Ewing's sarcoma of the femur

Prognosis in 69 patients treated by the CESS group

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We reviewed the treatment outcome of 69 patients with Ewing's sarcoma of the femur. The patients received chemotherapy according to the CESS 81 (n 14), CESS 86 (n 43), and CESS 91P (n 12) protocols. The 10-year relapse-free survival rates were 36%, 65%, and 65% (p = 0.01). 68 patients received local treatment. The primary tumor was treated by surgery without radiotherapy in 28 patients; 1 developed a local recurrence and 7 metastases. 10 patients received radiotherapy alone; 4 developed metastases and 4 local recurrences and metastases. 30 cases had a combination of surgery and radiotherapy; 7 developed metastases and 1 a local recurrence and metastasis. The survival of patients after radiotherapy alone was worse than that of patients after surgery with/without radiotherapy (p = 0.005). Pathological fractures (n 16) did not influence the prognosis.

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Submitted 96-03-09. Accepted 96-11-07

Treatment and outcome of Ewing's sarcoma may differ according to the anatomical site of the tumor. However, there are only a few reports focusing on specific sites (Frassica et al. 1993, Grubb et al. 1994, Ozaki et al. 1995). The first Cooperative Ewing's Sarcoma Study (CESS 81) was initiated in 1981 by the German Society of Pediatric Oncology and Hematology (Jürgens et al. 1988). Since then, 535 protocol patients have been treated according to CESS trials. We analyzed the outcome in 69 CESS patients with Ewing's sarcoma of the femur.

Patients and methods

The 69 patients in this study had Ewing's sarcoma (63) or primitive neuroectodermal tumor (PNET) (6) of the femur and were treated according to the CESS 81 (n 14) or 86P/86 (n 43) or 91P (n 12). The CESS 81 trial was composed of a 4-drug regimen (VACA) which consisted of vincristine, actinomycin-D, cyclophosphamide, and adriamycin (Jürgens et al. 1988). CESS 86 had 2 arms to the regimen: VACA in patients with standard risk (peripheral or small-volume tumor) and VAIA in those at high risk (central or large-volume tumors) in which cyclophosphamide was replaced by ifosfamide (Jürgens and Treuner 1989). As CESS 86P was a pilot study of CESS 86, 11 patients in CESS 86P and 32 patients in CESS 86 were analyzed together. In CESS 91P, high-risk patients received either VAIA or additional etoposide as a fifth agent (EVAIA) (Tables 1 and 2).

Patients with primary distant metastases were not in the study. However, 4 patients who had skip metastases in the same bone were included. The median age of patients was 14 (2–26) years. Pathological fractures before local treatment occurred in 16 patients (Tables 1 and 2).

Most tumors had a proximal localization (Figure 1). The volume of the tumor was calculated by the method described by Göbel et al. (1987) (Table 1). A tumor volume ≥ 100 mL was defined as large (60 patients) and < 100 mL as small (9 patients) according to the definition of the CESS group.

All surgical margins were classified according to Enneking (1980) (Table 3). The surgical specimen was examined histologically and the chemotherapy response was classified in 6 grades, according to Salzer-Kuntschik et al. (1983).

52 of the 69 patients underwent a reconstruction. 17 of 38 patients who had a tumor of the proximal femur underwent a prosthetic replacement, 9 had rotationplasties, 2 intercalary bone grafts, 3 were amputated, and 7 had no surgery. 14 of 31 patients with a tumor of the diaphyseal or distal femur had a prosthetic replacement, 8 had rotationplasties, 2 intercalary bone grafts, 3 were amputated, and 4 had no surgery. Functional evaluation was performed according to Enneking (1987).

Table 1. Patients with Ewing's sarcoma of the femur

Variable		n	Relapse (n)			10-year relapse-free survival rate	P-value univariate analysis
			Local	Local and Systemic	Systemic		
Site	Femur	69	1	5	19	0.59	0.7
	Other site	290	30	15	65	0.56	
Sex	Male	40	1	4	9	0.62	0.5
	Female	29	0	1	10	0.55	
Age (years)	<10	18	0	1	6	0.56	0.7
	10–20	43	1	4	12	0.57	
	20>	8	0	0	1	0.75	
Volume	Small	9	0	1	0	0.78	0.2
	Large	60	1	4	19	0.57	
Component	Proximal	38	0	4	12	0.56	0.3
	Others	31	1	1	7	0.63	
Pathological fracture	Positive	16	0	1	4	0.58	0.4
	Negative	53	1	4	15	0.60	
Protocol	CESS 81	14	0	4	5	0.36	0.02
	CESS 86P+86	43	0	1	12	0.65	
	CESS 91P [a]	12	1	0	2	0.65	
Local treatment	Surgery alone	28	1	0	7	0.61	0.005
	RAD alone	10	0	4	4	0.20	
	Surgery+RAD	30	0	1	7	0.73	
	None	1	0	0	1		
Histological response	Grades 1–2	34	1	0	4	0.78	0.005
	Grades 3–6	21	0	1	9	0.51	

[a] Including 4 skip metastases

Table 2. Treatment modalities according to the CESS protocols

Protocol	Surgery alone	Surgery and radiation	Radiation alone	None	Total
81	6	3	4	1	14
86	15	22	6	–	43
91P	7	5	–	–	12

Table 3. Surgical margin and relapse pattern

Margin	Radio-therapy	Relapses			Total
		Local	Local and systemic	Systemic	
Radical	–	0	0	0	0/5
	+	0	0	0	0/1
Wide	–	1	0	7	8/21
	+	0	0	4	4/23
Marginal	–	0	0	0	0/1
	+	0	1	2	3/5
Intralesional	–	0	0	0	0/1
Unknown	+	0	0	1	1/1
(–) [a]	+	0	4	5	9/11

[a] 10 patients with definitive irradiation and one with no local treatment

The median radiotherapy dose was 45 (36–61) Gy. The recommended dose for definitive radiotherapy for extremities was 46 or 60 Gy (randomized) in CESS 81 and 60 Gy in CESS 86 (Dunst et al. 1991). The recommended dose of postoperative radiotherapy was 36 Gy in CESS 81 and 45 Gy in CESS 86 (Dunst et al. 1991). The median dose of the preoperative radiotherapy in 5 patients in CESS 91P was 44 (36–50) Gy.

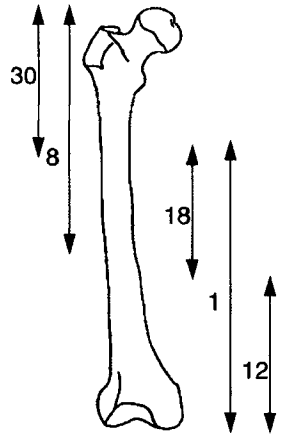

Figure 1. Location of tumor in the femur.

The median follow-up period of surviving patients was 60 (27–136) months. Relapses were classified as local (local recurrence alone), systemic (metastasis alone), and combined (local recurrence and metastasis).

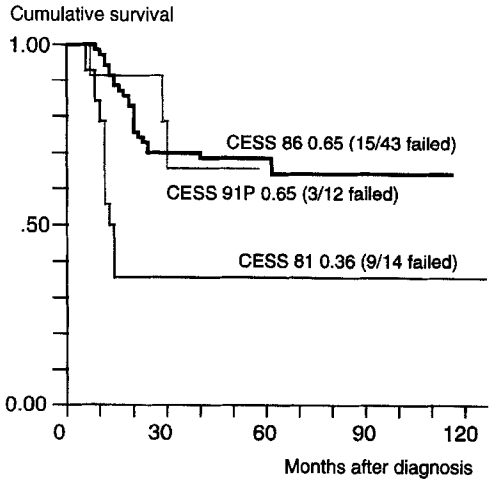

Figure 2. Relapse-free survival according to the trials of CESS 81 to 91P. The relapse-free survival of CESS 86, 86P, and 91P

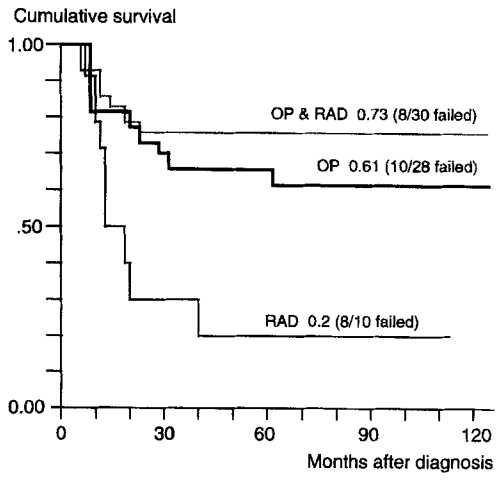

Figure 3. Relapse-free survival according to type of local treatment. The relapse-free survival of the patients who underwent definitive surgery or surgery with irradiation was significantly better than that of the patients who underwent definitive irradiation (p = 0.005).

Statistics

Differences in the relapse rate were compared with the chi-square test. The cumulative probability of relapse-free survival was calculated by the Kaplan-Meier method. Tests of the difference between or among survival curves were carried out using log-rank tests. Cox multivariate analysis of independent prognostic factors for relapse-free survival were performed. A p-value < 0.05 was considered significant.

Results

The 10-year relapse-free survival was 0.6 (27/69 failed). There were 1 local, 19 systemic, and 5 combined relapses (Table 1). Of 25 patients who had relapses, 22 patients died of disease and 3 patients are alive. 2 patients died without a relapse—i.e., 1 patient died of poor general condition and cachexia without detection of a tumor relapse and the other patient died of a treatment complication (heart failure).

Treatment modalities and prognosis

The local control rate differed between CESS 81 (4/14) and CESS 86 (1/43) or 91P (1/12) (p = 0.01). The relapse-free survival rate for the patients in CESS 81 was lower than that in CESS 86 or CESS 91P (p = 0.02) (Table 1, Figure 2). Sex, age, tumor volume and tumor location did not correlate with local recurrence or survival.

The local control rate for the patients who underwent surgery with/without radiotherapy was better than that for radiotherapy alone (p = 0.003). The systemic relapse rate for patients who underwent surgery with/without radiotherapy (14/58) was not different from that of patients with radiotherapy alone (4/10) (p = 0.4). The systemic or combined relapse rate for the patients who underwent surgery with/without radiotherapy was lower than that of patients with radiotherapy alone (p = 0.002). The relapse-free survival of patients treated with radiotherapy alone was lower than that of patients with surgery or with combined therapy (p = 0.005) (Table 1, Figure 3).

Pathological fractures and prognosis

9/38 proximal cases and 7/31 diaphyseal to distal cases had fractures before local treatment. 13 of these 16 patients had a fracture before chemotherapy. In 10/13 patients (6/8 proximal and 4/5 distal) who were treated with a hip spica the fracture healed before surgery. 7 patients underwent limb salvage surgery, 4 hip rotationplasty, 4 amputation, and 1 radiotherapy alone. In the 15 patients who underwent surgical resection of the tumor, 4 patients had a radical margin, 10 had a wide margin, and 1 a marginal margin. The presence or absence of a fracture did not correlate with the outcome.

Surgical margin and relapses

1 local and 11 systemic relapses occurred in 50 patients after surgery with adequate (6 radical or 44 wide) margins (Table 3). 1 local and systemic and 2 systemic relapses occurred in 7 patients after surgery with inadequate (6 marginal or 1 intralesional) margins.

Table 4. Multivariate analysis of factors related to relapse-free survival

Covariate	Coeff.	SE	RR	95% CI	P-value
Size	0.20	0.20	1.0	–0.1–1.0	0.2
Site	0.10	0.10	1.0	–0.1–0.3	0.4
Fracture	0.03	0.10	0.2	–0.2–0.3	0.8
Protocol	0.30	0.10	2.0	–0.02–1.0	0.07
Treatment	0.40	0.20	2.0	0.04–1.0	0.03

SE Standard error, RR relative risk, CI confidence interval

Histologic response and relapse

The relation between histologic response and relapse was evaluated in 55 patients (Table 1). The 10-year relapse-free survivals between grades 1–3 and 4–6 responses were not different (p = 0.10). However, there was a difference between grades 1–2 and 3–6 responses (p = 0.005).

Multivariate analysis

Tumor volume (< 100 or ≥ 100 mL), tumor site (proximal or others), pathological fracture, CESS protocol (81 or others), and local treatment (with or without surgery) were entered as nominal covariates into a Cox proportional hazards model (69 patients) (Table 4). Histological response to chemotherapy which was univariately significant was excluded from the multivariate analysis because the histological response of only 55 patients was available. Treatment without surgical resection of the tumor was an independently unfavorable prognostic factor. The type of protocol lost its univariate significance.

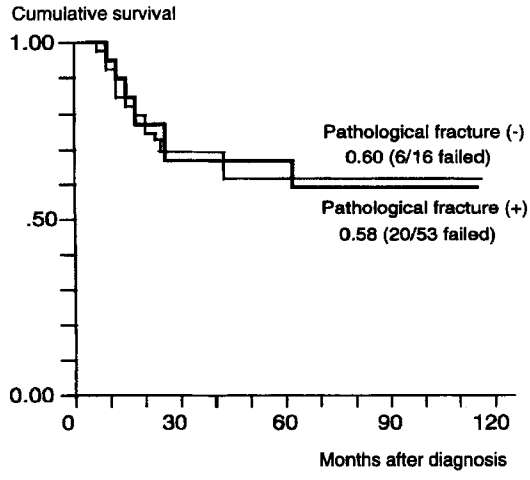

Figure 4. Relapse-free survival according to the existence of a pathological fracture before local treatment. Relapse-free survival of patients who had a pathological fracture was not significantly different from that of patients who did not have a pathological fracture (p = 0.4).

Discussion

The 10-year relapse-free survival of 69 patients with Ewing's sarcoma of the femur was 0.6. This is the same as that of 290 patients with Ewing's sarcoma in the other sites (121/290 failed, unpublished CESS-data) (Table 1). There are a few reports on survival rates for patients with Ewing's sarcoma of the femur: 0.4 in 32 patients with tumor of the proximal limbs (Wilkins et al. 1986), 0.4 (5–16 years' follow-up) in 27 patients with tumor of the femur (Bacci et al. 1989), and 0.6 (10 years median follow-up) in 16 patients with tumor of the proximal femur (Damron et al. 1996).

There was no difference in the relapse-free survival between patients with large and small tumors. In contrast, the CESS 81 study reported that tumor volume was a prognostic factor (Göbel et al. 1987). In the CESS 86 trial, patients with large tumors received an intensified regimen where conventionally-dosed cyclophosphamide was replaced by high-dose ifosfamide (Jürgens et al. 1989). With this risk-stratified regimen, tumor volume was no risk factor in the study.

16 of 69 patients had pathological fractures before local treatment. In 12 patients, the fractures consolidated during preoperative chemotherapy. Healing during preoperative chemotherapy has previously been documented (Rosen et al. 1978, Simon and Nachman 1986, Hayes et al. 1989). The existence of a pathological fracture did not influence the prognosis of the patients (Figure 4).

The CESS 81 study showed that patients with good response (grades 1–3) had a better relapse-free survival than those with poor response (grades 4–6) (Jürgens et al. 1988). Three quarters of the patients in our study have a good response and there was no difference in the prognosis between good and poor groups. In this study, we used a more restrictive cut-off point for the classification of histologic response. When the cut-off point was inserted instead between grades 2 and 3, the patients in the good response group had better prognoses than those with a poor response.

The high local or combined relapse rate of the 14 patients in CESS 81 was mostly caused by a high local failure rate when radiotherapy alone was used for local control. Of 4 patients who received radiotherapy alone in CESS 81, 1 patient developed a systemic relapse and 3 had combined relapses. A radiation planning center for CESS trials was established in 1983 (Jürgens et al. 1988), but the 3 patients who developed combined relapses were treated prior to this

time. Since 1983, the radiation portals were planned according to the extent of the disease at diagnosis before and not after chemotherapy (Jürgens and Treuner 1989). Surgery, however, was based on the radiographic examinations after preoperative treatment. In the 63 patients treated after 1983, the incidence of local failures decreased to 1 of 7 patients who underwent radiotherapy alone and none of the 56 patients who had a combination of surgery and radiotherapy.

In 1989, Bacci et al. reported no local recurrences in 120 cases of Ewing's sarcoma treated with surgery and radiation therapy, but with radiotherapy alone 10/30 patients had a local recurrence. The data in the Intergroup Ewing's Sarcoma Study (IESS)-II estimated the 5-year survival rate to be slightly better (not significant) for patients after resection of a tumor with/without radiotherapy, compared to patients after radiotherapy alone for local control (Burgert et al. 1990). In our study, 4 of 10 patients had a local or combined relapse after irradiation alone and 1 of 30 patients had local or combined relapses after surgery combined with irradiation.

2 patients had pathological fractures at the tumor site 8 and 12 months after local treatment by radiotherapy alone. Osteosynthesis failed, and hip disarticulation was finally performed in both. The optimal surgical margins for Ewing's sarcoma of the femur are still not known. The local or combined relapse rate after surgery was small in our series and the number of patients who underwent surgery with radical, marginal, or intralesional margins is too small to permit any conclusions (Table 3).

Since the initiation of CESS 91P, preoperative radiotherapy is recommended to sterilize further the tumor-bearing compartment before surgery in patients with a poor response to initial chemotherapy (Ozaki et al. 1996). Resection of the involved bone after preoperative irradiation would reduce the risk of postradiation sarcoma (Frassica et al. 1993). Local and systemic control with preoperative irradiation has not yet been reported in Ewing's sarcoma. However, preoperative irradiation and surgical resection of the irradiated bone may be a good treatment for preventing pathological fractures and second malignancies.

Acknowledgements

The authors thank Mrs. S. Jabar for the statistical analysis and her help in preparing the manuscript. Funds were received in total or partial support of the research or clinical study presented in this article. The funding sources were the "Deutsche Krebshilfe" (grant # M43/92/Jü2) and EC BIOMED I (grant # BMH1-CT92-1341).

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