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Prognostic factors predictive of survival for retroperitoneal soft-tissue sarcoma in The Netherlands

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Purpose: Surgery is the principle modality of therapy in the management of sarcomas. Retroperitoneally located soft-tissue sarcomas (RSTS) are rare and individual surgical experience is usually limited. This might lead to a defeatist attitude. There are no data available on the outcome in RSTS in the Netherlands. Therefore, prognostic clinical and histopathological factors in survival outcome were identified in patients with RSTS.

Methods: Using a national histopathological database, pathologists and surgeons were sent a questionnaire about all patients in the Netherlands in whom the diagnosis RSTS was confirmed histologically between 1988 and 1993 (n = 136). Data were obtained regarding 57 patients. Median age was 58 years and there were 30 men (53%). In 7 patients the tumour was considered irresectable, 3 patients had recurrent disease and 47 patients were surgically treated for primary RSTS. The prognostic importance of the following variables was evaluated: extent of surgery and the histopathological type and grade. The median follow-up, to July 1996, was 38 months.

Results: Hospital mortality was 7% for operated patients. 1-, 3-, and 5-year overall survival was 80%, 61% and 46% respectively. Median survival after radical tumour resection was 73 months, compared to 14 months after macroscopically irradical resection (p = 0.05) and 5 months in patients treated non-surgically (p = 0.008). The 3 patients who underwent resection of recurrent RSTS were alive 5 years postoperatively. Liposarcomas were associated with a more favourable median survival (85 months,) than fibrosarcomas (45 months, ns) and other histological types (25 months, NS). Low grade sarcoma was a significant prognostic factor when compared to high grade malignancy (p = 0.04).

Conclusion: The major factor in survival outcome after treatment of retroperitoneal soft-tissue sarcoma is the complete resection of the lesion. Surgical efforts should be aimed at a radical resection, defeatism is not justified.

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Surgical management of primary and recurrent soft tissue sarcomas of the retroperitoneum

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The purpose of this study was to identify prognostic factors for survival of soft tissue sarcomas of the retroperitoneum, and to determine the quality of the excision according to their extension to adjacent organs. One hundred seven patients treated for a retroperitoneal sarcoma between 1970 and 1995 were retrospectively reviewed. Univariate log rank analysis was used. Local recurrence rates were calculated after a complete macroscopic excision of the tumor whether an organ was attached to the tumor when resected, or not. Specific recurrence rates were calculated per attached organ types.

Complete excision, and a low histoprognostic grade were the most significant prognostic factors. Resection of attached organ to the tumor has significantly reduced the risk of local recurrence when the organ implicated was the bowel (from 28.2% to 0%), the upper urinary tract (from 45% to 3.7%), and the abdominal wall (from 40% to 14.3%). The resection of an organ attached to the tumor has not reduced the risk of local relapse for organs such as the liver, spleen, pancreas, blood vessels, nerves, and nondigestive pelvic organs. Complete surgical resection rates were the same regardless of tumor size, or whether they were primary or recurrent tumors.

Excision must be complete at initial surgery, and extended to the bowel, the kidney, and the abdominal wall when there is an obvious contact between the tumor and an adjacent organ.

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Recurrent gastrointestinal sarcoma: Survival analyses and patterns of failure

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Purpose: To identify prognostic factors in recurrent gastrointestinal sarcomas (GS).

Method: 60 patients with recurrent GS were identified from a prospective data base of 2865 soft tissue sarcoma admissions to a single institution between 1982–1995. Tumour specific mortality was estimated by the log-rank test and significant univariate ($p < 0.05$) factors subjected to multivariate analysis by Cox's regression.

Results: 23 female and 37 male patients were identified. Median age was 55 yrs. Sites of primary tumour were: 16 gastric, 36 small bowel, 4 colonic and 4 rectal. 48 primary tumors were high grade and 12 low. The median primary tumor and recurrent tumor size was 7 cm. In 15% of patients recurrence was diagnosed by non-symptom directed computed tomography, the remainder were symptomatic.

At a median follow up of 38 months from treatment of the primary and 13 months from recurrence 48 patients were dead of disease, 9 alive with disease and 3 with no evidence of disease. Complete resection (CR) of all visible disease was achieved in 20 and not related to site or size of recurrence, the remainder had partial resection (PR). The interval between treatment of the primary and recurrence (DFI) was a median of 20 months (range 1–164), 14 months for high grade and 65 months for low grade tumors, p = 0.02. By multivariate analysis tumour mortality was significantly related only to DFI, (p = 0.0004).

Conclusion: CR was possible in 1/3 cases but a survival advantage over PR could not be shown. Patients likely to do better following resection of recurrent disease were identified by a longer DFI (>20 months). Tumor biology was the dominant factor in determining survival following recurrence in this group of patients.

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Positron emission tomography (PET) and single photon emission tomography (SPET): Biological characterization of soft-tissue sarcoma. Preliminary results

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Purpose: Little is known about tumor metabolism of soft-tissue sarcomas (STS). In order to investigate sarcoma metabolism, PET with three tracers [F-18-Deoxyglucose (FDG), C-11-Aminoisobutyric acid (AIB) and O-15-Water] and SPET with Tc-99m-Sestamibi were performed in patients with non treated STS. Because of tracer accumulation in viable tumor, the detection of local recurrence, especially in the differentiation against scar tissue, was evaluated.

Methods: 9 patients with STS and 2 patients with a suspected local recurrence in Computed Tomography (CT) or Magnetic Resonance Imaging (MRI), were studied. Liposarcoma was the most common diagnosis (n = 5). Patients with STS underwent surgery and the specimen was histo-pathologically examined. Follow-up was used in the case were PET could not confirm local recurrence.

Results: STS showed an increased uptake of all tracers. Large tumors were characterized by an inhomogenous uptake with enhanced values in the rim and low uptake in central parts. Regions with low uptake were histologically evaluated as necrosis, hemorrhage or cystic tissue. FDG (glucose metabolism) standardized uptake values (SUV) ranged from 2 to 4, 6 with a tumor/muscle (T/M) ratio from 1.9 to 4.2. O-15-Water (tissue perfusion) SUVs ranged from 1.8 to 3.8 with a T/M ratio from 2.3 to 4.4. The AIB-uptake (alanine-like transport of amino acids) varied between 1.5 and 3.3 with a T/M ratio between 0.9 and 1.2. In patients with a suspicious lesion on CT/MRI, but no significant tracer accumulation in PET, no local recurrence was observed.

Conclusion: PET with FDG, AIB and O-15-Water and SPET with Tc-99m-Sestamibi is able to characterize metabolic differences in STS. All tracers accumulated in viable tumor. This method is expected to be helpful in the detection of local recurrence and evaluation of response to chemotherapy.

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Favorable outcome following early treatment intensification with Ifosfamide for high-risk extremity osteosarcoma. Long term results of study COSS-86

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Purpose: To improve the results of osteosarcoma therapy by early systemic treatment intensification. To evaluate the effect of locoregional intensification by giving cisplatinum (DDP) intraarterially (i.a.) as opposed to intravenously (i.v.).

Methods: All patients aged less than 40 years at diagnosis of a localized, de novo high-grade central extremity osteosarcoma registered within

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 × no surgery, 7 × 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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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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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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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 feasability 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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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/m^2/day as a continuous infusion days 1–5 with mesna 2.5 g/m^2/day and G-CSF days 6–15 or carboplatinum 150 mg/m^2/day days 1–4 plus VP 16 150 mg/m^2/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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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.