

3 weeks from biopsy into the German-Austrian-Swiss multicenter study COSS-86 between 2/86 and 11/88 were considered eligible. Doxorubicin, high-dose methotrexate, and DDP were given to low-risk patients. Patients fulfilling at least one of three defined high-risk criteria received early systemic intensification by adding ifosfamide. High-risk patients received preoperative DDP i.a. or i.v.

Results: 7-year event-free/overall survival of 171 eligible patients (128 high-risk; 41 low-risk, 2 dead prior to stratification) was excellent at 68%/76%, superior to that of all our previous studies. When 12 patients with severe protocol violations (5 x no surgery, 7 x major chemotherapy violation) were excluded, event-free/overall 7-year survival of 159 fully evaluable protocol patients was 72%/79%. Treatment results were not influenced favorably by giving DDP i.a. Cumulative treatment toxicity, especially cardio- and ototoxicity, was a significant problem.

Conclusion: Early treatment intensification for high-risk patients by adding ifosfamide as the fourth agent to an already intensive three-drug regimen led to excellent long-term outcome in our multicenter trial. No additional benefit was obtained by using the i.a. route to administer DDP. Toxicity was considerable.

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ORAL

Quality of life in sarcomas treated with limb salvage surgery or amputation

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Purpose: In the present study the functional outcome and quality of life after amputation (Amp) was compared with that after limb salvage surgery (LS).

Method: The functional outcome (Amp = 58 pts, LS = 89 pts) was evaluated by use of the Enneking System for Functional Evaluation (ES) and quality of life (Amp = 16 pts, LS = 28 pts) by use of the EORTC C-30 questionnaire (QLQ-C30) and the Activity Daily Living Scale (ADL). In the LS group the treatment was surgery alone in 50% and combined surgery and radiotherapy/chemotherapy in 50%. Median age 49 years (14-88). Median tumour diameter 8 cm (1-20). Median follow-up time 3.6 years (1-11). The two groups were comparable according to age, sex, size, location and of tumour and follow-up time.

Results: The functional scores were significantly higher after LS as compared to Amp, the median score being 85 and 47, respectively ($p < 0.001$). A similar difference was observed if the ES scores was subdivided into general health related scores and extremity related scores. The correlation between ES and QLQ-C30 was good in the LS group, but poor in the Amp group. In contrast, the correlation between ES and ADL was good in all patients. The reason for the poor correlation in the Amp group could be due to compensation or poor sensitivity of the QLQ C-30 in this group of patients.

Conclusion: The data may indicate that limb salvage surgery is associated with a better functional outcome than that observed after amputation, whereas a similar improvement in quality of life was not found. Further quality of life studies are needed in these patients.

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POSTER

Brachytherapy improves outcome of radiotherapy for soft-tissue sarcoma of the extremities

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Purpose: Local control in soft-tissue sarcoma can be improved with adjuvant external-beam radiotherapy (EBRT) or brachytherapy. This analysis was conducted to find if combining the two modalities can lead to further gains.

Methods: Of 85 patients with extremity soft-tissue sarcoma treated with adjuvant radiotherapy, 37 had their boost delivered via an interstitial implant. Survival and local relapse were computed using Kaplan-Meier methodology and differences between groups were tested using the log-rank test.

Results: With a median follow-up of 4 years, 21 patients (25%) relapsed locally. Five-year local control rates in patients treated with EBRT and EBRT+brachytherapy were 59% and 87%, respectively ($p = 0.04$). This difference was most pronounced in patients with macroscopically positive margins (86% vs. 48%, $p = 0.04$) or with high-grade tumors (83% vs. 60%, $p = 0.06$). Survival, however, was not significantly impacted (68% vs. 61%).

Conclusions: Superior local control can be achieved with an interstitial implant boost. This may result in better limb preservation and improved

quality of life. Patients with positive margins or with high-grade tumors stand to gain the most from this technique.

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POSTER

Preoperative radiochemotherapy in the treatment of Ewing's sarcoma

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Purpose: In the European study EICESS 92 preoperative radiochemotherapy was invented in the treatment of locally advanced Ewing's sarcomas. The feasibility of this modality and the local and systemic control are examined and compared with the standard local treatment.

Methods: From April 1991 to July 1995 83 patients with Ewing's sarcoma received simultaneous preoperative radiochemotherapy. The dose was either 44.8 Gy or 54.4 Gy depending on the expected margins of resection. Usually, radiotherapy was given as a hyperfractionated accelerated split course regime. 43 patients in EICESS received radiotherapy, 41 patients operation alone. 34 patients received postoperative irradiation. Chemotherapy consisted of either VAIA or EVAIA. In a subgroup of 52 patients treated at the University of Münster, the complication rate was examined. The median follow up of the study is 21 months.

Results: The operative and perioperative morbidity was not increased. Postoperative chemotherapy could be started without delay after a median interval of 17 days. After preoperative irradiation, 16 patients relapsed including 1 local relapse. After radiation alone 15 patients relapsed including 6 local relapses. Of the purely operated patients 4 relapsed with 1 local failure; after postoperative irradiation there were 7 relapses including 1 local failure.

Conclusion: Preoperative radiochemotherapy is a well tolerated treatment modality. The local control rate is good, especially considering the usually large primaries. Up to now, no reduction of systemic relapses could be observed.

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POSTER

Chemotherapy for heavily pretreated patients (pts.) with bone (BS) and soft tissue (STS) sarcomas

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Introduction: No second-line chemotherapy is established for bone and soft tissue sarcomas. Some activity has been reported for high-dose ifosfamide (HDI) in STS and carboplatinum plus VP 16 (CV) in BS.

Methods: A total of 51 pts. (39 males: median age = 29, 12 females: median age = 38) with BS (24) or STS (27) were treated with HDI (46 pts.) or CV (16 pts.). 11 pts received both therapies consecutively. Treatment consisted of ifosfamide 3.5 g/m²/day as a continuous infusion days 1-5 with mesna 2.5 g/m²/day and G-CSF days 6-15 or carboplatinum 150 mg/m²/day days 1-4 plus VP 16 150 mg/m²/day days 1-4.

Results: HDI: 3 pts. are still under treatment. So far, a CR/PR was seen in 16/43 pts. (37%), SD in 7/43 and PD in 13/43 pts. Toxicity was severe with 100% grade 3/4 myelotoxicity. In 5 pts. treatment had to be stopped after the first cycle due to CNS- or nephrotoxicity. 2 toxic deaths occurred.

CV: A PR was seen in 2/16 pts. (12%), SD in 1/16 and PD in 10/16 pts. Toxicity was very severe with 100% grade 3/4 myelotoxicity, grade 3/4 nephrotoxicity requiring hemodialysis in 2/16 pts. and septicemia leading to cessation of treatment in 1 and toxic death in 2 pts.

Conclusions: HDI shows activity in heavily pretreated pts. with both BS and STS. However, toxicity is substantial and patients selection crucial. CV cannot be recommended due to low activity and very severe toxicity.

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POSTER

Preoperative radio-chemo-therapy of soft tissue sarcomas – First results

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Purpose: Neoadjuvant therapy is a promising new treatment modality for organ preserving therapy of huge soft-tissue sarcomas.

Methods: From 1993 until 1996 17 patients (pts.) with primary (N = 11); recurrent (N = 4) or metastatic (N = 2) soft tissue sarcomas were treated with preoperative concurrent radio-chemo-therapy (RCT). Sarcomas were localized in the extremities (N = 10); the trunk (N = 4); head and neck region (N = 2) and in the penis (N = 1). Chemotherapy consisted of ifosfamide 1.5 mg/m² and mesna (d 1–5 and 29–33) as well as adriamycin 50 mg/m² (day 2 and 30). Accelerated-hyperfractionated radiotherapy (RT) was applied in 2 fractions/d of 1.5 Gy up to 56 to 60 Gy (day 1–45; after 30 Gy 1 week RT-break). After 4–8 weeks residual tumour mass was excised according to the guidelines of oncological surgery.

Results: Following neoadjuvant RCT 16/17 patients were treated by surgery. All the 16 pts had a histologically complete resection (R0). In 4/16 pts (25%) there was no vital tumour in the specimen. Limb sparing surgery was possible in 7/10 pts. Myelosuppression was most prominent with leucopenia grade 4 in 6/17 and grade 3 in 4/17 pts; thrombocytopenia in grade 3 in 2/17; grade 4 in 1/17. Skin toxicity was grade 3 in 5/17 and grade 4 in 1/17.

Conclusion: Preoperative RCT is feasible with acceptable toxicity. First results indicate that perhaps more R0 resections may be possible compared to surgery alone.

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POSTER

Serum levels of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) in patients (pts) with soft tissue sarcoma (STS)

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Purpose: To determine if elevated circulating levels of VEGF and bFGF can be detected in sera from pts with STS.

Methods: 18 healthy controls and 55 STS pts were enrolled in this study. In STS pts sera were drawn prior to initial resection (IR) n = 31 or prior to wide reexcision (WR) 2–4 weeks after inadequate local excision n = 24. VEGF and bFGF levels were determined by ELISA.

Results: Mean levels pg/ml (range) for VEGF and bFGF in healthy controls were 167 (22–404) and 3 (1–9). In STS pts with IR, VEGF levels were 628 (64–2000) and bFGF levels 16 (1–50). 17 STS pts with evidence of disease after WR showed following serum levels: VEGF 515 (44–2000), bFGF 26 (1–78). For 7 STS pts with no evidence of disease after WR the VEGF and bFGF levels were 350 (94–1150) and 23 (1–58).

Conclusion: Elevated VEGF and bFGF levels can be detected in sera from STS pts. Consecutive monitoring of VEGF and bFGF in the serum of STS pts might be a valuable new marker to monitor the tumor follow up.

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POSTER

Intraoperative (IORT) and external beam radiotherapy (EBRT) for extremity sarcomas

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Purpose: IORT offers maximum sparing of mobile radiosensitive tissues. Organs and tissues of the extremities are less radiosensitive. Nevertheless the minimum effective dose for soft tissue sarcomas should be >66 Gy. Late complications and subsequent limb function are related to dose and irradiated tissue volume.

Patients and Methods: 25 patients (mean age 51.5 years), suffering from a stage IIB–IIIB extremity sarcoma had IORT between 7/91–5/95 (recurrent sarcomas n = 10). 4 pat. revealed microscopically residual disease after surgery. IORT dose was 15.3 Gy (15–20 Gy), using a field size 5–26 cm. Mean EBRT dose was 44 Gy.

Results: After a median follow-up of 28.8 months a 92% local control rate could be achieved. The local control rate was independent of the extent of surgical margins and tumor stage. 2 pat. had a lymph node failure, 5 pat. a distant failure. The actuarial overall and disease-free survival was 77% and 58% at 4 years. Perioperative morbidity occurred in 17% of pat., requiring additional surgical treatment in 11% of pat. In 14% of patients a late adverse effect was observed.

Conclusion: Combined surgical resection and IORT for locally advanced extremity sarcomas can provide excellent local control. In view of the reduced late morbidity with subsequent good limb function, the results are encouraging.

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POSTER

Retroperitoneal sarcomas – Prognostic value of ploidy and other important factors

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Purpose: Grading and type of surgery are very important for prognosis in all types of sarcomas. For the better understanding of outcomes and possibilities of treatment retrospective analysis of different factors, including DNA content, was performed in retroperitoneal sarcomas.

Methods: The study was based on 70 patients treated between 1965 and 1994. Leiomyosarcoma and liposarcoma were most common histologic type of classified sarcomas. Different kinds of resection were performed in 49 patients and 33 of theirs available DNA specimens were analysed.

Results: The actuarial 5-years survival rate in resection group was 53% with the median survival of 57 months (compared with 10 months without resection). Patients with diploid resected tumours had better 5-years survival rate (58%), than with aneuploid (25%) – P < 0.005. Patients with grade I and II sarcomas had a significantly longer survival than with grade III (5-years survival rate 44% compared with 29%). There was no influence of adjuvant therapy, histology, type of surgery, localisation of tumour and S-phase on survival in the univariate analysis. In the multivariate analysis (Cox), only ploidy was independent prognostic variables for survival. Relative risk of death was over 3 times higher for aneuploid than for diploid tumours.

Conclusion: The DNA content analysis is an important prognostic factor, which should be performed in every case of retroperitoneal sarcoma for better follow-up and possibility of adjuvant therapy.

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POSTER

Ifosfamide (IFO) in continuous infusion (C.I.) for 21 days as second line therapy in advanced sarcomas: A phase I study

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Ifosfamide is an alkylating agent active in advanced soft tissue and bone sarcomas. Generally we distinguish between conventional doses and high doses (from 10 to 15 g/sqm for cycle). High doses, delivered in 4–5 days, of c.i. must be reserved to good P.S. pts and request CSF support. In poor P.S. pts or as a second-line therapy, the same total dose can be administered in longer time in order to avoid heavy toxicities with a comparable relative dose intensity. From this rationale, we planned a 21 days-therapy using a low-daily-dose (1 g/sqm). The solution including Ifo and Mesna (1 g/sqm/day equidose), was administered by portable pump as outpatient therapy. Pump was changed every 3 days and the course should be completed at 21st day. Therapy was discontinued until recovery when neutrophil counts was <1500/mm³ or creatinine >1.5 mg/dl. 6 patients (3 male, 3 female) with advanced soft tissue and bone sarcomas, relapsed after first line CT, entered the study. Mean P.S. was 1 and mean age was 37.5 years (median 35). 15 courses were administered (mean 2.5, median 3). No course was completed in 21 days. Only one was completed in 28 days and 14 in more than 28 days. Definitive D.I. was 63%. The delay was due to grade 3 but rapidly recovering myelotoxicity. No other side effects were seen. Generally toxicity appeared after 15 days of c.i. We recorded 1 CR (pelvis relapse of Ewing sarcoma), 1 PR and 4 PD.

Conclusions: Low doses of Ifo as a c.i. in advanced sarcomas seems to be a promising therapy with a good activity and a mild toxicity. However, 21 days c.i. is too much for pretreated patients; in a new protocol we'll use the same daily dose but only for 15 days infusion.

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POSTER

Evidence of circulating tumor cells of Ewing's sarcoma is associated with higher incidence of local relapse and metastatic spread

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Background: Different variables have been studied to predict the probability of recurrence and metastases in patients diagnosed of Ewing's sarcoma. In this study, we have evaluated the presence of tumor cells of Ewing's sarcoma (ES) in peripheral blood samples through a reverse-transcriptase polymerase chain-reaction (RT-PCR).