high-grade osteosarcoma and limb-sparing tumour resection nowadays can be performed in most patients. However, our data indicate that radiation therapy is a realistic and curative treatment option in individual patients which should be offered to patients with tumours not accessible to surgery (e.g. spine and pelvis) and to patients who definitely refuse (non-limb-sparing) surgery.

Conflict of interest statement

None declared.

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