Material and Methods: Forty-two patients diagnosed of localized Ewing sarcoma have been recruited. RNA was extracted from peripheral blood samples. RT-PCR was performed according to detect the EWS/FLI1 fusion mRNA.

Results: From forty-two patients, 16 were RT-PCR positive for EWS/FLI1. Nine of these 16 patients (56.25%) showed distant metastatic disease with a median follow-up of 20 months (10–33) and 3 relapsed locally (18.75%). From the 24 patients with no evidence of circulating tumor cells, 5 patients developed metastatic disease (20.8%) with similar follow-up and 2 patients showed local recurrence (8.3%).

Conclusions: These data suggest that the detection fo circulating tumor cells could define a group of patients with a significant higher rate of local failures and/or metastatic spread.

501 POSTER

Growth pattern and development of metastasis in orthotopically transplanted human osteosarcoma xenografts in nude mice

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Purpose: Experimental tumor models which resemble the clinical situation could be valuable in evaluation new treatment strategies in vivo. The aim of the present study was to establish a new human osteosarcoma spontaneous metastasis model using orthotopic transplantation of histologically intact tumor tissue into the tibia of nude mice.

Methods: Subcutaneously growing human osteosarcoma xenografts from the 32nd serial passage was used in the experiment. Solid tumor pieces were implanted into the proximal tibia in 31 nude mice. The animals were sacrificed and autopsied at 2, 4, 6, and 8 weeks after transplantation. The mice were examined macroscopically and microscopically for local tumor growth and metastases.

Results: Intratibial bone tumors were found in all mice at the site of the implantation. The tumors were radiographically and histologically similar to primary human osteosarcoma. Lung metastases were observed in all mice, local and distant lymph node metastases in 15 (48%), and liver metastases in 6 (19%) mice. The microscopic appearance of the metastases was similar to that observed in the donor patient-s tumor, corresponding subcutaneous xenografts and orthotopically transplanted intratibial tumors.

Conclusion: Since local tumor growth were found in all animals and spontaneous metastasis were observed in several mice this model seems suitable for further studies on local tumor growth, formation of metastasis and antitumor therapy.

502 POSTER

Intraoperative radiotherapy (IORT) in soft tissue sarcoma

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Purpose: In high risk patients with soft tissue sarcoma, percutaneous radiotherapy after extremity preserving surgery is the standard treatment. Local control can probably be improved by intraoperative radiotherapy. There is no data available concerning the function of thus treated extremities. The aim of this work was the evaluation of patients with soft tissue sarcomas (STS) of the extremities after IORT with respect especially to local control and function of the extremity.

Methods: From 1986–1996, 23 patients (T1: 6x, T2: 17x; recurences: 11x) were irradiated intraoperatively (12–15 Gy) and postoperatively (40–60 Gy). The course of disease was evaluated retrospectively by interviews of the patients, their relatives and treating physicians as well as evaluation of radiotherapeutical and surgical files. The function of the extremity was analysed by a standardised questionnaire and examination.

Results: Local control was obtained in 18 of 23 patients (78%). Survival rate was 65% (15/23 patients) after a mean observation period of 36 months (1–72). 7 of 20 patients who were initially free of distant metastases, developed distant disease. Of 15 patients alive, 11 patients revealed excellent function of the extremity or had only minor functional deficits.

Conclusion: The addition of intraoperative radiotherapy to routine treatment in high risk patients with STS of the extremity achieved 78% local tumour control during a mean of 36 months observation time. Compared to historical data, this could point towards improved local control. The functional result was excellent with no or minor deficits in 11 of 15 patients alive.

503 POSTER

Morbidity of a combined modality therapy of intra-arterial doxorubicin, neoadjuvant radiotherapy and surgery for locally advanced high grade soft tissue sarcomas (STS) of the extremities

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Intra-arterial doxorubicin, neoadjuvant radiotherapy, and surgery was introduced as limb-saving treatment for "unresectable" high grade STS of the extremities.

Patients and Methods: Between 1982–1986 11 pts, 9 ♂ and 2 ♀, median age 52 (range 24–70) yrs, with "unresectable" grade III STS of the extremities were treated by preoperative i.a. infusion of doxorubicin for 3 consecutive days (daily dose 20 mg/m^2). Within 24 hours after infusion preoperative XRT of the compartment (10 × 350 cGy) started. After chemo-radiotherapy the tumor was resected. Non-radical resections received 20–30 Gy XRT (9 pts).

Results: No local recurrences (median fu 110); pulmonary met's in 5 pts (45%). Local skin toxicity due to doxorubicin in 3 pts (27%). Preoperative 35 Gy XRT was well tolerated. Limb-saving treatment in 10 pts (91%); in 1 an exarticulation of the hip had to be performed. Three of the 5 longterm survivors (fu > 10 yrs) developed a severe fibrosis of the affected limb (60%). Two severe longterm complications: a stress fracture of the affected femur (91 months), and a severe radiation-induced motor and sensory neuropathy of the sciatic nerve.

Conclusion: The longterm results show a limb-saving rate of 91%, without increasing the risk of a local recurrence. Especially the longterm morbidity is extremely high (60%). This combination therapy should therefore no longer be advocated.

504 POSTER

Conservative possibilities of treatment in sarcoma of the limbs

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The study underlines the value of neoadjuvant and postoperative chemotherapy in the aim to realize a successful conservative surgery in locally-advanced sarcoma (LAS) of the limbs.

From oct. 1990 to dec. 1996 we treated 165 non metastatic sarcoma of the limbs: 96 osteo and chondrosarcoma (OS) and 69 soft tissue sarcoma (STS). From 165, 97 cases with LAS received after biopsy 3–4 courses of neoadjuvant chemotherapy with CIVADIC. 92% of all cases were submitted to conservative surgery: extensive bone surgery, with bone grafts or articulation prosthesis in OS; wide excision in 48% and marginal surgery in 45% of STS. Postoperative chemotherapy 6–8 courses with cisplatinum, farmorubicin in OS (CDDP 100 mg/m^2, farmorubicin 70 mg/m^2) and CIVADIC (cyclophosphamide 500 mg/m^2, vincristine 1 mg/m^2, farmorubicin 70 mg/m^2, DTIC 250 mg/m^2/day × 2), alternating with CIVADACT (actinomycin D 500 γ/day × 3) in STS. The tolerance to chemotherapy was good with mild manageable side-effects. In the cases with marginal surgery, compartimental radiotherapy was performed with 50 Gy plus local boost. The median follow-up was 4 years. The disease free survival was 8–24 months.

In conclusion, even in the LAS of the limbs complex treatment chemo-radiotherapy makes possible a conservative surgery with good, long lasting results.

505 POSTER

Neoadjuvant long-term continuous intra-arterial chemotherapy of soft tissue sarcomas

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Purpose: The efficacy of preoperative long-term continuous intra-arterial infusions of cisplatin (CDDP)+adriamycin (ADR) was investigated.

Methods: 26 patients (15 M., 11 F, mean age 40 years) with soft tissue sarcomas of the extremities (15 synovial sarcomas, 8 malignant fibrous histiocytomas, 3 nonclassified sarcomas) were included in this study. All patients had extracompartmental lesions, tumor size >8 sm, volume >100 sm^3. The schedule of chemotherapy consisted of a 5-day

course of alternating 6-hour CDDP 25 mg/m² and 18-hour ADR 20 mg/m² infusions (120-hour continuous infusion, total dose CDDP 125 mg/m², ADR 100 mg/m²).

Results: Complete and partial response was achieved in 42.3%. In 2 weeks after chemotherapy all patients were operated. Good histological response (necrosis more than 70% tumor cells) was in 57.7% of cases. 3 courses of adjuvant chemotherapy CAP were used in patients with good histological response. In that group local recurrences were 13.3%, metastasis – 26.7%, 3-years survival – 82%. In the group of patients with poor histological response frad following figures: local recurrences – 45.5%, metastasis – 45.5%, 3-years survival – 47%.

Conclusion: So neoadjuvant approach to treatment of soft tissue sarcomas with long-term continuous i.a. chemotherapy can improve survival and its quality.

506 PUBLICATION

Soft tissues granular cell tumor: Disease description and treatment

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Purpose: This retrospective study was designed to characterize this rare disease and determine the best treatment.

Methods: We have review 12 charts (10 women, 2 men) of patients treated between 1980 and 1995. Thirteen soft tissues granular cell tumors were found. Average age was 35 years (from 12 to 55 years), and all were in good health.

Results: Lesions were located in the breast area 5 times, on the thoracoabdominal area 7 times, and once on the arm. Once there was a suspect lymph node in the drainage area. Always subcutaneous, the lesion was attached to the skin twice, averaging size of 12.5 mm. In 3 patients, it was recurrence (always after a previous incomplete resection). The fine needle aspiration reported malignant cells 60% of the time. The macroscopic examination revealed a white, firm, homogeneous, and uncapsulated mass. The frozen section misdiagnosed a malignant lesion 1 on 7, and was good 6 on 7. Most part of the time, the paraffin diagnostic was relatively easy but 3 times, electronic microscopy and immunohistology were needed to do the diagnosis. All lesions were benign. All patients were treated with microscopically complete local resection. No recurrence was observed after a median follow-up of 4 years. One patient had an unrelated cutaneous basocellular 5 years later.

Conclusion: Soft tissue granular cell tumor presents as a small subcutaneous lump, sometimes infiltrating the skin or associated with benign lymph node histiocytosis. It is a benign lesion, sometimes difficult to identify. Fine needle aspiration and frozen section examination are not good diagnostic tools in this condition. Microscopic complete surgical excision is the goal of the treatment because if incompletely excised, recurrences rates are high. In case of recurrence, we recommend a 1 cm resection margins.

507 PUBLICATION

Phase II study with Docetaxel (Taxotere) as second line treatment of advanced soft tissues sarcomas in adult

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A recent phase II study (ASCO 1994) showed that Docetaxel is active in adult soft tissue sarcomas as second line treatment warranting studies on first line efficacy and/or inclusion in combination. To confirm these data we started a multicenter phase II study with Docetaxel administered at the dose of 100 mg/m2 in a 1-h infusion q 3 weeks with corticosteroid premedication and without antiemetics as a second line chemotherapy in relapsed or metastatic soft tissues sarcomas. 37 pts, median age 43 yrs (20–65), WHO performance status 0: 19 pts, 1: 11 pts, 2: 6 pts, 3. 1pts entered the study. Histological subtypes were: fibrosarcoma 2 pts, malignant fibrous histiocytoma 4 pts, leiomyosarcoma 9 pts, liposarcoma 2 pts, rhabdomyosarcoma 2 pts, synovial sarcoma 8 pts, malignant schwannoma 4 pts, miscellaneous and unclassified sarcomas 6 pts. Twenty four pts have had one line of chemotherapy, 9 pts two lines, 4 pts four lines. Three pts are not evaluable for response: 1 pt had early death due to malignant disease, 1 pt died before response evaluation, 1 pt was unfit for evaluation. The responses observed were as follows: partial remission 1 (3%, C.I. 95% 0–17), stable disease 10, progression 23. CTC grade ≥3 leucopenia occurred in 76% of pts, and neutropenia in 90% of pts, while CTC grade ≥3 trombopenia was observed only in a pt. Fever and documented infection were noticed in 20% and 33% of pts respectively. No severe anaphylactoid type reaction and sensory neurotoxicity were observed. Nail changes and skin reaction were noticed in <20% of pts. Peripheral edema and fluid retention occurred in 2 pts. A pt died due to toxicity.

According to this phase II study, Docetaxel seems to be devoid of activity in adult soft tissue sarcoma and thus, in particular, its inclusion in first line chemotherapy would not seem justified.

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508 PUBLICATION

Treatment response in childhood rhabdomyosarcoma (RMS) related to apoptotic and proliferation fraction

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Purpose: Proliferation fraction analysis does not take into account the fraction of cells undergoing apoptosis. Relationship between proliferation fraction and outcome is often tenuous. We compared apoptosis corrected proliferation fraction with treatment outcome in rhabdomyosarcoma.

Methods: Of 30 consecutive, unselected cases of rhabdomyosarcoma (M: 18, age 3 m–16 years; F: 12, age 2 m–15 years), pre-treatment, routinely processed archival tissue was used for analysis of S-phase (cDNA defined mono-clonal antibody against Ki-67 antigen MM1, Novacastra, UK) and apoptosis (DNA in-situ labelling of apoptotic DNA fragments, Frag-EL, Cal-Biochem, USA). Quantisation of fractions: blinding, systematic random sampling.

Results: Mean apoptotic fraction: 51.3% (7–90%), no difference between subtypes. Apoptosis corrected S-fraction: 43.7% in survivors (n = 13) and 74% in non-survivors (n = 16) ($p < 0.01$, Wilcoxon). High proliferation fraction (>40%) predicted poor outcome in 15/16 cases (sensitivity 94%); 15/20 cases of high proliferation rates had unsuccessful treatment (specificity 75%).

Conclusions: 1. Apoptosis affects a variable proportion of cells in rhabdomyosarcoma. 2. Apoptosis corrected proliferation fraction is an accurate predictor of treatment outcome in childhood RMS.

509 PUBLICATION

Local hyperthermia in the treatment of soft-tissue sarcomas

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Purpose: It is evident that local electro-magnetic hyperthermia enhances the efficacy of radiation therapy in the clinic. However up to the present time the optimal combination of irradiation and local hiperthermia has not been established.

Methods: 138 pts with inoperable soft-tissue sarcomas have-been treated with preoperative radiation therapy. In 92 pts radiation therapy was combined with local hyperthermia (thermo radiotherapy – TRT); 46 pts received only radiation therapy (RT). Radiation therapy was given twice a week with a single dose 4–5 Gy; total dose 30–42 Gy. Local hyperthermia was carried out on apparatus working with frequency 460 Mhz. Temperature inside the tumour during 60 min was maintained in the range of 41–45°C. Local hyperthermia was provided by two variants; just before irradiation or 3–4 hrs after radiation exposure.

Results: In 2–3 weeks after TRT complete or partial tumour regression was observed in 50 pts, and after RT – in 12 pts 46% of pts who received TRT weve undergone conservative surgery and only 27% after RT.

Conclusion: Local hyperthermia improves the results of preoperative radiation therapy in pts with soft-tissue sarcomas. The best results were seen in pts with hyperthermia 3–4 hrs after irradiation and the temperature inside the tumor above 43°C.