

Scandinavian Sarcoma Group

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Report from the Scandinavian Sarcoma Group Central Registry

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The Registry was initiated in 1986 and includes patients with sarcomas of the trunk wall and extremities reported from orthopedic oncology centers in Norway and Sweden. In this report we have analyzed trends in referral, preoperative investigations, and treatment of patients with bone sarcomas (BS) and soft tissue tumors (STS).

Referral. A total of 1252 (322 BS; 930 STS) sarcoma patients have been reported between 1986–92. Approximately 60 patients with BS and 150 with STS were reported annually and the number does not appear to increase. 75% of patients with BS were referred with untouched lesions as compared to only 36% of patients with STS.

Preoperative investigations. Cytology of BS has increasingly been applied, from 3% in 1986–87 to 32% in 1991–92. Corresponding figures for STS patients were 40% and 52%, respectively. Hence, for both BS and STS fine needle aspiration cytology is increasingly replacing surgical biopsy.

Treatment. 12% of patients with BS and 9% with STS had no surgical treatment, mostly due to metastatic disease at diagnosis. Regarding surgical treatment, 27% of BS and 6% of STS were amputated and the incidence of amputations has not changed over time. The surgical margin for STS has been reported as wide or better in 50% of patients, except for 1991–92 with 60% wide or better surgical margin. Radiotherapy has only been given postoperatively and only half of the patients with a marginal margin were given radiotherapy.

Local recurrence in soft tissue sarcoma Analysis based on the Scandinavian Sarcoma Group Central Registry

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Local recurrence after surgery was analyzed in a multicenter study of soft tissue sarcoma patients reported to the Scandinavian Sarcoma Group Central Registry 1986 through 1990.

Patients and methods. 542 patients (308 men, 234 women) without metastasis at diagnosis were included. The median age was 64 (16–91) years. Subcutaneous tumors (n 168) were smaller than deep (n 374), median diameter 4 and 10cm. Local surgery was performed in 93 % of the cases, only patients with deep tumors were amputated (9%). The final surgical margin achieved was marginal in 31 % of superficial lesions and in 54 % of deep. iotherapy was only given after marginal surgery, and in only half of those patients.

Results. The median follow-up was 4 years. The overall local recurrence rate at 5 years was .27. The rate was equal for patients with subcutaneous tumors (.52 after marginal surgery, .16 after wide) or deep tumors (.54 after marginal surgery, .20 after marginal with radiotherapy, .22 after wide, .17 after myectomy, and 0 after compartmental surgery). Risk factors for local recurrence in subcutaneous tumors were surgery without biopsy (relativ risk, RR, 5), marginal surgery (RR 5), large tumor size (RR 1,1 per cm increase), and high grade (RR 3). For patients with deep tumors, truncal localization (RR 3) and marginal surgery without radiotherapy (RR 3) and also large tumor size (RR 1,1) and high grade (RR 2) were risk factors for local recurrence.

Discussion. Local control can be achieved in the vast majority of subcutaneous soft tissue sarcomas by surgery solely. For patients with deep tumors, only myectomy and compartmental procedures gave acceptable local recurrence rates without radiotherapy. Interestingly strong risk factors for metastatic disease such as large tumor size and high malignancy grade were only weak risk factors for local recurrence.

Pediatric sarcomas in Sweden 10 years experience 1982–1991

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The Swedish cooperative group for Pediatric solid tumors (VSTB) was formed in 1974. In 1982 a registry for pediatric malignancies in Sweden was started on a national scale. All patients under 15 years of age with malignant disease (other than leukemia) has since then been registered. During 10 years, 1982–91, 1,706 patients have been registered. 40% are children with tumors in the central nervous system. The rest of the patients are distributed among the following diagnosis: retinoblastoma (2.4%), neuroblastoma (7.9%), Hodgkins lymphoma (5.4%), non-Hodgkins lymphoma (8.0%), Langerhans cellhistiocytosis (4.0%), Wilm's tumor (8.3%), rhabdomyosarcoma (4.9%), Ewing's sarcoma (2.8%), osteosarcoma (3.2%), and others (13%).

The last four groups will be further analyzed with accordance to age, sex, localization and survival. The last group (others) consist of children with very different diagnosis such as: teratomas, hepatoblastomas and rare types of soft tissue sarcomas.

The registry is not suitable for comparison of different treatment protocols. All patient are followed up until December 31, 1992.

Epidemiologic studies in Southern Sweden in soft tissue sarcoma—is an SSG-study also possible?

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Background. Risk factors of soft tissue sarcomas are still only partly known. Suggested risk factors include exposure to herbicides, radiation exposure and family history. It is therefore important to further investigate risk factors and to confirm the suggested factors.

A comparison was made between 127 newly diagnosed cases identified through the regional tumor registry and 350 referents from the general population, matched with the cases for age, domicile (parish) and sex. A further comparison was done with 413 referents chosen from the general population but matched with the cases for age, domicile (county) and sex.

Results and Discussion. Family history of sarcoma and

height at puberty and at diagnosis were associated with the risk of developing sarcoma (p 0.03). Weight at early puberty or at diagnosis was not associated with sarcoma development. These results point to the importance of genetic and probably early hormonal factors for tumor development. Slight risk elevations were also seen for trauma and for herbicide exposure. The picture for herbicide exposure was somewhat puzzling as by using parish referents a decreased odds ratio was seen while using county referents a slightly increased risk appeared. This could be due to the possibility of overmatching cases and referents by using parish referents and needs to be analysed in more detail. Further, a lack of dose-response for herbicide exposure made a causal inference difficult. There was no significant association between alcohol use and risk for sarcoma. Neither could a significant association between being an ever smoker and sarcoma risk be seen. However a protective effect between the amount of smoking on sarcoma development was seen although not statistically significant (p 0.20). The duration of herbicide exposure was not associated with sarcoma risk.

Prognostic value of PCNA in soft tissue sarcoma

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Grading schemes based on histopathologic features are of value in predicting survival in soft tissue sarcoma. Since these systems require subjective interpretation of some parameters, interobserver variability exists. Variation in clinical behaviour in tumors of the same grade promotes a search for additional factors that correlate with prognosis to supplement grading.

Cell kinetics play an important role in tumor behaviour. Mitosis count is the simplest assessment of cell proliferation, but limited to the shortest phase (M) of the cell cyclus. Proliferating cell nuclear antigen (PCNA) is expressed in proliferating cells and is present in greatest concentration during the long S-phase.

To evaluate the prognostic implication of PCNA, 75 soft tissue sarcomas (8 grade II, 19 grade III, 48 grade IV) with a minimum follow-up of 2 years were immuno-histochemically studied. PC10, a monoclonal antibody directed against PCNA, allows evaluation of cell proliferation in formalin-fixed, paraffin-embedded sections.

A semiquantitative PCNA grading scheme (group A: <25%, B: 25–75%, C: >75%) was applied to all stained cells of a complete section. 22 of 25 patients in group A (3 grade II, 10 grade III, 12 grade IV) were alive with no evidence of tumor, while 8 of 13 patients in group C (1 grade II, 4 grade III, 8 grade IV) had developed metastases, 7 were dead and one alive with tumor.

Our findings show, that immunohistochemical evaluation of cell kinetics in soft tissue sarcomas by PCNA might be a useful adjunct to conventional tumor grading.

Combined S-phase and DNA-ploidy analysis in soft tissue sarcoma—a prognostic tool?

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Flow cytometric DNA ploidy status has been reported to give prognostic information in soft tissue sarcoma. We investigated if estimation of S-phase fraction (SPF) provides additional prognostic information in diploid as well as non-diploid sarcoma.

Material and methods. SPF was estimated planimetrically with no background correction. Previous experience has shown that sarcoma with small non-diploid populations (G0/G1 peak <15% of total number of recorded events in the histogram) and/or high background debris do not give reliable SPF results.

Such histograms were therefore excluded in this study.

Control study. Correlation of SPF in fresh-frozen tissue and formalin-fixed and wax-embedded from the same sarcoma sample was performed in 48 sarcomas.

Clinical study. We analyzed wax-embedded tissue from 262 sarcomas 1964–1989 (median follow-up for survivors 8 years). SPF was estimated in 99 out of 108 diploid/near-diploid sarcomas (DNA-index <1.3) (92%) and in 67 out of 154 of the remaining non-diploid sarcomas (44%).

Results. Good correlation of SPF was found in fresh frozen and wax-embedded tissue, respectively (rs 0.78; p<0.001). Cut-off for low resp. high SPF-categorization: 3.0% for diploid/near-diploid and 12.0% for the remaining non-diploid sarcomas. By combining ploidy status and SPF two groups with different metastasis free survival (p 0.0002) could be suggested.

Good prognosis group: Diploid/near-diploid tumors with a low SPF.

Bad prognosis group: Diploid/near-diploid tumors with a high SPF and remaining non-diploid tumors.

Conclusions.

1. There was a good correlation between SPF in fresh-frozen and wax-embedded tissue.

2. As SPF only could be estimated in 44% of the non-diploid sarcomas, its clinical usefulness seems to be restricted to the diploid/near-diploid group.

p53 expression in mesenchymal tumors

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Overexpression of p53 has been demonstrated by immunohistochemistry in a wide variety of malignancies, and has also been shown to correlate to poor prognosis. Inactivating mutations of p53 suppressor gene have been revealed in osteosarcoma

and soft tissue sarcoma. In a search for markers capable to foresee clinical outcome the expression of the nuclear phosphoprotein p53 was studied immunohistochemically in a series of 105 benign and malignant mesenchymal tumors. Using the monoclonal antibody CM-1 on paraffin sections, the tumors were divided into three groups on the basis of immunohistochemical results. 90 tumors (86%) were negative. 5 showed positive staining, and 10 tumors showed weak staining which could not be ascertained as positive or negative. Among the negative cases malignant and benign tumors occurred in equal proportions. In the group of positively stained tumors there were 3 MFH, 1 chondrosarcoma and 1 chordoma. In the weakly stained group there were malignant as well as benign tumors; 2 liposarcomas and 1 chordoma, clear cell sarcoma, leiomyosarcoma, mesothelioma, giant cell tumor of bone, enchondroma, aneurysmal bone cyst and schwannoma. Staining of p53, when positive, was confined to a small number of heterogeneously distributed nuclei. Although there are evidences for mutation of the p53 suppressor gene in a high proportion of sarcomas this could not be demonstrated with the immunohistochemical method herein used. Thus immunohistochemical analysis of p53 by use of the monoclonal antibody CM-1 seems to be of limited clinical value in the diagnosis of mesenchymal tumors.

Chondroid tumors—a Helsinki material 1980–1990

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58 chondroid tumors in bone excluding osteochondromas and chondromas were treated at Töölö Hospital during the years 1980–90. The original diagnoses were 48 chondrosarcomas, 8 chondroblastomas, and 2 chondromyxoid fibromas. After re-evaluation of the material 44 tumors were classified as chondrosarcomas, 1 tumor was classified as an osteosarcoma, and 3 as chondromas. In the other tumor groups no changes were made.

The chondrosarcomas were divided into four groups according to malignancy. In GI we had 16 cases, in GII 20, in GIII 7, and in GIV 1 case. The most common location was pelvis (15), followed by femur (12), humerus (6), scapula (3) and tibia (2). Single cases were seen in other locations. The mean follow-up was 3.3 years, but many patients were lost to other central hospitals in Finland. During the follow-up only one of the operatively treated GI tumors showed recurrent tumor, but the second operation was curative. In GII and GIII tumors local recurrence or metastases were found in half of the cases. Four patients died in metastasizing disease, their histological grades were II or III.

The chondroblastomas and the chondromyxoid fibromas behaved as they should as benign tumors.

Aneuploidy in benign musculoskeletal tumors and nonneoplastic lesions

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We studied 28 benign tumors and 7 nonneoplastic lesions originally mistaken for malignancy. In the DNA flow cytometric studies, a broad diploid peak, $CV > 7.5\%$, was found in a giant cell tumor of bone and in a subcutaneous lipoma. A shoulder in the diploid peak, suggesting a diploid and a neardiploid population, was found in two DNA histograms, a condensing osteitis of the clavicle and a giant cell tumor of the bone. The latter lesion also had a tetraploid population. Six benign tumors, two enchondromas, one osteochondroma, one subcutaneous and one intramuscular lipoma, and a calcifying aponeurotic fibroma, showed clear aneuploidy. Typical for all these lesions was a low DNA replicative activity. The highest aneuploid population, DI 1.70, in a subcutaneous lipoma, was very small (5%) with an undetectable S phase. In spite of non-radical operations, no recurrence were observed after a median follow-up of 49 (28–73) months. We conclude that small aneuploid populations with low DNA synthetic activity are compatible with a benign histologic picture and clinical course of a tumor.

Margins in oncological surgery

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Malignancies may be viewed as a process, but also as structures that may be pictured by radiographic studies, identified preoperatively and delineated by the histopathologist.

The words and notions used in reports to purport the operative procedure in tumor surgery are inadequately defined. Terms like "radical", "excision", "extirpation", and "resection" are used, with no uniform respect for their meaning. Designations are not given to the tumor and to the tumor bearing organ separately: denominations are related sometimes to the surgical procedure itself, sometimes to its effect, its consequence, or to the clinical result in years to come. At other times they pertain to the protocol for postoperative, adjuvant treatment.

Honor should be paid to SSG that has strictly prescribed the terms to be related to the surgical procedures. Accordingly, local recurrence may follow radical operations, and postoperative prescription for adjuvant treatment, should probably be given in different terms, divorced the terms related to the operative procedure.

Confidence that excision of a malignant tumor may result in clinical cure is prevalent. Bare resection of the tumor propagates tumor regrowth. In Halstedian thinking local and regional regrowth increase the likelihood of distant spread. Some

early randomized breast cancer trials supported this belief. However, epidemiological studies give evidence that microscopical tumor tissue does not unavoidably surface clinically, and several recent randomized studies have failed to recognize local recurrence as a hazard for distant metastases or reduced survival.

Cytologic diagnosis of bone tumors

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This prospective study was based on 211 patients referred between 1986–92 for diagnosis and treatment of a bone lesion. Patients with a known malignancy were not included. The median age was 49 (1–86) years. The most common locations were vertebra (14), pelvis (43), humerus (20), femur (52), and tibia (21). The fine-needle aspiration biopsy was performed under fluoroscopic control, except for tumors with a large palpable mass. The cytologic diagnosis was compared to the histologic diagnosis after open biopsy and/or surgery in 139 cases, whereas there was no histologic confirmation of the diagnosis in 72 cases. Among these were 39 patients with a cytologic diagnosis of metastasis in whom the diagnosis was confirmed by identification of the primary malignancy. In 27 patients, clinical findings, radiologic appearance, and cytology all indicated benignity, and no surgical biopsy or treatment was performed. Finally, 6 sarcomas were only diagnosed by cytology, 3 patients had inoperable pelvic lesions and in 3 chromosomal analysis of the aspirates revealed an 11:22 translocation confirming Ewing's sarcoma.

Results. Cytology was inconclusive in 33 (insufficient material in 16 cases) of the 210 lesions, 24% of the benign, 9% of the primary malignant, and 7% of the metastatic lesions. The cytologic diagnosis was conclusive in 178 cases. 79 lesions were cytologically diagnosed as benign. This was correct in 73 (92%), but in 6 cases histology revealed sarcoma. Among 36 lesions cytologically assessed as primary malignant, 32 proved to be sarcomas. One of the discrepant cases was benign, and 3 were metastatic lesions. Finally, 63 lesions were diagnosed as metastatic, which proved correct in 62, one was diagnosed as a sarcoma upon open biopsy.

Regarding the 45 lesions finally diagnosed as primary bone sarcomas, cytology provided the correct diagnosis in 32 (71%). In 4, cytology was inconclusive, necessitating open biopsy. However in 6 cases, the cytologic diagnosis was incorrect; 4 were called benign and 2 metastatic. Three were chondrosarcomas, and there were one each of MFH, osteosarcoma and malignant giant cell tumor. In fact, cytologic diagnosis of chondrosarcoma proved the most unreliable; only 7 of 13 could be diagnosed.

Conclusion. Sufficient material for cytologic diagnosis was obtained in 84% and, among these, the diagnosis was correct in 94%. Fine needle aspiration biopsy provides a means of

simple and accurate diagnosis of bone lesions. However, similar to open biopsy, the cytologic assessment must articulate with clinical and radiologic findings for correct diagnosis.

Clinical course after surgery of local recurrence in soft tissue sarcoma

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The importance of local recurrence for metastases was assessed in 348 patients treated for soft tissue sarcoma. None had metastasis at the time of diagnosis and all were treated surgically. Patients who developed metastatic disease before the first local recurrence were excluded.

Using Cox multiple regression techniques, increasing malignancy grade (Relative Risk 6), deep tumor location (RR 3), and tumor size (RR 1.12 per cm increment) were identified as risk factors.

Among the 105 patients who had surgical resection of their first local recurrence, 24 had a second local recurrence without concurrent metastasis. The probability of survival assessed for this subgroup was not affected either by the second local recurrence. During recent years the role of local recurrence as a prognostic factor for metastasis has become controversial. The results of this study supports the contention that local recurrence after surgical treatment of soft tissue sarcoma is of minor importance for survival.

Lower extremity resection endoprostheses

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For reconstruction after surgery of malignant bone tumors one choice is between allografts and massive endoprostheses. In the 70's we used allografts. From 1981 we have instead used massive endoprostheses.

Patients and methods. We have used massive endoprostheses in the treatment of 37 patients with lower extremity bone tumors with a follow-up time of at least two years. The mean age of the patients was 49 (12–79) years. There were 6 osteosarcomas, 8 chondrosarcomas, 12 giant-cell tumors, 2 Ewing's sarcomas, 1 malignant lymphoma, 1 anaplastic sarcoma, 1 plasmacytoma, and 6 metastatic lesions. 22 proximal femoral tumors were reconstructed after resection with massive hip endoprostheses, and 10 distal tumors with resection endoprosthesis of the knee. One patient with Ewing's sarcoma had his whole femur reconstructed. The 4 tibial tumors were reconstructed with resection endoprostheses of the knee (3) and with resection endoprostheses of the ankle (1). Since 1986 the Kotz modular endoprosthesis (28–73) has been used in 14 cases.

Results. One proximal femoral component broke a few months after operation and one knee joint bearing has worn totally needing replacement. Two patients have been amputated due to local recurrence. Most of the patients walk without cane with no or only slight limp.

Conclusion. The Kotz resection endoprosthesis seems to function well on the long run. The detection of tumor recurrence is difficult if not impossible by MR or CT which may be considered a limitation.

Bone-segment transport after resection of tumor

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Two patients with bone tumor were treated by resection of the involved bone segment and bone transport by callotaxis using an Orthofix apparatus.

A 15-year-old girl with a big giant cell tumor in the upper tibia was first treated by curettage of the tumor and the cavity was filled with bone cement. Owing to refracture the bone was resected and the defect closed with transported bone. The bone healed without any leg length discrepancy and normal knee function.

A 48-year-old woman had a solitary metastasis in the lower part of tibia from a melanoma operated 10 years earlier. 9 cm of the tibia was removed. An arthrodesis was performed between the fibula and talus and after osteotomy of the upper part of tibia bone transport was started using an Orthofix frame. The transport (1 mm/day) lasted for 10 weeks. The apparatus was removed after 12 months when the lengthening area and the arthrodesis were healed. The patient could continue her work as principal of a kindergarden during the treatment time. She also drove her car.

Low dose radiotherapy and hyperthermia in recurrent superficial angiosarcomas Presentation of two patients

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Two patients with locally recurrent, superficial angiosarcomas were treated with 45 min hyperthermia twice weekly during three weeks of daily fractionated radiotherapy (2.30 Gy x 15 = totally 34.5 Gy). The anatomical regions of the recurrent tumors were earlier treated with operation and postoperative radiotherapy and the patients had also got cytostatic drugs due to the recurrent tumors.

According to the temperature measurements during the hyperthermia sessions the tumor tissues were easily heated compared to the normal tissues. A very rapid local regression

of the angiosarcomas were observed during the three weeks of treatment. At follow-up four weeks later a locally complete remission was observed in both patients and was still seen 6 and 36 months later, respectively, when the patients died of brain metastasis.

It is known from experimental studies that the vascular endothelium is very sensitive to hyperthermia. Furthermore tumors with a coarse, pathologic vascular system with a slow blood circulation has been shown to easily develop local thromboses, hemorrhages and finally necroses after hyperthermia. As the vascular component is pronounced in angiosarcomas this may be the reason for the good local tumor control in our cases.

Marginal surgery and postoperative radiotherapy in soft tissue sarcomas—the Scandinavian Sarcoma Group Experience

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Marginal surgery of soft tissue sarcomas is accompanied by local failure in 40-90%. When radiotherapy is added local control is achieved in 80-95%.

Patients and methods. From 1981 to 1986, 240 adult patients with high-grade STS were entered into a randomized SSG trial of adjuvant chemotherapy. Postoperative radiotherapy was recommended in case of marginal surgery. The recommended protocol target dose was 51 Gy / 17 fractions / 24 days or CRE equivalent. 28 patients were given radiotherapy, and were included in this analysis. These patients had non-visceral STS, and had no gross tumor at start of radiotherapy.

Results. 3- and 5 years local control rates for patients with a reviewed marginal surgical margin were 79% and 73%. 15 patients had some complication: 9 were moderate or worse (30% at one year, and 35% at 3 years). 2 amputations were performed within one year, and a third after three years. 20 patients with extremity tumors survived more than one year. Eight experienced moderate to major late complications. Of these complicated cases, 7 had received a dose per fraction > 2.7 Gy, in 3 the whole circumference of the extremity was irradiated, 5 received doxorubicin, and in 7 the treatment field was larger than 300 cm².

Discussion. Our rate of complications is higher than usually reported. This may be due to the higher than conventional dose per fraction. However, the radiation technique was not optimised in all our patients. Moreover, the 28 patients studied were treated at 12 different institutions.

Treatment of advanced soft tissue sarcoma with etoposide, ifosfamide and G-CSF (VIG regimen)—current status for the SSG-X trial

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From October 1989 to March 1993, 64 patients (pts) from nine institutions have been included in this phase II trial. There are 36 male and 28 female pts of median age 52 years (range 15-70). 86% had metastatic disease, 30% in combination with a primary tumor or local recurrence. The most common histological types were leiomyosarcoma (33%), malignant fibrous histiocytoma (26%) and synovial sarcoma (13%). 87% of the pts had tumors of high grade malignancy.

The patients have received median 3.5 VIG courses (range 1-9), and response evaluation has been performed after 3, 6 and 9 courses. Evaluation of response has been reported in 50 pts, of which 3 have obtained a clinical complete response (CR), and a further 3 had complete necrosis of residual tumor at surgery. Partial response has been reported in another 14 pts (28%), stable disease in 16 pts (32%), and progressive disease in 14 pts (28%). The current overall response rate is thus 40%, of which 12% are clinical or pathological complete responders.

The study also addresses survival after surgical removal of metastatic disease in combination with pre-and postoperative VIG chemotherapy. So far, macroscopically radical "metastasectomy" has been accomplished in 14 out of 16 operated pts, surgery following 3-6 preoperative VIG courses (data are missing in a further 3 operated pts). Lung resections have been performed in 9 pts, retro-peritoneal dissections in 2 pts, resection of a soft tissue lesion in 1 pt, hemipelvectomy in 1 pt, and data is missing in 1 pt. In 10/14 pts, surgery was preceded by clinical response to VIG chemotherapy. 6 pts have relapsed following complete surgery, and 7 (54%) remain free from detectable disease at median 4 months (range 1-9 months) from surgery (data missing in 1 pt).

Preliminary data indicate that the addition of G-CSF to the etoposide/ifosfamide regimen has significantly reduced leucopenia, and has allowed a significantly higher dose level and better schedule adherence, as compared to a pilot series treated without G-CSF supplement. The response rate is encouraging, particularly the presence of complete responders.

Treatment of high-grade osteosarcoma with the SSG-II (T-10) protocol—a follow-up report

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Since the previous publication of this material (1), an additional 4 patients (pts) have been reported to the secretariat. One patient who previously had major data missing is also includ-

ed in the present analysis. The material thus comprises 102 pts with non-metastatic, extremity-localized high-grade osteosarcoma treated at eight institutions from June 1982 to Dec 1989. There were 69 men and 33 women (m/f ratio 2.1) of median age 16 (6–36) years. 56% of the tumors were localized to the femur, 26% to the tibia, 13% to the humerus.

Following preoperative chemotherapy with four courses of high-dose methotrexate (HDMTX 8 g/m² for pts > 8 years of age, and 12 g/m² for younger pts), only 18% of the pts obtained a good histological response (Huvos grade III or IV). 28% of the pts were operated with resections and limb salvage, the rest underwent amputations.

Median follow-up for living pts is now 72 (20–127) months. Metastasis-free (MFS) and overall survival is 56% and 61%, respectively. Survival remains significantly better for pts who obtained a good histological response (grade III or IV) to preoperative chemotherapy, compared to pts with grade I or II response (79% vs. 53% MFS, *p* 0.03). 7/44 pts who have developed metastases are currently free of disease at median 35 (13–78) months after their first metastatic event. The local recurrence rate is 6%, with 4 recurrences following amputations and 2 following limb salvage procedures.

Reference 1. Saeter G et al. Treatment of osteosarcoma of the extremities with the T-10 protocol, with emphasis on the effects of pre-operative chemotherapy with single agent high-dose methotrexate. A Scandinavian Sarcoma Group Study. *J Clin Oncol* 1991; 9: 1766–75.

Treatment of high-grade osteosarcoma Current status to the SSG-VIII protocol

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From May 1990 to March 1993, 41 patients (pts) with non-metastatic, extremity-localized high-grade osteosarcomas have been entered into the SSG-VIII protocol from nine different institutions. There are 24 men and 17 women (m/f ratio 1.4) of median age 15 (2–39) years. 49% of the tumors were localized to the femur, 29% to the tibia, 15% to the humerus, and 7% to other sites. Treatment consists of 2 preoperative and 3 postoperative chemotherapy cycles, each containing 2 courses of high-dose methotrexate (HDMTX) and 1 course of cisplatin/doxorubicin. Poor histological responders to preoperative treatment are crossed over to receive 5 courses of etoposide/ifosfamide as postoperative treatment.

Histological response has been reported in 37 pts. Of these, 7 (19%) had total tumor necrosis (Huvos grade IV), 13 (35%) had grade III response, 12 (32%) had grade II response, and 5 (14%) had no identifiable effect (grade I). Thus 54% have obtained a good histological response, and the preliminary data indicate a significant improvement compared to the previous SSG-II protocol (18% grade III/IV responders, *p*

0.0001). 19/38 pts (50%) have been operated with limb salvage, as compared to 28% in the SSG-II protocol (*p* 0.02).

6 pts have developed distant metastases and 3 have died. Major protocol violations were present in one of these cases. No pts have developed local recurrence. Median follow-up from diagnosis is currently 13 (0–31) months, and projected two-year metastasis-free survival is 78%. For good responders metastasis-free survival is 95%, and for poor responders 67% (*p* 0.11).

Protocol modifications as of 93/03/01 include HDMTX dose escalation to 12 g/m² for all patients and courses, and postoperative cross-over to etoposide/ifosfamide for both grade I and II responders.

Preliminary results of the SSG IX protocol in Ewing's sarcoma

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In June 1990 a new treatment protocol of Ewing's sarcoma, the SSG IX, was activated by the Scandinavian Sarcoma Group. The protocol features an intensive chemotherapy (CT) program of four cycles, each consisting of two courses VAI (Vincristine 1.5 mg/m² day 1, Adriamycin 30 mg/m² day 1 and 2, and Ifosfamid 1 g/m² + mesna day 1–5) alternating with one course PAI (Platinol 90 mg/m² day 1, Adriamycin 30 mg/m² day 1, Ifosfamid 1 g/m² + mesna day 1–5) at three weeks interval. Total treatment time is 35 weeks. Local therapy, which should include surgery if possible, is given after one CT cycle at week 9. Inoperable or non-radically operated patients receive hyperfractionated radiotherapy 1.5 Gy twice daily between CT courses to a total dose of 42 to 60 Gy, depending on surgical radicality and tumour localisation.

Of 46 patients (30 male, 16 female, mean age 22 years) 39 had M0 and 7 M1 disease at the time of diagnosis. The metastases were spread to lung, bone and CNS. The mean size of the primary tumour was 11 cm (SD 6 cm). Tumour was located as follows: pelvis (9), femur (6), scapula (5), tibia (3), fibula (2), foot (2), humerus, radius, ulna, costa (each 1) (missing data in 15 pts).

As local therapy irradiation was given to 16 patients, 19 patients received surgery, amputation in 4 and local excision in 15. Histologic response available was GI in 4, and GII in 5, GIII in 5, and GIV in 2 tumors. The 2-year overall and DSF survival of all 46 patients were 67% and 60%, respectively; correspondingly those of the 39 patients with M0 disease 87% and 70%. Only one local recurrence was observed. Side-effects, mainly hematological, were common ranging from G3 to G4 (WHO).

Histopathological aspects of chondrosarcomas—conventional grading

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Subjective malignancy grading of chondrosarcomas has been proved to yield prognostic information, but the results are not quite satisfactory. In order to test the applicability of subjective grading as a basis for treatment allocations, we decided to investigate the reproducibility of the results between three independent observers.

Material and methods. Selected haematoxylin-eosin stained sections from 104 primary osseous chondromatous tumors originally diagnosed as chondrosarcomas or chondromas with possible malignant transformation. The tumors were classified as benign, borderline, or malignant. The sarcomas were graded I, II or III (Evans/Gitelis).

Results. The overall agreement was 0.55. The Kappa statistic (Svanholm) was 0.33 which signifies a poor agreement. Disagreement was most pronounced in the benign/borderline categories. However, when the grading was modified and reduced to two categories, low-grade (<I) or high-grade (II+III), the overall agreement was 0.80 with a Kappa value of 0.57 which is acceptable.

Conclusion. Conventional grading of chondrosarcomas shows a high interobserver variation and needs improvement if it is to be used as a basis for a more detailed stratification of patients. However, distinction between low-grade and high-grade lesions, as suggested in the new SSG protocol for treatment of chondrosarcomas, is more reproducible. DNA measurements and possibly other methods can yield important supplementary information.

Chondrosarcoma treatment in Gothenburg

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110 cases of skeletal chondrosarcoma were collected from our files, 74 male and 36 female. The mean age was 48 years. The average tumor size was 10 cm. 70 tumors were located in the trunkal skeleton. 92 chondrosarcomas were primary tumors, 18 were secondary. 3 chondrosarcoma were of clear-cell type, 2 were mesenchymal and 5 were dedifferentiated chondrosarcoma. More than two third of the tumors were low grade.

110 patients were operated on, 9 were inoperable. The margins were: intralesional 32, marginal 14, wide and radical 55. 27 patients were primarily operated outside our center, 23 of these had intralesional or marginal margins.

23 patients developed a local recurrence, 16 developed pulmonary metastases, and 9 other metastases. At follow-up, 2.4-31 years postoperatively (mean 13 years), 34 of the 101 operated patients were dead (24 had tumor related death, 10 died of other causes). 67 patients are alive (62 NED and 5 AWT).

In spite of the tendency for trunkal or proximal location, and hence difficulties to achieve wide surgical margins, the over all long-term survival after surgical treatment of chondrosarcoma is good, reflecting the low malignancy grade of the majority of these tumors.

Treatment of chondrosarcoma at the Norwegian Radium Hospital

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We present a retrospective analysis of 59 chondrosarcoma patients treated at the Norwegian Radium Hospital in the period 1981 to 1992.

31 patients were admitted with untouched tumor and 7 after fine needle cytology, while 20 were admitted after open biopsy or partial excision. One patient had recurrent local disease. The preoperative investigations included clinical examination, conventional x-rays, computerized tomography, magnetic resonance imaging and bone scan with dynamic registration. The patients and results were then evaluated at the weekly sarcoma meeting by specialists in oncology, radiology, histology, cytology, nuclear medicine, surgery and orthopedic surgery. Only 20% of the tumors were of high grade malignancy. 51 patients were treated by surgery. Reconstructions were performed by allografts or endoprostheses in 16 patients. Amputation was performed in 6 cases and wide excision in 12 cases. Local recurrences have not been seen, and only 2 patients have developed lung metastases. All are alive. Marginal excisions were performed in 26 cases. 9 of these patients developed a local recurrence, 5 developed metastases and 2 have died. 6 patients had partial excisions without adjuvant treatment; 5 are alive. 48 of the 51 patients treated by surgery for the primary tumor are alive. The median observation time is 4 years.

Radiotherapy was used in 7 inoperable patients. Local control was not achieved in 4 cases. The observation time was short for 2 patients who died after 5 and 12 months. One patient had a relatively small tumor in the basis cranii. The volume was irradiated with a total dose of 82 Gy. The patient is alive without symptoms after 29 months. The size of the tumor has not changed radiologically.

Chemotherapy has been given as adjuvant treatment to one patient. Histological examination of the tumor showed 20-50% necrosis, possibly an effect of the preoperative treatment with high-dose methotrexate, cisplatin and doxorubicin. Chemotherapy was given to four patients with metastatic disease, but no effect was found.

Conclusions. Chondrosarcomas of any malignancy grade should be treated by wide excisions. If wide margins have not been obtained, the patient should be reoperated if possible. Postoperative radiotherapy should not be used routinely after marginal excisions.

Treatment of chondrosarcoma in Helsinki

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The principal treatment of chondrosarcoma is surgical with wide resection as adjuvant therapies have been of little help.

Patients. At our department there have been 45 patients with chondrosarcoma during the last 12 years. The mean age was 47 (22-79) years.

Treatment. Of 13 cases of chondrosarcoma of the femur, 6 were operated on with an endoprosthesis, 4 with curettage and spongiosa grafting or cementation, and 3 with amputation. Of 6 tumors of humerus, 3 were operated on with an endoprosthesis and 3 with curettage and spongiosa grafting or cementation. 15 pelvic chondrosarcomas were mainly resected, with 3 hemipelvectomy and 1 resection endoprosthesis. Of the 2 ankle chondrosarcomas 1 was resected and the other was amputated. Of the 4 phalanx tumors 2 were resected and 2 amputated.

Conclusion. In the treatment of chondrosarcoma limb-saving surgery is often possible. Primary surgery has to be definitive without contamination to avoid local recurrence. Conventional radiography does not suffice in the follow-up as recurrences are mainly uncalcified.

Chondrosarcoma of the extremities 61 patients followed for 2–25 years

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Patients and methods. Our study included 61 patients with chondrosarcoma of the extremities treated 1967-89. There were 39 patients with low-grade (Grade I) lesions, and 22 with high-grade (19 Grade II and 3 Grade III). One patient in the latter group had metastases on admission. Patients with low-grade chondrosarcoma were younger and had smaller tumors than those with high-grade (Table 1). They were also predominantly intracompartmental and located distally. Patients with low-grade chondrosarcoma underwent either intralesional curettage or en bloc resection. One third of patients with high-grade lesions were amputated (Table 2). The most common mode of reconstruction after local resection was prosthetic replacement. The median follow-up time was 7 (2–25) years. No patient was lost to follow-up.

Results. The 7-year local recurrence rate was 0.08 for patients with low-grade chondrosarcoma and 0.41 for those with high-grade (p 0.007). None of the patients with low-grade lesions have developed metastases nor have anyone died of tumor related causes. For those with high-grade chondrosarcoma the 5-year metastasis-free survival was 0.49; the overall 5-year survival 0.69. Among patients with metastasis, only 50% survived 1 year after diagnosis of metastatic disease.

Table 1. Clinical features of 61 patients with chondrosarcoma of the extremities

	Low-grade	High-grade	p-value
Number of patients	39	22	
Sex, male	20	15	n.s.
Age	46 (14-70)	57 (20-82)	<0.02
Location prox humerus	11	4	
distal to prox humerus	1	1	
prox femur	5	11	
distal to prox femur	23	6	
Tumor diameter (cm)	5 (1-12)	10 (3-30)	<0.001
Compartment, intra	33	7	

Table 2. Surgical treatment. Local recurrence in parenthesis

		Low-grade	High-grade
Procedure	local excision	38	15
	amputation	1	6
Margin	intralesional	22 (1)	4 (2)
	marginal	6 (2)	4 (2)
	wide	10 (0)	10 (1)
	radical	1 (0)	2 (0)
Reconstruction	autogenous bone	12	–
	acrylic cement	7	–
	endoprosthesis	9	13
	allograft	1	1

Conclusions. The study shows that low- and high-grade chondrosarcoma exhibit a strikingly different clinical course. Low-grade chondrosarcoma entails a low-risk of local recurrence even after intralesional curettage. The risk of metastatic spread seems almost non-existent. Wide resection necessitating reconstruction with allograft or endoprosthesis should be avoided in most cases. High-grade lesions, on the other hand, are associated with a high risk of local recurrence and metastasis. The local recurrence rate was clearly related to surgical margin. A wide or compartmental excision is necessary for local control.

Magnetic resonance of benign peripheral nerve sheath tumors

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In a retrospective, nonblinded review of magnetic resonance (MR) imaging of 15 benign peripheral nerve neoplasms in 13 patients, the signal pattern of the tumors (including contrast enhanced scans) and stage were assessed. There were 2 men (22 and 24 years) and 11 women (28–55 years). One lesion was subcutaneous, 9 intramuscular, 2 intermuscular (intra-compartmental) and 3 extracompartmental (by origin). One lesion was located to the trunk, 5 to the upper extremity and 9 to the lower.

The signal on T1-weighted spin echo images was lesions homogenous isointense compared to adjacent muscle in 11

lesions and in 2 slightly hyper- and in one slightly hypointense. T2-weighted spin echo images, aquired in all but one examination, showed a hyperintense signal, homogenous in 7 and centrally inhomogenous in 6 lesions. Post contrast T1-weighted images, of 11 lesions, showed a strong signal, with an inhomogenous enhancement in the centers of the lesions similar to that obtained in T2-weighted images. In 2 cases, there were signal characteristics indicating bleeding in the tumor. In one lesion both the inenchanced and contrast enhanced T1-weighted scans showed a hypointense signal in tumor center suggesting intramuscular myxoma. All lesions were well delineated without reactive oedema. In all cases, stage was correctly assessed.

Although the findings were not specifically diagnostic for neurinoma, MR imaging provided valuable confirmation of the clinical and cytologic diagnostic.

Evaluation of treatment response in nude mice with osteosarcoma xenografts using 2-(18F)Fluoro-2-Deoxy-Glucose

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The prognosis of osteosarcoma has improved significantly after the introduction of aggressive chemotherapy, usually following neoadjuvant strategy. However in about 1/3 of the patients the primary tumor does not respond to the preoperative chemotherapy. Such patients belong to a poor prognostic group. Therapy failure is not possible to diagnose on non-invasive conventional imaging modalities.

The purpose of our study was to examine the uptake of FDG reflecting the tumor cell viability and hence the chemotherapy effect.

To mimic the clinical situation osteosarcoma xenografts, OHSX, growing in nude mice were treated with Adriamycin (8mg/kg i.v.), CCNU (20mg/kg i.p.), Cisplatin (5mg/kg i.v.) or Ifosfamid (240mg/kg i.v.), 11 and 4 days before the FDG study. The FDG were injected i.v. in the tail vein and after 60 minutes the animals were killed and the tumors, brains and blood were removed and the radioactivity was measured.

Table

Tumor uptake of FDG (%/g)		Histological evaluation
CCNU mean	1.5	Total necrosis
Ifosfamid	1.6	Total necrosis
Cisplatin	2.8	Areas with viable cells
Adriamycin	2.8	100% viable cells
Control	3.0	100% viable cells

Our results indicate that the "FDG uptake method" reflects the chemotherapeutic effect on osteosarcoma xenografts. The aim is to extend such studies into the clinical situation using positron emission tomography (PET).

Cytogenetic studies of bone tumors at the University of Helsinki in 1987-1992

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Chromosome analysis was performed on 304 samples of 249 patients operated on at the Helsinki University Central Hospital between October 1987 and April 1992. The diagnoses consisted of 86 non-neoplastic disorders, 108 benign bone tumors and 110 malignant bone tumors. The last group consisted of 78 primary bone tumors and 32 other bone malignancies.

Methods. Cell suspension was obtained mechanically and/or enzymatically. Part was exposed directly to colcemid, part was cultured for various lengths of time. For staining trypsin-Giemsa-banding was used; at least 20 metaphases were analyzed.

Results. One sample from an infectious process demonstrated a simple clonal aberration. 6 specimens of 75 successfully cultured benign tumors demonstrated clonal aberrations, most of which were simple structural aberrations. A clonal chromosome aberration was detected in 21/54 successfully cultured samples of primary malignant tumors and in 8/21 other malignant tumors, the aberrations being in general chaotic. The specific translocation of Ewing's sarcomas t(11;22), was detected in 6/8 Ewing's sarcomas. The most frequent non-clonal aberration was telomeric association, which was specific to giant cell tumors.

Conclusions. Cytogenetic study provides increasing knowledge of the biology of bone tumors and is a valuable adjunct in their evaluation.

Flow and image DNA-analysis of soft tissue sarcoma

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We performed flow cytometric DNA-analysis (FCM) on cell suspensions and image DNA-analysis (ICM) on touch preparations from the same tissue piece in 127 sarcoma specimens (67 primary sarcomas and 28 recurrences).

Histogram evaluation. The ICM histograms were evaluated according to the Auer classification for breast carcinoma (AI-

IV) in which AI was considered to correspond to ICM-diploid tumors, AII to ICM-tetraploid, AIII to ICM-aneuploid or diploid with a high proliferation and AIV to aneuploid.

The FCM histograms were evaluated according to Hiddeman et al.: one cell population corresponding to a diploid tumor and > one population to a non-diploid tumor. No respect was taken to the S-phase fraction.

Results. Of 53 FCM diploid samples 19 were AI, 11 AII, 5 AIII and 18 AIV and of 74 FCM non-diploid and tetraploid histograms 2 were AI, 3 AII, 5 AIII and 64 AIV. The reasons for the discrepancies may be non-representative samples, preparation artefacts of FCM suspensions or touch preparations, differences in sensitivity and resolution between FCM and ICM or that FCM S-phase fraction was not taken into consideration.

Conclusion. A considerable fraction (64%) of FCM-diploid samples was found to be AII-AIV. Therefore, all FCM-diploid analyses should be supplemented with ICM of a touch preparation or suspension.

Flow cytometric DNA-analysis in soft tissue sarcoma—which parameter is best for prognostication?

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We performed flowcytometric DNA-analysis in 305 patients with primary soft tissue sarcoma of extremity and trunk wall to determine the best parameter for prediction of metastasis.

Patients. The median age was 64 (18–90) years. Half of the tumors were located in the hip girdle, thigh and knee. 88 tumors were superficial. MFH was the most common histotype (43%), and grade IV (four-grade scale) the most common malignancy-grade (52%). All but one patient were operated on. 111 patients developed metastases. Follow-up was complete with a median of 9 (2–27) years for the survivors.

Observations. Ploidy status (histogram types 1–4 (diploid) and 5 (tetraploid) versus 6–8 (aneuploid)) and the number of non-diploid populations (none versus one or more) both were univariately prognostic for metastasis, but ploidy status gave the best prognostic information. Increasing DNA-index was not associated with a higher rate of metastasis.

In a univariate analysis tumor size >8 cm, aneuploidy, deep location, and malignancy-grade were all prognostic. In a multivariate analysis with all four factors included only size and malignancy-grade had independent prognostic value. In a multivariate analysis with malignancy-grade excluded size and ploidy status had independent prognostic value.

Conclusion. We propose ploidy status for quantification of prognostic DNA-analyses.

Soft tissue sarcoma should be treated at a Tumor Center—a comparison of quality of surgery in 375 patients

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We analyzed the quality of surgery in patients with primary soft tissue sarcoma of extremity and trunk wall. Patients referred before surgery (n 195), patients referred after surgery (n 102), and patients not referred for their primary tumors (n 78) were compared.

Patients. 329 tumors were located in the extremity. 121 were subcutaneous. MFH was the most common histotype (46%) and grade IV the most common malignancy-grade (49%). Follow-up was complete (minimum 2 years). Incisional biopsy, but not fine-needle aspiration, was classified as an operation. Patients referred before surgery had larger and more often deep-seated tumors, otherwise there were no differences between the groups as regards clinico-pathologic factors, amputation rate, use of radiotherapy, or survival.

Observations. A total of 218 operations were performed for the primary tumors in the 195 patients referred before surgery. This ratio was 1.7 times higher for patients referred after surgery, and 1.4 times higher for patients not referred. The local recurrence rate in patients referred before surgery was 18 percent. It was 1.3 times higher in patients referred after surgery, and 2.4 times higher in patients not referred.

Conclusions. Soft tissue sarcoma patients should be treated at a tumor center and the patients should be referred before surgery.

In vitro drug sensitivity testing of tumor cells from patients with sarcomas using the fluorometric microculture cytotoxicity assay (FMCA)

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Cytotoxic drug sensitivity data from an in vitro test could be used to select the best drugs for each patient but also for development of new drugs by performing "phase II trials in vitro". The fluorometric microculture cytotoxicity assay (FMCA) based on cleavage by viable cells of fluorescein diacetate to fluorescent fluorescein (Larsson and Nygren, Int J Cancer 46;67,1990), has been found to give drug sensitivity data correlating well to clinical outcome for patients with acute leukemias and non-Hodgkin's lymphomas. This assay has now been used also for testing solid tumors, among them sarcomas.

Materials and methods. 26 tumor samples were obtained from 23 sarcoma patients at surgery or by needle biopsy.

Tumor cells were prepared by mincing the tissue to mm³ sized pieces followed by collagenase digestion. The fraction of tumor cells was determined by inspection of stained cyto-centrifuge slides. Tumor cells in culture medium were then added to 96-well microtiter plates prepared with the drugs to be tested. After 72 hr incubation, cell viability was determined by measurement of fluorescein fluoroscens in a micro-fluorometer.

Results. Technically successful assays, defined as an initial fraction of tumor cells of >70% and a signal to noise ratio of >5, for up to 25 drugs or drug combinations were obtained for 19 samples (73%). Enough cells for testing up to 10 drugs could also be obtained from needle biopsies. The sarcoma samples were much more resistant to all drugs than acute leukemias and non-Hodgkin's lymphomas. For the most commonly used cytotoxic drugs the sarcomas were approximately as drug sensitive as samples from breast cancer. An untreated Ewing sarcoma was considerably more drug sensitive than other sarcomas but more resistant at relapse after chemotherapy. The most active drugs in sarcomas were etoposide, cyclophosphamide and anthracyclines.

Conclusions. A high fraction of sarcoma samples, including those from needle biopsies, can be successfully analyzed by the FMCA, which seems to report drug sensitivity data in correspondence with known clinical drug activity. It may thus be suitable for future tailormaking of chemotherapy for sarcoma patients and for development of new drugs. Two patients have been treated according to in vitro assay results and will be discussed.

Molecular genetic mapping of chromosome 22 in sporadic and NF1-related peripheral schwannoma, neurofibroma and neurofibrosarcoma

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Benign tumors, Cytogenetics studies, Nerves

Peripheral schwannomas occur sporadically or in association with neurofibromatosis (NF) type 1 and type 2. The NF1-gene has been localized to chromosome 17q by linkage analysis and the NF2-gene has been localized to chromosome 22. Acoustic schwannoma in NF2-patients show loss of genetic material in chromosome 22 in the same region as the NF2-gene. Cytogenetic analysis of sporadic schwannomas have shown clones with chromosome 22 monosomy as well as clones without microscopically detectable aberrations. Thus it is of interest to study whether schwannomas, occurring in NF1 patients, show any loss of genetic material from chromosome 22. Neurofibroma and neurofibrosarcoma are the other tumors associated with NF1. We have therefore studied a series of schwannomas, neurofibromas and neurofibrosarcomas from patients with and without NF1 regarding loss of genetic material from chromosome 22.

Material and methods. 22 well mapped loci on chromosome 22 have been studied. In 2 neurofibrosarcomas, 8 neurofibromas and 18 schwannomas tumor cell DNA and DNA from peripheral blood were compared with restriction fragment length polymorphism (RFLP) analysis.

Results. The NF1-related schwannomas showed results indicating monosomy of chromosome 22 while the NF1-related neurofibrosarcoma showed loss of alleles at certain informative loci and retention of heterozygosity for other alleles in conformity with partial deletion of chromosome 22. One case of neurofibrosarcoma without known relation to NF1 showed results as for monosomy #22. Of the 7 NF1-related neurofibromas 6 showed results indicating interstitial or terminal deletion of chromosome 22, 1 case showed monosomy #22. One sporadic neurofibroma showed no genetic loss of chromosome 22. Among the sporadic schwannomas results indicated in some cases partial deletion and in others monosomy for chromosome 22.

Conclusions. Loss of genetic information from chromosome 22 occurs in NF1-related and sporadic peripheral schwannomas, neurofibromas and neurofibrosarcomas.

Experimental osteosarcoma—preliminary results of different treatment modalities

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We have developed an experimental model to evaluate local bone tumor formation and subsequent pulmonary metastases by orthotopic implantation of the viral Ki-ras oncogene transformed KRIB cell line derived from the human osteosarcoma cell line TE85. This preliminary report presents our first experience in evaluating treatment protocols using the orthotopic osteosarcoma model.

Animals and methods. Female athymic nude mice were injected with 5–20x10³ KRIB cells (in 10 microliters of DMEM) into the proximal tibia using a 30G needle. Two treatment protocols were used.

Protocol 1. 13 mice were injected with KRIB cells; of these 7 were given Suramin (0.35 mg/g mouse) 30 minutes before, and on the sixth day after the tumor implantation, and 6 mice had no further treatment.

Protocol 2. 25 mice had KRIB cell injections; of these 10 mice had 6-OH-Fulvene (10 mg/kg, 3x/week), 10 mice had Cisplatinum (3.2 mg/kg, 1x/weekxIII), and 5 mice had no further treatment.

Results. Protocol 1: 6 of 7 Suramin treated mice formed primary local KRIB osteosarcomas in the tibia of which 2 had none, 2 only scant, and 2 wide-spread lung metastases. 5 of 6 control mice formed local tumors and all 5 had wide-spread lung metastases.

Protocol 2. 9 of 10 6-OH-Fulvene treated mice formed local tumors, while only 2 of them had lung metastases 6

weeks after injection. 3 of 10 Cisplatin treated mice had local tumors and all of them had lung metastases. 4 of 5 control mice formed local tumors and 4 had lung metastases.

Conclusions. The results indicate that Suramin and 6-OH-Fulvene do not prevent local tumor formation, but may diminish the risk of forming lung metastases, while Cisplatin diminish the risk of forming local tumors, but does not diminish the risk of forming lung metastases among those who develop local tumors.

Chondrosarcoma in cell culture Treatment with tumorsuppressive agents

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Chondrosarcomas are treated by surgical excision. Adjuvant treatment is not generally used, because of the difficulty to accumulate sufficient clinical data to support such a program. As a first step towards use of adjuvant treatment, human chondrosarcoma cells in culture have been tested for sensitivity to chemotherapeutic agents.

Microtiter plate cultures of human chondrosarcoma cell-lines were performed in cell culture medium with and without the presence of chemotherapeutic agents. DNA was analyzed with a colorimetric method and with a fluorescence method. S-100 protein was determined with an ELISA method. Cell-protein and -viability was determined spectro-photometrically.

The chondrosarcoma cells showed linear cell growth. Chemotherapeutic agents were added to cultures on day 2. Cultures were evaluated after six days and contents of cell-protein, DNA, S-100 protein and cell-viability were determined. Several different human chondrosarcoma cell lines were tested and showed sensitivity to pharmacological concentrations of adriamycin, methotrexate and cisplatin.

In clinical practice chondrosarcomas are regarded to be insensitive to chemotherapeutic agents. To resolve the apparent inconsistency with our results, we are implanting human chondrosarcoma cells into nude mice, to develop an animal model, to study different types of adjuvant therapy and different ways of administration of tumor suppressive agents.

Angiosarcoma secondary to chronic lymphedema

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The occurrence of cutaneous and subcutaneous angiosarcoma (AS) secondary to chronic lymphedema is well known; the development of AS in a lymphedematous upper extremity following mastectomy for breast carcinoma is the most common clinical setting (Stewart-Treves Syndrome, STS).

Many of the questions concerning etiology, histogenesis, tumor progression and clinical behavior remain unsolved and conclusive diagnostic criteria, especially for the early, lymphangioma-like stages, are deficient. We report the results of a clinicopathological study of 33 patients with AS, all of which have a previous history of surgery and/or irradiation with secondary lymphedema in the region of the body, in which the AS eventually developed. 29 of the patients were women with STS. Median age at diagnosis was 74 years (51-90). The AS developed 2 months to 25 years (median 11 years) after mastectomy with or without irradiation. 3 patients developed AS in a lymphedematous lower extremity.

Light-microscopically, immunocytochemically, lectin histochemically and ultra-structurally a sequential development from local or multicentric proliferation of blood vessels and/or lymphatic vessels to highly malignant solid sarcomas with hardly recognizable vessel differentiation could be demonstrated.

Of the 33 patients 31 were dead 2 months to 12 years after the diagnosis of AS; in 20 of those the AS (multicentric growth and/or metastatic spread) was the main cause of death.

Conclusions.

- 1) AS secondary to chronic lymphedema is a highly malignant tumor disease.
- 2) A long delay of diagnosis is common.
- 3) The etiological importance of irradiation treatment is unclear.
- 4) AS secondary to chronic lymphedema is an interesting model for further clinical, morphologic, cytogenetic and molecular biological analyses.

Benign peripheral nerve sheath tumors adjacent to the axial skeleton with extensive bone destruction

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11 patients with large classical and cellular schwannomas and neurofibromas adjacent to the axial skeleton causing extensive destruction of vertebra and/or sacrum are reported. 9 patients were women and 2 were men; age ranging from 24 to 71 years. 3 of the tumors were located in the sacrum, 5 in the lumbar spine, 2 in the thoracic spine and 1 in the cervical spine. The tumors were large, up to 21 cm in diameter, 1300 g. Neurologic symptoms were present in 6 patients. All tumors were surgically removed, 3 patients had intralesional excision of the tumor, the remaining had excision with a marginal margin. 5 of the tumors were classical schwannomas, 4 cellular schwannomas and 2 neurofibromas. At follow-up, 6 months-9 years, 3 patients were alive with tumor, 8 NED. 5 patients had remaining neurologic symptoms.

Conclusions. Benign peripheral nerve sheath tumors adjacent to the axial skeleton can reach considerable size and may cause extensive bone destruction and neurological symptoms.

i.e. they may both clinically and radiologically simulate a malignant neoplasm. Surgical treatment in order to preserve nerve function and stability appears to be the treatment of choice. Decompression may sometimes, however, be the only possible procedure.

Long survival after simultaneous treatment with chemotherapy and radiotherapy for an inoperable synovial sarcoma

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With this case report we want to elucidate the potential growth rate of soft tissue sarcomas and an unusual good response to a combined treatment of chemotherapy and radiotherapy. The patient is 31-year-old man, previously healthy, with a history of pain to the right in the neck of about a year before a paravertebral tumor, C7-Th1, was diagnosed by CT. Cytology and two preoperative biopsies indicated a neurilemoma. On that basis the tumor was enucleated.

However, the final histology showed a monophasic synovial sarcoma, grade III, with tumor growth in the surgical margin. The patient was referred to radiotherapy. CT just before radiotherapy start revealed a 9x8x8 cm local recurrence, judged as inoperable. Because of this situation we started chemotherapy using adriamycin, cisplatin, ifosfamide and vincristine according to SSG IX. The neurological symptoms in the right arm disappeared but came back at the start of the 2nd course. CT after two courses showed progress with intraspinal growth. So there was evidence of response to chemotherapy but also of very rapid growth rate. Therefore radiotherapy was interfoliated between the chemotherapy courses using accelerated treatment with 2x1.5 Gy/day to a tumor dose of 60 Gy and a spinal cord dose of 42 Gy, according to SSG IX.

3 years after diagnosis the patient is without symptoms and in full time work.

The Gothenburg experience of osteosarcoma treatment with the SSG VIII protocol

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Since the start of SSG VIII program, 8 patients with osteosarcoma have been treated at the departments of general and pediatric oncology in Gothenburg. The age range was 8-27 years.

Due to hyperbilirubinemia one patient with lungmetastases was treated with Ifosfamide/Vepesid and died 11 months later. Because of infection in the tumorarea one patient was ampu-

tated before chemotherapy. The treatment was stopped after four cycles because of a hepatitis B infection. The patient died 14 months later with widespread disease. One child had multifocal disease and died after only two cycles of chemotherapy. 5/8 patients were treated according to plan. Two were children and received 12g/m² of methotrexate. No significant dose-reductions were needed and no life-threatening toxicity was observed. Only one tumor showed histopathologically complete necrosis after pre-operative chemotherapy. The remaining four showed no signs of response. All these patients are living free of disease 1, 3, 10, 10, and 19 months post-chemotherapy. Methotrexate-concentrations were measured at 24, 48 and 72 h after start of the infusion. In contrast to what has been reported, almost no intraindividual variations were found when comparing different courses. The value of measuring methotrexate-concentrations will be discussed.

Dedifferentiated chondrosarcoma, clinical and morphologic analysis

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Dedifferentiated chondrosarcoma, defined as a low grade chondrosarcoma with abrupt transition to a high grade sarcoma, such as osteosarcoma, fibrosarcoma and malignant fibrous histiocytoma, is a rare subtype of malignant cartilage tumor.

Since 1972 we have treated 5 patients with dedifferentiated chondrosarcoma. All 5 were men, 42-71 years of age. Average tumor size was 10 cm. 4 tumors had pelvic location and one was located in the sternum. All tumors were highly differentiated chondrosarcomas with a component of high grade osteosarcoma (2), teleangiectatic osteosarcoma (1), malignant fibrous histiocytoma (1), and fibrosarcoma (1). Teleangiectatic osteosarcoma has previously not been described as a component of dedifferentiated chondrosarcoma.

The 4 pelvic tumors were treated with hindquarter amputation, 3 with wide, and 1 with intralesional margin. The tumor in the sternum was resected with a marginal margin. All patients had post-operative treatment with chemotherapy and 3 patients received post-operative radiotherapy. 2 patients survived for 2 and 10 years respectively, before they died with local recurrence. The other 3 patients died within 9 months with metastatic spread.

Conclusion. Dedifferentiated chondrosarcoma is a highly malignant tumor and difficult to control even with extensive surgery and adjuvant therapy.

Current status of soft tissue tumor classification—special emphasis on malignancy grading and on borderline malignancies

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The first WHO-classification "Histological typing of soft tissue tumors" was published 1969. A WHO expert committee was formed 1988 and has drafted a new classification which was presented in its final form at the International Academy of Pathology Congress in Madrid, Spain in October, 1992.

Even if the new classification may be referred to as being "histogenetic" it is based on the "line of differentiation." The classification adds more than 40 new entities to the old classification. In some categories, e.g. the new category "Fibrohistiocytic tumors" are included groups of borderline or intermediate tumors, many of them newly described entities. The committee encourages the practise of grading soft tissue sarcomas using whatever regional system that has been devised and systematically validated. To day there is no malignancy grading system which has been accepted worldwide.

Cytogenetics and molecular genetics of soft tissue sarcomas

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Cytogenetic analysis of short-term tissue cultures from soft tissue sarcomas have revealed recurrent chromosome aberrations in several tumor types. Several of these aberrations are highly tumor specific and hence of diagnostic significance. These include t(12;16)(q13;p11) in myxoid liposarcoma, t(2;13)(q35;q14) in alveolar rhabdo-miosarcoma, t(X;18)(p11;q11) in synovial sarcoma, t(9;22)(q22-31;q11-12) in extraskeletal myxoid chondrosarcoma, and t(12;22)(q13-14;q12-13) in clear cell sarcoma of tendons and aponeuroses. Infantile fibrosarcomas are characterized by hyperdiploid karyotypes with gain of in particular chromosomes 11, 17, and 20. Supernumerary ring chromosomes of unknown origin are found in borderline or low grade malignant tumors such as well differentiated liposarcoma, malignant fibrous histiocytoma (MFH), and dermatofibrosarcoma protuberans. High grade MFH and leiomyosarcomas have complex chromosome rearrangements with some recurrent but seemingly unspecific changes. These include for example 19p+ marker chromosomes, which seem to be associated with increased relapse rate in MFH. Secondary, at least in part nonrandom, aberrations are frequently found and intratumor cytogenetic heterogeneity demonstrating clonal evolution is common, and may turn out to be of importance in prognostication.

Molecular genetic isolation and characterization of genes of pathogenetic significance have just begun in soft tissue sarcomas. Two transcription factor genes, CHOP in 12q13 and

PAX3 in 2q35, that are rearranged in liposarcomas with t(12;16) and rhabdomyosarcomas with t(2;13), have been identified. Additional genes that have been implicated in soft tissue sarcoma tumorigenesis are TP53 in patients with Li-Fraumeni syndrome as well as with sporadic soft tissue sarcomas, and MDM2, which has been found to be amplified in some soft tissue sarcomas.

MRI in the surgical staging of soft tissue sarcomas—anatomical localization

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For preoperative surgical staging of soft tissue sarcomas MRI is preferred to CT because of better tissue contrast and spatial resolution. Furthermore, MR permits orientation of the images in a plane best suited for the part to be examined. To avoid incorrect interpretation of a MR study special attention has to be paid to the size of the tumor, its location and whether the tumor is located close to a fascia.

A large tumor, relative to site, distorts the local anatomy. This leads to difficulties in assessing the borders of the tumor and whether the tumor is intra- or extracompartmental. In proximal locations, there is often fat between muscles and fascial planes, making it easy to identify anatomical structures, i. e. correct assessment of tumor compartmentalization is usually easy. However, distal to elbow and mid-calf, identification of muscles is often difficult due to the lack of fat, leading to often unreliable assessment of the tumor compartment.

Although, sarcomas do not commonly extend through fascias, there are problems in staging subcutaneous tumors juxtaposed to the deep fascia. These tumors may grow deep in the subcutis and exert pressure on the underlying fascia. Together with a reactive edema, tumor delineation may be very difficult and MRI will give the false impression that subcutaneous tumors extend extracompartmentally beneath the fascia. Hence, MR imaging has a tendency to exaggerate rather than underestimate tumor extension. Although MRI is very sensitive for bleeding we have not found that fine needle aspiration biopsy impedes the correct interpretation of MR images. However, one should refrain from open biopsy until all preoperative staging studies are completed.

Surgery based on fine needle aspiration cytology

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Omitting of open biopsy in the preoperative diagnosis of soft tissue sarcoma decreases the risk for local recurrence. We have substituted open biopsy with fine-needle aspiration cytology

and our preoperative evaluation of soft tissue lesions is based on the combined information from clinical, cytologic and radiographic examinations.

In a retrospective study of a 20-years-material (1972–91) of 517 patients, referred with untouched soft tissue tumors of the extremities and trunk wall we have analysed the accuracy of cytodiagnosis and consequences of false cytodiagnoses.

Patients and methods. 315 patients had benign tumors and 202 sarcomas. The cytodiagnoses were classified as sarcoma or benign lesion or non-diagnostic (inconclusive or insufficient). From 1982 a cytologic malignancy grade (low, high or inconclusive) was recorded for all 127 sarcomas.

Results. Conclusive diagnoses were rendered in 92%, inconclusive in 6, and insufficient in 2. Benign tumors were correctly diagnosed in 95% and sarcomas in 93%. The cytologic malignancy grade was correctly assessed in 103 sarcomas and was inconclusive in 24.

Open biopsy was performed in 13 patients (3%). 28 out of the 475 conclusive diagnoses were false, 14 sarcomas and 14 benign lesions, and caused overtreatment of two patients.

Conclusion. The combined information from clinicoradiologic findings and fine-needle aspirations cytology allows primary, definitive surgery in most soft tissue lesions.

Limbsparing surgery without radiotherapy

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The first concern when treating extremity soft tissue sarcoma is local control, the second is preservation of function. There are different ways to address this problem. Surgery is the common denominator in all studies. The controversy is whether radiation should always be included or not.

In several centers the Stener principle is employed. This means that, provided certain prerequisites are met with, biopsy may be omitted. As a consequence surgery can be limited, but still be adequate. When histologic proof of malignancy is needed, fine-needle aspiration cytology is in most cases sufficient. This may also allow less extensive surgery than after incisional biopsy. When these methods are used the local recurrence rate after adequate surgery is below 10%.

In many centers advocating incisional biopsy, pre- or post-operative radiation is given to make less extensive surgery possible, than would otherwise be required. Local recurrence rates range around 10% with this treatment, as well. The hazards of radiation treatment are edema, soft tissue necrosis, vascular compromise, fracture, fibrosis, amputation, and radiation sarcoma.

With a proper analysis of tumor location and avoidance of incisional biopsy, about two thirds of the patients could have limbsparing surgery with good postoperative function without adjuvant radiation. To reach a widely accepted consensus on local treatment long-term prospective studies of different methods are needed.

Indications for radiotherapy in soft tissue sarcoma

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In 20 studies of non-radical surgery combined with post- or pre-operative irradiation published between 1981 and 1991 a mean rate of local control of 17% was reported.

Several recent studies of preoperative irradiation have documented a local control rate even better than with postoperative irradiation. The risk of complications, however, seems to be higher. In the absence of controlled trials no firm evidence exist favouring pre- or postoperative irradiation; however, in large inoperable sarcomas, where even marginal surgery is impossible or associated with excessive morbidity, pre-operative irradiation may be preferable.

After radical or wide surgery without wound contamination SSG does not recommend postoperative radiation in soft tissue sarcoma. After intralesional or marginal surgery postoperative irradiation is indicated. The recommended total dose is 50 Gy in 2 Gy fractions, 5 days a week, followed by a 10–20 Gy boost after intralesional surgery or in case of tumor cell contamination during the operation. In locally advanced inoperable soft tissue sarcoma preoperative irradiation with 50 Gy in 5 weeks is to be considered.

The biology of metastasis An update review

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To develop a malignant phenotype a normal cell must undergo initiation and transformation (through oncogene activation, carcinogenic insult, or chromosomal rearrangement). Such malignant phenotypes undergo certain evolutionary steps at the primary tumor site, are then detached and transported to a secondary tumor site (location of metastasis) where they continue to proliferate.

Primary tumor site events. The malignant cell line undergo evolution and progression in the primary localized neoplasm resulting in growth, vascularisation (angiogenesis), and invasion. To metastasize the cell need to be detached from the primary tumor site and become motile (a process controlled by integrins and other cell surface receptors) through the underlying stroma and penetrate the vascular epithelial basal lamina. Tumor cells can turn on the fos-oncogene, encoding transin, a proteolytic enzyme disrupting the basement membrane giving access to the humoral system.

Transportation. The malignant cell then has to be transported with the venous or lymphatic system. Only one of one thousand tumor cells may survive this event. The majority of the tumor cells are lysed by lymphocytes, monocytes, natural killer cells, and mechanical damage.

Secondary tumor site events. Surviving tumor cells become arrested in the secondary organ, adhere to the capillary endothelial cells, and extravasate into the stromal tissue. Here the tumor cell will continue to progress and proliferate.

The metastatic process is a non-random, complex, dynamic series of mutually dependent interrelated events. The microbiologic correlates for these events will be presented.

Adjuvant treatment and prognosis of soft tissue sarcoma—a randomized trial

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From 1981 to 1986, a total of 240 patients with primary, malignancy-grade III or IV soft tissue sarcoma were entered into an adjuvant chemotherapy multicenter trial. Of these patients, 181 were evaluable. After radical surgery (wide and compartmental) the patients were randomized to treatment with single-agent doxorubicin 60 mg/m² administered as an intravenous bolus once a month for 9 months (group 1, n 77) or to control (group 2, n 77). If the surgical procedure was marginal, the patients initially received postoperative radiotherapy, followed by doxorubicin (group 3, n 16) or control (group 4, n 11). With a median follow-up of 90 (2–145) months, and for 104 survivors 112 (84–145) months, there was no significant difference between the four groups in overall survival, disease-free survival or tumor control. The conclusions were the same whether the total group or evaluable patients only were included in the analysis.

Intratumoral vascular invasion (RR: 2.6), histologic malignancy-grade IV (RR: 2.6), tumor size >10 cm (RR: 2.1), DNA aneuploidy (RR: 2.0) and male sex (RR: 1.7) were found to be independent prognostic risk factors in 148 high-grade soft tissue sarcomas of the extremities and trunk.

It is recommended, that all SSG I-patients will be followed for at total of 10 years from the randomization date and reported to the SSG-secretariat.

Treatment of metastatic high-grade soft tissue sarcoma—the Norwegian Radium Hospital experience since 1989

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From April 1989 to January 1993, 36 patients (pts) with distant metastases from soft tissue sarcoma of high grade malignancy have been treated with etoposide 600 mg/m² (72h continuous infusion) and ifosfamide 1500 mg/m²/day for three days, with 3 week intervals. 13 pts have in addition received G-CSF 5 µg/kg subcutaneously for 12 days following chemotherapy (VIG regimen). The median age was 45 (14–73) years, and the median total number of courses was 6 (2–9). 14 pts had

local recurrence or an intact primary tumor in addition to metastatic disease. 25 pts had pulmonary metastases (6 pts with additional metastatic sites), 9 had liver metastases, and two had retroperitoneal or subcutaneous manifestations only. The commonest histological types were malignant fibrous histiocytoma (10), leiomyosarcoma (7) and synovial sarcoma (5).

Response was evaluated by WHO criteria after 3, 6 and 9 courses. 17 pts obtained clinical partial remission, of which 2 pts had complete tumor necrosis on subsequent surgical resection. None of the 9 pts with liver metastases responded to chemotherapy, which indicates a response rate of 63% for extrahepatic lesions.

Following median 5.5 (2–9) preoperative chemotherapy courses, surgical removal of all residual macroscopic disease was attempted in 18 pts and was accomplished in 11. In the latter group, 6 pts had lung resections (4 bilateral, and 2 in combination with extrapulmonary surgery), 3 pts had liver resections, 1 had a hemipleurectomy and 1 had a soft tissue resection. 8/11 pts had responded clinically to preoperative chemotherapy, and there was good correlation between, the clinical and histological responses. Of patients with complete surgery, 6 have relapsed at median 7 (1–23) months from surgery (1 of these is again free of macroscopic disease after additional lung surgery), and 5 remain relapse free at 1+, 2+, 4+, 6+, and 9+ months. More patients and longer follow-up is necessary to determine the potential of this treatment approach.

Treatment of soft tissue sarcoma An overview

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Genetics. Children with familial retinoblastoma have about a 7% incidence of osteosarcoma. Many sarcomas carry the 13q chromosomal deletion originally observed in retinoblastoma. Patients with neurofibromatosis have a 7 to 10% lifetime risk of developing a sarcoma. Germ line p53 mutations have been implicated in some families with childhood sarcomas, breast cancer and other tumors (Li-Fraumeni syndrome). Characteristic cytogenetic abnormalities have been associated with sarcomas and oncogenes have been found at the translocation points of several of these characteristic cytogenetic abnormalities.

Randomized adjuvant chemotherapy trials. Adjuvant chemotherapy is currently established in the treatment of rhabdomyosarcomas, osteosarcomas, and Ewing's sarcomas, but remains unproven in other adult soft tissue sarcomas.

Of the 12 reported adjuvant studies, 2 studies (Rizzoli Center, Bologna and Foundation Bergonie, Bordeaux) show a significant overall survival advantage for chemotherapy. Subset analyses in two additional studies (M.D. Anderson Hospital and the National Cancer Institute) report a significant disease-free survival advantage for adjuvant chemotherapy in extremity lesions but no significant improvement in survival.

The survival of the observation arm exceeds that of the chemotherapy arm in 3 studies (Mayo Clinic, ECOG, Scandinavian Sarcoma Group study).

A meta-analysis of the published soft tissue sarcoma adjuvant studies using disease-free and overall survival from each institutions' most recent publication does show a significant advantage for adjuvant therapy. The results of this meta-analysis cannot be applied to central body sarcomas. In addition, high grade sarcomas of <5 cm have a >90% survival and should not be treated with adjuvant chemotherapy. For patients with high grade extremity lesion >5 cm in size, the answer will await a formal meta-analysis based on original data as was done for breast cancer by the Oxford Group.

Advanced soft tissue sarcomas. Based on recently completed large randomized cooperative group studies ifosfamide and doxorubicin is probably the optimal regimen in terms of tumor

response rate. The median survival in these trials is in the range of about 12 months with no differences in survival generally observed. The lack of an effect on survival despite significant differences in response rates is probably multifactorial.

1. A response rate substantially under 50% will not translate into a survival advantage.
2. The survival of patients with macroscopic disease (107 to 1012 tumor cells) will not be affected by regimens that provide a half a log (a PR) or 2 logs (a CR) of tumor cytotoxicity.

Dose intensive therapy in sarcoma. Autotransplants have also been used to ensure prompt marrow recovery after high doses of chemotherapy. Ewing's sarcoma, rhabdomyosarcoma and osteosarcoma are optimal tumor for studies of the role high dose therapy.