yr. (p<0.001), low malignancy grade (p=0.02), lipomatous histomorphology (p=0.003), non-invasive growth (p<0.001), and the absence of distant metastasis (p=0.005) were associated with favourable outcome. Malignancy grade, and the extent of surgical treatment remained independent prognosticators in a multivariate context. The level of experience was associated with a higher rate of radical resections (p=0.009), but did not affect outcome.

Conclusion: Survival of patients with RSTS was determined independently by the extent of surgery, and malignancy grade. The level of experience, although influencing the result of surgery, did not affect long term outcome.

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Long term results of expanding prostheses for limb salvage surgery of children

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Introduction: Conservative surgery for young children with bone sarcoma of lower limb remains a challenge. In 1985 we proposed an expandable prosthesis and present here our long-term results.

Patients: 44 patients (20 males and 24 females aged 4–28 years) with tumors of the limbs were treated by our team between 1984 and 1999. Histology was mostly osteosarcoma (32) and Ewing's sarcoma (9). Locations were distal femur in 30, upper tibia in 5, total femur in 5 and proximal femur in 4.30 were first hand patients (28 with localized disease and 2 already metastatic) en bloc resection. The 14 other patients were referred to us after induction therapy, with progressive disease, metastase (3) or local recurrence (1).

Method: In 14 patients the expanding prosthesis was inserted immediately after the resection, in 8 during the following year and for the 22 other patients later on to treat a length discrepancy. 107 sequences of lengthening have been performed in 40 patients. All patients were followed up by their surgeon and their chemotherapist every 3 months during 2 years, then every 6 months for 2 other years and yearly thereafter.

Results: 6 patients died from illness. All other are disease free survivors with a median follow up of 91 months (maximal 192 - minimal 6). Half (22) of the patients are adults. The average lengthening is 4.07 centimeters (minimal 0.5 - maximal 12). Half of the patients had to be reoperated for complications. Deep infection occurred in 10 patients (22%) resulting in amputation for 3 of them. According to EMSOS criteria the functional result is excellent in 14, good in 15, fair in 10 and poor in 5.

Conclusion: Long term results of lengthening prostheses confirm that this procedure is an excellent alternative to amputation and permit to keep a functional limb in nearly 90% of patients. The most severe complication is deep infection underlining the interest of last generations of grower with minimally invasive lengthening.

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Intraperitoneal chemotherapy (IPC) after complete resection of peritoneal sarcomatosis (PS): Results of a monocentric randomized study

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Purpose: In order to decrease locoregional relapse after complete resection of PS, the role of IPC was prospectively evaluated.

Methods: Patients (pts) with complete resected PS were randomised between adjonction of IPC or not. IPC consisted of Doxorubicin, 0.1 mg/kg and Cisplatine, 15 mg/m^3 every day for 5 consecutive days.

Results: Thirty-eight consecutive pts have been enroled in the study, 19 in each group (IPC–, IPC+) with a M/F sex ratio of 14/24. Median age was 58 (39 to 72) and 48 yrs (31 to 71) in IPC– and IPC+ group respectively. Ratio of retroperitoneal (RPS) and visceral (VS) sarcomas were 9/10 and 6/13 in IPC– and IPC+ group respectively. Histoprognostic grade were similar in both groups. Sugarbaker score of sarcomatosis were 13 (3, 27) and 13.7 (2, 20) in IPC– and IPC+ respectively. Mean number of resected organs in each group (IPC–, IPC+) was 3.1 and 2.7 respectively. There was no toxic deaths and morbidity was similar in both groups (4 pts in each group). Median time of hospitalization was 22 days (range 11 to 39) for IPC– and 24 days (range 15 to 42) for IPC+. The median follow-up is 36 months. The median local relapse-free, metastatic relapse-free survival and overall survival were identical in both groups, 12.5, 18 and 29 months respectively with no difference between RPS and VS.

Conclusion: Addition of IPC did not modify outcome of pts after complete resection of RPS and VS. OS and DFS of this study are similar to those observed in phase II studies combining IPC with hypertermia. An optimal surgery of PS remains the only pronostic factor for survival.

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Efficacy of the neoadjuvant chemotherapy with regional hyperthermia in high-risk soft tissue sarcomas. 1

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Purpose: The efficacy of neoadjuvant thermochemotherapy was investigated.

Methods: We report the results of phase I/II studies of treatment of 22 patients with II and III grade extremities soft tissue sarcoma (STS). All patients had extracompartmental lesions, tumour size > 8 cm (mean 12 cm). Mean tumour volume was 540 cm^3. The preoperative chemotherapy with Cisplatin (DDP) 120 mg/m^2 and Adriamicin (ADR) 90 mg/m^2 (1 day) for 6 weeks (2 cycles) combined with 2 fraction of regional hyperthermia (RHT), (60 min., 43.0° C.) day 1, 3.

Results: Limb - saving surgery was performed in 19 (86.4%) cases consisting of wide compartmental excision of the tumour. Mutilating surgery was performed in 3 cases. Treatment efficacy was assessed by clinical, morphological response and follow - up for systemic and local relapse. The efficacy rate was 50% or more. The mean tumour necrosis (>70% cells) rate in the resected specimens was 81.8%. There was no correlation between the histological response and the observed reduction in tumour volume. Postoperative complications were observed in ten (45.5%) patients; among these, 4 patients developed wound infection that required surgical treatment as a complication of surgery performed in the early stage following the preoperative treatment. After a mean postoperative follow-up of 27 months, distant metastasis occurred in six (27.3%) patients resulting in 5 fatalities. The three-year cumulative survival rate was 64.3%. No local recurrence was observed in any patient during the follow-up, thus confirming our hypothesis that DDP + ADR + RHT treatment has an excellent local efficacy.

Conclusions: The results of this study suggested that DDP + ADR + RHT was an effective local treatment for limb salvage in limb-threatening STS. We think that it would be valuable to conduct, at many facilities, phase III studies on the treatment of soft tissue sarcoma by a combination of surgery and preoperative multidisciplinary treatment using hyperthermia.

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Neoadjuvant chemotherapy in limb soft tissue sarcoma: the significance of C-ERBB-4 expression

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Purpose: ErbB-4 is a recently described member of the epidermal growth factor receptor (EGFR) family. Relatively little is known about the expression of erbB-4 in human tumors. In the present study we assessed the possible role of c-erbB-4 expression product as a tissue marker for STS, and its correlation with the response to chemotherapy.

Patients: The histological specimen of 29 patients with STS of a limb who had received preoperative doxorubicin-based chemotherapy were studied. The extent of tumor necrosis was evaluated histologically. Paraffin blocks of preoperative incisional biopsy were available for immune staining (avidin-biotin-peroxidase technique) from 29 patients, and blocks of the surgical specimen after pre-operative chemotherapy were available from 27.

Results: The objective response rate to preoperative chemotherapy was 34%. Wide resection of the tumor was feasible in 12 patients, marginal resection in 14 cases, amputation in 2 patients with disease progression, and no surgery in one case. The tumor necrosis was above 90% in 9 patients, 60-90% in 12, and less than 60% in 7 patients. An increase in C-erbB-4 expression was more common in cases with no response to chemotherapy, while no change of or decrease in C-erbB-4 was more common in responsive tumors (p=0.004). No correlation could be found between the degree of necrosis or the chemotherapeutic regimen and the change in expression of c-erbB-4. The median DFS was longer for patients with a decrease or no change in expression of C-erbB-4 than for patients with increased expression.

Discussion: It is believed that post chemotherapy new expression or no down-regulation of the erbB-4 molecule represents tumor aggressiveness and increased capability of growth and spread.

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Isolated limb infusion for the treatment of advanced extremity soft tissue sarcomas

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Extremity soft tissue sarcomas (STS) are often large at presentation and as a result resection without compromise to limb function can be difficult or impossible. Regional high dose chemotherapy can be used to avoid amputations in patients with advanced or recurrent STS. Isolated limb infusion (ILI) is such a technique, performed using percutaneous catheters, which makes it a simpler and less invasive procedure than conventional isolated limb perfusion (ILP). Response rates in patients with advanced melanoma after ILI with melphalan and actinomycin-D have been comparable with results obtained after ILP. To evaluate the role of ILI in advanced soft tissue sarcoma all patients treated with this technique at the Sydney Cancer Centre were studied to assess short and long- term results.

Between 1994-2000 a total of 19 patients underwent 20 ILI procedures (4 upper limbs, 15 lower limbs). Three patients presented with multiple tumours whereas all other patients had a single tumour. In all but one patient melphalan was used in combination with actinomycin-D (n=15), mitomycin-C (n=3) or both (n=1). The remaining patient was infused with a combination of mitomycin-C, adriamycin and cisplatin. In 9 patients the ILI was performed with the aim of decreasing tumour size and enabling a radical tumour resection. In the other 10 patients the ILI was performed for local control to avoid amputation and was not followed by surgical resection. All ILIs were performed under hypoxic and mild hyperthermic conditions (mean maximum temperature 37.8°C).

Wieberdink Grade II limb toxicity occurred in 7 patients, Grade III toxicity in 10 patients, and Grade IV toxicity in 3 patients. Fasciotomy was necessary in two of the latter group of patients. Overall clinical response after ILI was 79% (complete response 26%, partial response 53%, no change 11%, progressive disease 11%). None of the patients treated with an additional surgical resection of the tumour developed a local recurrence (mean follow-up 20 months (9-42)). Of the patients treated with ILI only, local control was maintained for a mean of 11 months (1-37). Four of these patients eventually came to amputation, and in one patient local control for a further period was achieved with local radiotherapy.

In conclusion, ILI for advanced STS using melphalan and actinomycin-D as the infused drugs is a feasible and useful technique, with low morbidity and a high overall clinical response rate.

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Histamine enhanced antitumor effect of docetaxel and dacarbazine in human clear cell sarcoma xenografts in nude mice

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Background: Clear cell sarcoma has melanocytic features and is intimately associated with tendons and aponeuroses. It is rare. In the Scandinavian sarcoma registry 18 cases (0,8%) of clear cell sarcoma were registered between 1986 and 1996. Extensive surgery so far the primary treatment.

The aim of the present study was to investigate if histamine enhances the antitumor effect of dacarbazine (DTIC) and docetaxel.

Method: Human clear cell sarcoma tumor tissue was obtained during operation of a 58-year old woman. The tumor (UMCCS-I) was maintained by serial s.c. transplantations in nude mice. DTIC (200mg/kg, i.p.) given 3 times with an interval of 2 days, docetaxel (20 mg/kg, i.p.) single dose and histamine (4 mg/kg, s.c.) daily, 5days per week was administered in tumorbearing nude mice. DTIC and docetaxel was given separately or in combination with histamine. Tumor volume in the groups (n=7) was measured repeatedly and compared with a control group (given saline i.p.). The antitumor effect is considered significant when TC-ratio is 0.4 or less.

Results: The tumors were followed until day 21. The lowest TC-ratio was noted at day 21 in the DTIC group - 0.54. The corresponding TC-ratio value for the combination histamine-DTIC was 0.37. In the docetaxel-group the lowest TC-ratio- 0.39 was observed at day 13. TC-ratio in the combination docetaxel-histamine was 0.33. The TC-ratio was reduced at all measuring occasions when histamine was given in adjunction with DTIC and docetaxel.

Conclusions: Histamine seems to enhance the antitumor effect of dacarbazine and docetaxel in this clear cell sarcoma tumor model.

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Primary soft tissue sarcomas of the extremities: Treatment outcome with postoperative radiotherapy

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Purpose: The outcome of adult patients with primary localized soft tissue sarcoma of the extremities with conservative surgery and adjuvant irradiation (RT) was evaluated.

Methods and Materials: From 1975 to 1996, 107 patients (pts) with a median age of 44 years (range, 16 to 86 years) were treated at the Institut Gustave Roussy (IGR) with conservative surgery and adjuvant radiotherapy. The median tumor size was 7 cm (range, 1 to 20 cm) with 27, 36 and 36% stage I, II and III respectively. Histologic examination revealed negative histologic margin in 16%, close or positive margin in 75.5%, grossely positive in 2% and undocumented in 6.5%. The most common histological subtype was: malignant fibrous histiocytoma (27%), synovialosarcoma (27%), liposarcoma (6.5%), and leiomyosarcoma (6.5%). The histologic grade was 1 for 14 patients (13%), 2 for 40 pts (37%), 3 for 50 pts (46%) and unknown for 3 pts (3%). All patients underwent a function-sparing surgery. Forty six patients (43%) were reoperated;residual tumor were found in 82% of pts (38/46). All adjuvant radiation therapy was performed at the IGR. The median external beam dose was 50 Gy (36-65). Chemotherapy was used selectively in 18 patients.

Results: With a median follow-up was 132 months (36-288), the 5- and 10-year local control rates were 81% [CI, 72-88%] and 74% [CI, 63-83%] respectively. The 5-year disease-free and overall survival rates were respectively 53% [CI, 43-62] and 69% [CI, 59-78]. Histologic grade was a significant predictor for local recurrence (p=0.04). There was no significant association between local recurrence and margin status, histology, re-resection, residual disease, size, RTdose, or depth. Significant independent adverse prognostic factors for DFS were RT dose less than 50 GY (p=0.008) and grade 3 tumors (p=0.02). Despite the moderate dose, a substantial rate of long-term side effects was observed. Most of these complications were mild or moderate. No patient had to be amputated because of treatment-related toxicity.

Conclusion: Based on our experience and a review of the literature, we concluded that, in the postoperative setting a radiation dose below 50 Gy did not seem optimal. The optimal dose and long-term sequelae should be evaluated in a prospective randomized trial.

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Localized osteosarcoma of adult patients: Comparison with pediatric population in the same institution over a 16-year period

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Objective: To evaluate outcome of patients (pts) with localized osteosarcoma (LO) treated in two Departments (Adult-AD- and Pediatric-PD) of IGR.

Methods: All pts treated for a LO with induction chemotherapy (CT) either in AD (n = 71) or in PD (n = 149) between 1982 and 1998 are included in the analysis. Pts treated in PD received a MTX-based regimen while 3 different protocols were used in AD: modified-T10 (1983–1992), DOX-CDDP (AP) (1983–1993) and DOX-CDDP-IFO (API-AI) since 1992 (ASCO-2001).

Results: Median age and median tumor size were 20.8 yr [15.4–63] and 10 cm [3–25] in AD and 12.4 yr [range = 4.4–20] and 12 cm [1–29] in PD respectively. High-dose MTX was more toxic in adults than in younger pts. Good responders to CT (≥95% necrosis) were 36% and 48% in AD and PD respectively (p = 0.08). In AD, this rate varied according to the protocol from 25% (AP), 30% (T10) to 48% (API-AI). The 5-year overall survival (OS) of the entire population was 73% [66–79%] and the event-free survival (EFS) was 60% [53–67%]. OS and EFS were significantly better in PD than in AD: 5-yr OS = 79% [72–85%] in PD versus 59% [46–70%] in AD (p = 0.001) and 5-yr EFS = 65% [57–73%] in PD versus 48% [36–61%] in AD (p = 0.003). This difference was similar when we restricted analysis to the teenagers (35 in AD and 33 pts in PD). The pts treated in AD with API-AI regimen had a similar EFS to those treated in PD.

Conclusion: Over this period of 16 years, pts treated in PD had a better outcome than pts treated in AD. However this difference seems to disappear