Scandinavian Sarcoma Group

Trondheim, April 16–18, 1997

Editors: Thor A Alvegård and Anders Rydholm

The Pediatric Tumor Registry in Kiel

D Harms

Institute of Pediatric Pathology, Kiel, Germany

The Kiel Pediatric Tumor Registry was established in 1977 as the morphologic central tumor registry of the German Society of Pediatric Oncology and Hematology (GPOH). The principle functions of this registry are: 1) collection and evaluation of tumor specimens; 2) providing consultations on and classification and grading of tumors; 3) publication of acquired knowledge and new data; and 4) to function as a reference center in cooperative therapy studies.

Until now (X/96) 22,332 cases are documented in the registry encluding 3,177 (14%) soft tissue malignancies (STS). In decreasing order of frequency the most frequent STS are: rhabdomyosarcoma (RMS) (42% of the cases; embryonal RMS 30%, alveolar RMS 12%, other RMS 2%), pPNET (16%), extraosseous Ewing¥s sarcoma (9%), malignant peripheral nerve sheath tumor (7%), synovial sarcoma (5%), leiomyosarcoma (4%), fibrosarcoma (2%), and malignant extrarenal rhabdoid tumor (2%). All other STS (including intermediate fibrohistiocytic tumors) make up only 13% of the cases.

The registry participates in many cooperative therapy studies of the GPOH including neuroblastomas, nephroblastomas, soft tissue sarcomas, Ewing¥s sarcomas, germ cell tumors, histiocytoses and hepatoblastomas. Due to generally good cooperation with the local pathologists, reference pathology is available in most cases before start of the therapy.

Survival in children with rhabdomyosarcoma in Sweden

T Möller[1], H Anderson[1], G Andersson[1], S Garwicz[2], and T Wiebe[2]

[1]Regional Tumour Registry and [2]Dept. of Pediatrics, Lund University Hospital, Sweden

Children with rhabdomyosarcoma in Sweden are reported to the register of solid tumours (VSTB-register) and practically all incident cases are included.

Objectives: The aim of the study was to analyse time trends in survival of children with rhabdomyosarcoma.

Patients: From the VSTB-register all cases with rhabdomyosarcoma diagnosed in Sweden 1982–1991 were selected. Vital status was updated to October 31, 1996.

Results: In the period 1982–1991. there were 82 cases, 37 girls and 45 boys (median age 6 (0–17) years) at diagnosis. During 1982-86, there were 40 children of which 19 were 6 years or younger at diagnosis. During 1987–1991, there were 42 children of which 27 were ≤6 years. The fraction of girls was the same (0.45) in both time periods.

Survival was analysed by sex, time period and age at diagnosis. No difference in survival was found between boys and girls. There was a survival improvement from 1982–1986 to 1987–1991: the 5-year survival was 42% for the first period versus 67% for the second period (p=0.02, logrank test). Children ≤6 years at diagnosis also lived longer than those older than 6 years with a 5-year survival of 68% versus 40% (p=0.01). In a Cox analysis including both age and time-period, the hazard ratio was 0.5 for age ≤6 years versus 6+ years (95% CI 0.3-0.9, p=0.03). Also the effect of time period remained: The hazard ratio was 0.5 for the later period versus the earlier (95% CI 0.3-1.0, p=0.04).

Conclusion: Survival in children in Sweden with rhabdomyosarcoma has improved and at present two thirds of the patients survive 5 years. Younger children do better than older.

Canadian soft tissue (STS) tumor bank/ correlative clinical data base

V Bramwell, I Andrulis, R Kandel, R Bell, R Turcotte, W Temple, M Gross, C Duncan

OCTRF, London Regional Centre & Mount Sinai Hospital, Toronto, Ontario, Canada

A network established by a tumor specific, multi-disciplinary clinical research group (Canadian Sarcoma Group - CSG), and grant funding from the National Institute of Canada, offered a unique opportunity to establish a STS tumor bank/correlative clinical data base.

Methods: Specialized oncological surgeons at multiple locations provide cryo-preserved normal tissue, tumor and blood samples with detailed clinical data, stored centrally in Toronto (tissue) and London (data). Central pathology review is performed. A coordinating committee has estab-

lished policies governing operations, and access to material.

Results: Accruals January 1993 – December 1996 (target 100 pts/yr)

Participating centre	Patients	Tumor samples
Calgary	21	22
Halifax	17	18
Montreal	61	64
Vancouver	18	18
London	45	50
Toronto	232	281
	394	453

Tumor RNA/DNA has been successfully extracted from an initial cohort of 50 samples. Grant funding has been renewed for 1996–1999.

Conclusions: A variety of biological material is available for molecular investigations. Samples for pilot studies have been supplied to scientists within and outside Canada. The potential for clinical correlative studies increases as follow-up data mature.

Malignant fibrous histiocytoma revisited—an SSG Morphology peer review committee study of 400 cases

LG Kindblom[1], M Åkerman[2], B Bjerkehagen[3], TB Halvorsen[4], O Larsson[6], P Lilleng[7], J Meis-Kindblom[1], O Myhre-Jensen[8], E Stenwig[3], M Virolainen[5], H Willén[2]

Depts. of Pathology, [1]Sahlgren University Hospital, Gothenburg, [2]Univesity Hospital, Lund, Sweden, [3]The Norwegian Radium Hospital, Oslo, [4]University Hospital, Trondheim, Norway, [5]University Hospital, Helsinki, Finland, [6]Karolinska Hospital, Stockholm, Sweden, [7]University Hospital, Bergen, Norway, [8]University Hospital, Aarhus, Denmark

Design and material: 400 sarcomas primarily diagnosed as malignant fibrous histiocytoma (MFH) and included in the SSG Registry (1986-1993) were reviewed by the 11 members of the review committee. The primary histologic material was reevaluated with regard to tumor classification, malignancy grade, presence of necrosis, vascular invasion, mitotic activity, and of margins or tumor interface with normal tissue.

Results: Approximately 70% of the cases were retained in the MFH group, i.e. they displayed varying degrees of myxofibrohistiocytic differentiation and lacked other types of differentiation. Approximately 20% of the cases were reclassified as other types of sarcoma (e.g. leiomyosarcoma, liposarcoma, fibrosarcoma, malignant peripheral nerve sheath tumor). Occasional cases were reclassified as either metastatic or primary carcinoma or melanoma. A few cases were excluded because of inadequate material and in some cases a definite diagnosis has been postponed until additional immunostainings have been performed. Approximately 10% of the cases were reclassified as "borderline" or low grade malignancies such as dermatofibrosarcoma protuberans, atypical fibroxanthoma of the skin, and angiomatoid (malignant) fibrous histiocytoma. There were several benign tumors such as spindle cell lipoma with extensive myxoid change, cellular myxoma, and deep cellular or hemorrhagic fibrous histiocytoma which were erroneously diagnosed as sarcomas. A few cases were reclassified as non-neoplastic inflammatory/reactive lesions.

Conclusions: A morphologic review of registry cases of sarcomas by soft tissue experts is essential to make any prognostic analysis meaningful. The relatively high incidence of changed diagnoses from high grade malignancy to borderline or benign tumors suggests that an expert "second opinion" should be a frequent practice in the diagnosis and treatment of soft tissue sarcomas.

Histologic reexamination of 100 malignant fibrous histiocytoma (1986–1996) from the Musculoskeletal Tumor Centre, Lund—is reappraisal of MFH of clinical importance?

M Åkerman[1], C D M Fletcher[2], H Willén[1], P Gustafson[3]

[1]Depts. of Pathology & Cytology and [3]Orthopedics, University of Hospital, Lund, Sweden, [2]Brigham & Womens Hospital, Boston, USA

Malignant fibrous histiocytoma (MFH) is the most common soft tissue sarcoma diagnosis. However, a specific histogenesis has not been proven and there is clinical and morphological heterogeneity between the subtypes. 1995 the various subtypes of MFH were reappraised: Storiform-pleomorphic, giant cell and inflammatory MFH were suggested to represent a morphologic pattern of dedifferentiation; when any line of differentiation could be proved in these tumors they should be diagnosed as a poorly differentiated example of that specific histotype. Myxoid MFH (myxofibrosarcoma) and angiomatoid MFH were considered as specific clinicopathologic entities. In order to investigate this hypothesis 100 sarcomas, primarily diagnosed as MFH 1980-1996, were re-examined. The median follow-up time for the survivors was 6 (1.5-6) years.

Results: 1 tumor, primarily diagnosed as myxoid MFH, Grade 2, was re-diagnosed as nodular fasciitis. In the remaining 99 sarcomas a specific line of differentiation was diagnosed (69) or suggested (15). The most common diagnosis was myxofibrosarcoma (33) followed by leiomyosarcoma (20) and sarcomas of myogenic origin nos (9).

Clinical follow-up: 37/ 99 sarcomas developed metastasis, all had been re-diagnosed as high grade malignant. 10/20 leiomyosarcoma and 7/9 myogenic sarcoma nos had developed metastasis.

Conclusion: It was possible to prove or suggest a specific line of differentiation in 84/99 sarcomas diagnosed as MFH. Sarcomas re-diagnosed as leiomyosarcoma and myogenic sarcoma nos developed metastasis in two thirds compared to one third in the remaining sarcomas.

Table 1. Final diagnosis after re-examination of 100 tumors primarily diagnosed as MFH (all types) 1980-1996 at the Musculoskeletal Tumor Centre, Lund University Hospital

	Metastasis		Median time to metastasis
Myxofibrosarcoma	*31*		
High-grade	22	8	42 (7–90)
Intermediate grade	6		
Low grade	3		
Myogenic sarcoma	*30*		
Leiomyosarcoma	20	10	9 (0–22)
Pleomorphic rhabdomyosarcoma	1		
Myogenic sarcoma NOS	2	7	3 (0–11)
Suggested myogenic sarcoma	7		
Liposarcoma	*5*		
Pleomorphic	3	2	15 (4-26)
Dedifferentiated	1		
Low grade	1		
Myofibroblastic sarcoma	*9*	*4*	*5 (0-15)*
Myofibroblastic sarcoma	2		
Suggested myofibrobl. sarcoma	7		
MPNST	*2*		
High grade	1		
Low grade	1		
Malignant mesenchymoma	*2*	*1*	*53*
Soft tissue osteosarcoma	*2*	*1*	*8*
DFSP with fibrosarcomatous areas	*1*		
Low grade fibromyxoid sarcoma	*1*		
Sarcoma NOS	*15*		
Pleomorphic	11	2	29 (25-33)
Spindle	2	1	5
Pleomorphic/myxoid	1		
Spindle/myxoid	1		
Nopdular fasciitis	*1*		
Suggested metastatic sarcomatoid carcinoma	*1*	1	8

Sarcomas not otherwise specified =High grade
MPNST= Malignant Peripheral Nerve Sheath Tumor
DFSP=Dermatofibrosarcoma protuberans

A reproducible prognostication system for soft tissue sarcoma based on tumor size, tumor necrosis, and vascular invasion

P Gustafson[1], M Åkerman[2], H WillÈn[2], J M Coindre[3], C D M Fletcher[4], T A Alvegård[5], A Rydholm[1]

Depts. of [1]Orthopedics and [2]Patholgy, University Hospital, Lund, Sweden, [3]Bordeaux, France, [4]Boston, USA, [5]Dept of Oncology, University Hospital, Lund, Sweden

Prognostication in soft tissue sarcoma (STS) is hampered by the lack of a reproducible system that sufficiently separates the good prognosis group from the poor prognosis group.

Patients and methods: In a population-based series of 508 patients from the Musculoskeletal Tumor Center, Lund Sweden, tumor size >10 cm, microscopic tumor necrosis, and vascular invasion were found to be independent prognostic factors for metastasis. A prognostic system based on these factors could separate a good prognosis group (0 or 1 factor) from a poor prognosis group (2 or 3 factors) with 80% vs. 30% 5-year survival. The reproducibility in classification of necrosis and vascular invasion was tested in 100 STS samples from Lund examined in Bordeaux and Boston. Also 100 samples from a Bordeaux STS series were analysed in Lund and in Boston. Concordance in judging was determined.

Results: The concordance in grading of the Lund material was 76%. The positive and negative predictive values for metastasis was in Lund 63% and 79%, in Bordeaux 63% and 77%, and in Boston 64% and 72%. Similar results were found when the Bordeaux material was examined.

Conclusion: We present a prognostication system for soft tissue sarcoma that is simple, reproducible and can identify a good and a poor prognosis group.

Adjuvant chemotherapy in soft tissue sarcoma—an overview

V Bramwell

London Regional Cancer Centre, London, Ontario, Canada

Tremendous controversy surrounds the use of adjuvant chemotherapy in adult soft tissue sarcoma. An individual patient data meta-analysis (IPD-MA) of outcome for 1555 patients included in 14 randomized trials of adjuvant doxorubicin (DOX) based chemotherapy versus control has been published in abstract (Tierney J Clin Oncol 14, p1751, Abstract 2024, 1996).

Methods: Critical qualitative review of studies included in IPD-MA; description other randomized trials adjuvant/neoadjuvant chemotherapy, completed or ongoing. Outline of methodology and summary results IPD-MA, with clinical interpretation.

Results: IDP-MA remedies deficiencies of individual studies such as inadequate sample size, variable exclusion criteria and heterogeneity in reporting relevant outcomes. Other problems remain, e.g., restrictive inclusion criteria limiting generalizability, variability in pathological typing/grading, variations in timing/delivery of chemotherapy, issues concerning toxicity and quality of life.

IPD-MA has shown improvements in local recurrence free interval (p=0.02), distant recurrence free interval (p=0.0003), overall recurrence free survival (p=0.00008), but only a trend for improved overall survival (p=0.09).

Conclusions: Although IPD-MA demonstrates a clear effect of DOX-based chemotherapy many questions remain regarding its appropriate application. Are there subgroups of patients based on age, sex, histology, location, etc. that may benefit? Should DOX be used alone or in combination (with which drugs?) and what is the optimum dose/schedule?

A multicentric randomized trial of adjuvant chemotherapy (Italian Co-operative Group) for soft tissue sarcomas of the extremities in adult patients—preliminary results

F Gherlinzoni[1], S Frustaci[2], A De Paoli[2], G Pignatti[1], H Zmerly[1], A Azzarelli[3], A Comandone[3], S Ferrari[1], P Olmi[3], V Ippolito[3], E Barbieri[3], F Bertoni[1], G Bacci[1], M Campanacci[1], P Picci[1]

[1]Istituto Ortopedico Rizzoli, Bologna, [2]Centro Riferimento Oncologico, Aviano and [3]Collaborating Institutions, Italy

From June 1992 to October 1996, 104 adult patients with high risk STS of the extremities (grade 3 and 4, deeply located, minimum diameter > 5 cm) were entered into a randomized trial. After local treatment (amputation or wide excision with pre- or postoperative radiotherapy) patients were randomized to control (51) or treatment arm (53). Characteristics of the 104 pts are: male/female: 61/43; median age 47 (17-65) years; MFH 28, synovial sarcoma 27, liposarcoma 21, malignant schwannoma 9, others 19; grade III 45, grade IV 59. There were 86 primary tumors, 18 relapses and 6 cases of radicalization of previous inadequate surgery. In 80 patients the site of primary tumor was the lower extremity and in 24 the upper extremity. Stratification was: primary </> 10 cm 36/50, relapse </> 10 cm 10/8. Treatment consisted of Epirubicin 60 mg/m^2 day 1 and 2, Ifosfamide 1.8 g/m^{2}day 1-5 and Mesna 20% of the Ifosfamide dose at hr 0,4,8 for 5 days; plus G-CSF 300 mg/d sc. day 8 to day 15.

At a median follow-up of 21 (1-51) months, 38 patients have relapsed: 15 in the treatment and 23 in the control arm. Furthermore, 20 patients are dead: 6 in the treatment and 14 in the control arm. The median disease-free survival was 13 months for the control group, whereas it was not reached in the treatment group (p=0.001). The difference in survival was again highly significant (0.007) in favor of the chemotherapy arm. At the interim analysis performed in November 96, after half of the planned number of patients were randomized, we decided to stop accrual due to the differences in disease-free and survival, even though the follow-up is still short.

200 isolated limb perfusions with tumor necrosis factor and Melphalan for limb salvage in patients with locally advanced soft tissue extremity sarcomas—the European experience

A M M Eggermont

Dept. of Orthopedics, Academisch Ziekenhuis, Rotterdam, The Netherlands

Objective: Achieve limb salvage in patients with locally advanced soft tissue sarcomas (STS) that can only be treated by amputation or functionally mutilating surgery by performing an isolated limb perfusion (ILP) with TNF + melphalan (M) as induction biochemotherapy to obtain local control and make limb sparing surgery possible.

Summary background data: In order to increase the number of limb sparing resections in the treatment of locally advanced extremity STS preoperative radiotherapy or chemotherapy or a combination of the two are often applied. ILP with cytostatic agents alone is another option but is rarely used because of rather poor results. The efficacy of the application of TNF in ILP has markedly changed this situation.

Methods: In 8 cancer centers 186 patients were treated over a period of almost 4.5 years. There were 107 (57%) primary and 79 (43%) recurrent sarcomas, mostly high grade (110 grade III, 51 grade II and 25 very large, recurrent or multiple grade I sarcomas). The composition of this series of patients is unusual: 42 patients (23%) had multifocal primary of multiple recurrent tumors; median tumor size was very large (16 cm); 25 patients (13%) had known systemic metastases at the time of the ILP. Patients underwent a 90 minutes ILP at 39–40 °C with TNF + melphalan. The first 55 patients also received IFNg. A delayed marginal resection of the tumor remnant was done 2-4 months after ILP.

Results A major response was seen in 82% of the patients rendering these large sarcomas resectable in most cases. Clinical response rate were: 33 (18%) complete response (CR), 106 (57%) partial response (PR), 42 (22%) no change (NC) and 5 (3%) progressive disease (PD). Final outcome was defined by clinical + pathological response: 54 (29%) CR, 99 (53%) PR, 29 (16%) NC and 4 (2%) PD. At a median follow up of 22 (6–58) months, limb salvage was achieved in 82%. Regional toxicity was limited and systemic toxicity minimal to moderate, easily managed with no toxic deaths.

Conclusions: In the setting of isolated perfusion TNF is an active anticancer drug in patients. ILP with TNF + melphalan can be performed safely in many centers and is and effective induction treatment with a high response rate that can achieve limb salvage in patients with locally advanced extremity STS.

Adjuvant interferon (IFN) alpha treatment in patients with soft tissue sarcoma

S Friesland[1], JO Fernberg[1], O Larsson[2], H Strander[1]

Depts. of [1]Oncology and [2]Pathology, Karolinska Hospital, Stockholm, Sweden

During the period 1992–1996 we have treated 10 patients (median age 48 (30–70) years, 5 women) with soft tissue sarcoma in complete remission (CR) with IFN alpha. The histological subtypes were: 2 MFH, 2 synovial sarcomas, 2 epithelioid cell sarcomas, 2 leiomyosarcomas and 2 liposarcomas. Adjuvant IFN treatment was given at first CR in 3 patients and in remaining 7 following relapse treatment. At the initiation of IFN treatment all patients were considered free from disease.

Interferon alpha (Wellfron®) was given in a dose of 3x10^6 U daily s.c. Median treatment time was 20 months (5-60). The treatment was generally well tolerated and side-effects were moderate. Hematological toxicity WHO grade I was seen in 6 patients. Fatigue was reported by 4 patients and 3

patients displayed liver toxicity grade I. 1 patient developed hypothyreosis which was attributed to the IFN treatment. 2 patients have developed metastases and are off IFN treatment. 1 patients upon retrospective analysis had remaining tumor disease at initiation of IFN therapy and progressed. The remaining 7 are still treated with IFN and free from disease. IFN exerts direct and indirect antitumor activity as shown in several tumor types including osteosarcoma. In addition to direct and indirect cytotoxic effects, antiangiogenesis could possibly be a mechanism of action especially in the adjuvant situation when the tumor burden is low. We suggest a further evaluation of IFN in soft tissue sarcomas.

Radiation therapy in soft tissue sarcoma—preoperative versus postoperative treatment

I J Spiro

Dept. of Radiation Oncology, Massachusetts General Hospital, Boston, USA

The use of external beam radiation therapy, delivered either preoperatively or postoperatively, or with interstitial brachytherapy has been shown to reduce the risk of local recurrence following conservative surgery for soft tissue sarcoma. External beam radiation therapy is the most common method of treatment although there is controversy as whether preoperative or postoperative treatment is superior. This presentation will explore the advantages and disadvantages of preoperative and postoperative radiation therapy. Existing data will be reviewed with regard to technical considerations of the radiation delivery, margin status, control rates, complication rates and functional outcome. The role of chemotherapy and the sequencing of this treatment modality with respect to surgery and radiation therapy will be considered , finally, the current National Cancer Institute of Canada randomized trial comparing preoperative versus postoperative radiation therapy will be discussed.

Effects of preoperative radiotherapy in primary soft-tissue sarcoma—tumor response and postoperative complications in 11 cases

O Brosjö, H Bauer, G Jenner, JO Fernberg

Orthopedic Oncology service, Karolinska Hospital, Stockholm, Sweden

Preoperative radiation in soft-tissue sarcomas may lead to less extensive or ablative surgical procedures combined with a low local recurrence rate. However, high postoperative complication rates have been reported. We present tumor response and postoperative complications in our first 11 cases.

Patients and methods: 11 patients treated since 1994, age 16 - 82 years, with primary deep-seated soft tissue sarcomas were selected for preoperative radiation (50 Gy) because of close relation to major nerves and vessels. Diagnoses were based on MRI and fine-needle aspiration biopsy in 9 cases and open biopsy in 2. Median tumor size was 11 (4-16) cm. Surgical staging showed IIA (2 lesions), IIB (7), and IIIB (2). A new MRI was performed after radiotherapy and prior to surgery. Surgery was performed approximately 3 weeks after termination of radiotherapy.

Results: 9 local excisions and 2 amputations were performed. All patients had preoperative antibiotics, the wounds were extensively irrigated before closure and drains were left in place for a median time of 6 days. A wide surgical margin was achieved in 4 cases, a marginal in 6, and an intralesional in 1 case. Complete tumor necrosis was achieved in 5 cases, subtotal necrosis in 1 whereas in 5 no effect of radiotherapy was seen histologically. Postoperative skin necrosis and/or deep infection developed in 3 cases which necessitated reoperation or prolonged hospital care. Another 3 patients were treated because of superficial infection. The most common cause of infection was *S. aureus*.

Conclusion: The preoperative radiotherapy was surprisingly effective with total or subtotal tumor necrosis in 6 of 11 large, deep seated, high-grade soft-tissue sarcomas. The high incidence of postoperative complications is troublesome but manageable. All 6 wounds with infection/skin necrosis healed after reoperation and/or antibiotics. No local recurrences has so far been detected but the follow-up is short. We will continue to select patients, mostly with Stage IIB and IIIB tumors, for preoperative radiotherapy in combination with extensive efforts to decrease the rate of postoperative complications. This will include surgery in an operating room with laminar air flow, use of muscular flaps, and prolonged postoperative antibiotics.

Reasons for abstaining from radiotherapy after a poor surgical margin in soft tissue sarcoma—a SSG Register study

H Bauer[1], Ö Berlin[2], J Høie[3], H Russwurm[4],A Rydholm[5], S Skjeldal[6], B Uhlin[7]

[1]Oncology Service, Dept. of Orthopedics, Karolinska Hospital, Stockholm, [2]Dept .of Orthopedics, Sahlgren University Hospital, Gothenburg, [3]Dept. of Surgery, The Norwegian Radium Hospital, Oslo, [4]Dept. of Orthopedics, Lund University Hospital, Lund, [5]Dept. of Orthopedics, Trondheim Hospital, Trondheim, [6]Dept. of Orthopedics, Ullevål Hospital, Oslo, [7]Dept. of Orthopedics, Linköping University Hospital, Linköping, Sweden

Although adjuvant radiotherapy is recommended after a marginal margin in soft tissue sarcoma, only approximately half of such patients are actually treated. We tried to determine why patients were not referred for radiotherapy. Seven sarcoma centers participated in this retrospective study of patients treated 1990–1995. A total of 197 patients with an intralesional or marginal margin, operated for primary tumor at a center, were identified. Other inclusion criteria were: age older than 15 years, no metastases at diagnosis, situated to the trunk wall or extremities, and not Kaposi's sarcoma or

sarcoma protuberans. Among these 172 patients, 88 did not receive adjuvant radiotherapy. Data for reasons not to treat was available in 82 of these 88 patients. In another 7 cases, recorded data was incorrect, 5 had a wide margin and 1 patient had been treated.

The most common reason for non-treatment was low-grade (I-II) lesions, 36 cases. Other common reasons were old age and concommittant disease or sarcoma secondary to radiotherapy. In 11 cases we could not identify any obvious reasons for non-compliance.

Among the whole group of 88 patients, follow-up data was available in 87 with a mean follow-up time of 3 years. The 3 years local recurrence rate was 0.27 (Kaplan-Meier). After exclusion of 27 patients with Grade I lesions, among whom there was only one recurrence, the rate was 0.38. For comparison, the recurrence rate was 0.19 for the group of 109 patients that received radiotherapy (p=0.005 Mantel-Haenszel).

Although follow-up is still short, the study shows a high local recurrence rate. The results imply that more patients, despite old age or unfavorable anatomic location, should receive adjuvant radiotherapy after a poor surgical margin in soft tissue sarcoma.

Reason for non-treatment	n	Local recurrence
Low grade	36	3
Old age or other disease	17	4
Secondary to radiotherapy	6	2
Anatomic location	6	3
Wound problem	6	2
No obvious reason	11	4
Total	82	18

Local recurrence and survival in soft tissue sarcoma—a SSG Central Registry project

C Trovik[1], H Bauer[2], T A Alvegård[3], H Anderson[3], C Blomqvist[4], Ö Berlin[5], P Gustafson[3], G Saeter[6], A Walløe[1]

[1]Haukeland University Hospital, Bergen, Norway, [2]Karolinska Hospital, Stockholm, [3]University Hospital, Lund, Sweden, [4]University Hospital, Helsinki, Finland, [5]Sahlgen University Hospital, Gothenburg, Sweden, [6]The Norwegian Radium Hospital, Oslo, Norway

Multivariate survival analysis was based on 818 patients with extremity and trunk wall sarcomas reported to the Scandinavian Sarcoma Group Register 1986-91. They were followed for a median time of 6 years. The overall expected 5-years metastasis-free survival was 0.68 ± 0.02.

High malignancy grade and large tumor size were the most important risk factors for metastases. Poor surgical margin, deep tumors and high age were weaker risk factors. Local recurrence increased the risk of metastasis (RR = 2.4 [2.8–2.0]), when analysed as a function of survival time. When local recurrence was introduced as a prognostic factor in the model, the effect of an inadequate surgical margin was no longer statistically significant.

Patients with high grade and large tumors had often early metastasis and in this group, those who had time to develop a local recurrence, formed a subset with a comparatively better prognosis. Local recurrence was a stronger risk factor among patients with low grade and/or small tumors (RR = 3.7 [4.7–2.9]); the 5 year survival rate was 0.80 ± 0.02 in this group. Among patients who survived for more than 2 years without local recurrence, a late local recurrence was an even stronger marker of bad prognosis.

The study reiterates that tumor related risk factors are most important for survival. However, a local recurrence is associated with impaired survival in patients with an otherwise good prognosis.

Multiple Hazards models for the rate of metastasis or death from tumor. Model A includes all variables found significant by univariate analyses. Model B includes the significant variables from A, and local recurrence as a time-dependent variable. N = 818 patients

	A			B		
	RR	(95%C1)	*p*	RR	(95%C1)	*p*
Malignancy grade	4.2	(5.4-3.2)	<0.0001	4.0	(5.2-3.0)	<0.0001
Tumor size	2.5	(2.9-2.2)	<0.0001	2.6	(3.0-2.2)	<0.0001
Tumor depth	1.5	(1.8-1.2)	0.03	1.5	(1.8-1.3)	0.02
Age	1.4	(1.6-1.2)	0.04	1.4	(1.6-1.2)	0.05
Surgical margin	1.3	(1.5-1.2)	0.03	1.2	(1.3-1.0)	0.2
Local recurrence	not included			2.4	(2.8-2.0)	<0.0001
Tumor location	1.1	(1.3-1.0)	0.5	not included		
Sex	1.0	(1.1-0.9)	0.9	not included		

Malignancy-grade was analysed as low (Grade I-II) versus high (Grade III-IV). Tumor-size was <=7 cm versus >7 cm. Tumor-depth was subcutaneous versus deep. Surgical margin was wide or better versus intralesional/marginal. Tumor location was extremities versus central location (trunk wall, shoulder, groin or gluteal). Local recurrence was now or yes. Sex was female versus male. Age was <=50 years versus >50 years.

Prognostic implications of various mathematical models for calculation of S-phase fraction in soft tissue sarcoma

P Gustafson[1], B Baldetorp[2], M Fern[2], M Åkerman[3]

[1]Depts of Orthopedics, [2]Oncology and [3]Pathology University Hospital, Lund, Sweden

The S-phase fraction (SPF) in flowcytometric DNA histograms in soft tissue sarcoma (STS) can be calculated according to various mathematical methods. The traditional planimetric method of Baisch has been shown to be prognostic, but is hampered by a failure rate of 40%. We therefore tested other models to see if this rate could be decreased with still retained prognostic value.

Patients and methods: In 259 STS of the locomotor system the SPF was calculated according to the Baisch and the commercial parametric MultiCycle®-software with different corrections for background events in the histograms. The prognostic value for metastasis was compared using Kaplan-Meier plots.

Results: Using the Baisch model, 159 histograms of the 259 could be evaluated for SPF. The 5-year metastasis-free survival rate (MFSR) was 0.94 for the low-risk group (defined only with SPF), and 0.53 for the high-risk group. In the low-risk group, 4 of the 7 patients who developed metastasis did so after 5 years. Using the MultiCycle®-software, SPF could be calculated in 253 tumors. Depending on type of background correction used, the 5-year MFSR varied between 0.67 and 0.82 for the low-risk group, and between 0.47 and 0.53 for the high-risk group. The late metastasis pattern in the low-risk group was not seen using the MultiCycle®-software.

When SPF as determined by Baisch was combined with tumor size, necrosis and vascular invasion, a group (1/6 of all STS patients) with extremely good prognosis (5-year MFSR 0.97) could be identified.

Conclusion: We conclude that calculation of SPF according to Baisch is preferable in clinical use due to better separation between a low-risk and high-risk groups, and also the possibility to identify patients who metastasize late.

Diagnosis, treatment and prognosis in synovial sarcoma —a Scandinavian Sarcoma Group Register project

B Skytting[1], H Bauer[2], Ö Berlin[3], L G Kindblom[3], G Saeter[4], C Blomqvist[5], M Åkerman[6], O Larsson[2]

[1]Söder Hospital, [2]Karolinska Hospital, Stockholm, [3]Sahlgren University Hospital, Gothenburg, Sweden, [4]The Norwegian Radium Hospital, Oslo, Norway, [5]University Hospital, Helsinki, Finland, [6]University Hospital, Lund, Sweden

Between March, 1986 and December 1994, 127 patients with synovial sarcoma were reported to the SSG Register. In 104 cases, the diagnosis was confirmed by the SSG pathology board, in 13 the diagnosis was not accepted, and 10 await further review. Patient charts have been reviewed and the follow-up has been continuously updated. No patient has been lost to follow-up, and the median follow-up time for survivors was 6 years.

The median age was 38 (7–87) years and there was an even sex distribution. 12% of the tumors were localized to the trunk, 17% to the upper extremity and 71% to the lower. 9% were subcutaneous, 17% intramuscular, and 73% extramuscular. The median tumor size was 5 cm. 6% of the patients had lung metastasis at the time of diagnosis.

48% of the patients were referred before surgery, *i.e.*, 40% untouched and 8% after needle biopsy. 12% were referred after open biopsy, 35% after an intralesional or marginal excision, and 5% after local recurrence. Surgery with an adequate margin, *i.e.*, wide, myectomy, compartmental, was achieved in 60% and an inadequate margin in 40%. The amputation rate was 15%. Postoperative radiotherapy was given in 25% and 8% had adjuvant chemotherapy.

The 5-year local recurrence rate was 0.14 and the metastasis-free survival rate was 0.68. All 11 local recurrences and 27 of 29 metastases appeared before 5 years. Analysis for prognostic factors with flow cytometry, comparative genomic hybridization and immunohistochemistry will soon start.

Orthopically transplanted human synovial sarcoma xenografts in nude mice

S Crnalic[1], L Boqvist[2], R Löfvenberg[1]

Depts. of [1]Orthopedics and [2]Pathology, University Hospital, Umeå, Sweden

This study was initiated to establish a new human spontaneous metastasis model using orthotopic transplantation of histologically intact human synovial sarcoma tumor tissue into the thigh of nude mice.

Methods: Tumor tissue from two different subcutaneously growing human synovial sarcoma xenografts in nude mice was used. Intact tumor pieces, obtained from the 3rd and 7th serial passages were implanted into the distal thigh in close proximity to the knee joint in 46 nude mice. The animals were killed 4, 8 and 11 weeks after transplantation and examined macroscopically and microscopically for local tumor growth and metastases.

Results: Local tumor growth was observed in all animals. The tumors were histologically similar to the primary human tumors as well as the subcutaneously growing tumors. Lung metastases as well as metastasis to the liver, spleen and lymph nodes were observed.

Conclusion: The take rate, occurrence of metastasis and resemblance with the primary tumor makes this new spontaneous metastasis model of human synovial sarcoma in nude mice suitable for studies on local tumor growth, metastases formation and therapy.

Synchronous and metachronous radiosensitive myxoid liposarcoma—a clinicopathologic study of 2 cases

P Bergh[1], B Gunterberg[1], LG Kindblom[2], J Meis-Kindblom[2], G Stenman[2], W Ryd[2], Ö Berlin[1], C Engström[3]

Depts. of [1]Orthopedics and [2]Pathology and [3]Oncology, Sahlgren University Hospital, Gothenburg, Sweden

There is limited information in the literature regarding the effectiveness of radiotherapy in liposarcomas. However, well differentiated and myxoid types are generally regarded as unresponsive to radiotherapy.

Patients and methods: 2 patients with 3 and 6 synchronous and metachronous myxoid liposarcomas were

reviewed. Cytogenetic analysis demonstrated the characteristic 12:16 translocation of myxoid liposarcoma. One patient had a family history of lipomatous tumors. The other patient had a strong family history of malignancy (no constitutional p53 mutation was detected). All tumors were surgically removed. 5 tumors were treated preoperatively with radiotherapy.

Results: The 4 non-irradiated tumors were classified as myxoid liposarcoma. 4 of 5 irradiated tumors decreased in size; all 5 demonstrated maturation similar to a benign lipoma with occasional foci of hypocellular myxoid liposarcoma. One patient is free of disease (follow-up 12 months). The other patient developed 9 further extrapulmonary tumors, which are currently under treatment (follow-up 29 months).

Conclusion: The observations of radiation-induced maturation of myxoid liposarcoma to nature adipose tissue (which have not been previously described), suggest that preoperative radiotherapy is a useful complement to surgical treatment of certain types of liposarcoma. Whether this response to radiation is unique to multicentric, familial cases of myxoid liposarcomas, or potentially useful in isolated cases of myxoid liposarcoma is unclear.

Metastasizing neurothekeoma—a previously undescribed phenomenon

JM Meis-Kindblom, F Remotti, LG Kindblom

Dept. of Pathology, Sahlgren University Hospital, Gothenburg, Sweden

Neurothekeoma (nerve sheath myxoma) is recognized as a histologically distinctive benign peripheral nerve sheath tumor (PNST) occurring in the head, neck and upper extremities of young adults. Local recurrences are rare and metastases, to our knowledge, have not been previously reported.

Design: Histologic sections of all available pathologic material were examined and immunostains and ultrastructural studies were performed on local recurrences and metastasis of a single case.

Results: A 44-year-old woman had a lesion removed from the dorsal right thumb. Since the clinical impression was a ganglion cyst, the initial lesion was not histologically examined. She developed 3 local recurrences 1, 7, and 17 years later and metastasis to the right axillay lymph node 27 years after removal of the primary tumor. Histologic examination of all local recurrences and the metastasis revealed characteristic neurothekeomas which were multilobulated with fibrous septa, a prominent myxoid matrix and paucicellular. Lesional cells were stellate to spindle shaped and cytologically bland, arranged in a net-like pattern or syncytia. Immunohistochemically they stained strongly for S100 protein, GFAP, and vimentin; HMB-45, NFP, EMA, cytokeratins, smooth muscle actin and p53 immunostains were negative. Ki67 values were low (<1%). EM confirmed PNST features with duplicated external lamina investing tumor cells, myelin figures, interdigitating elongated cell processes, and desmosome-like junctions.

Conclusions: 1) Neurothekeoma may be considered yet another example of a so-called "benign metastasizing" tumor; the risk of metastasis and death from this particular lesion is essentially nil. 2) The broader questions of criteria for malignancy and mechanisns of metastasis/multicentricity arise when apparently indolent lesions such as neurothekeoma behave in a clinically deviant manner.

Diagnosis of neuroblastoma in fine needle aspirates

M Åkerman, B Carlén

Dept. of Pathology, University Hospital, Lund, Sweden

We investigated wether it was possible to reliably diagnose neuroblastoma in fine needle aspirates (FNA).

Material and methods: 19 FNA from 19 patients with neuroblastoma diagnosed 1969–1996 (10 from primary tumors and 9 from metastases) were re-examined. Electron microscopic examination of the aspirate was performed in 14 tumors and immunocytochemistry in 12.

Cytologic reexamination: In one FNA extensive necrosis made the reevaluation impossible. In all the other FNA:s except one the yield was rich. In the 18 smears a mixture of dispersed cells and cell-tight clusters was seen. Stripped nuclei were common. The following cytologic features were especially looked for (number of cases found in): Rosettes (3), neuropil in the background of cell clusters (15), tumor cells arranged in indian file (7) or in moulded clusters (18), thin cytoplasmic processes connecting adjacent cells (14) and ganglion cell like cells (2). The combination of neuropil, moulded clusters and cytoplasmic processes were seen in 12 of the 18 FNA:s.

Adjunctive methods: Immunocytochemistry (neuron specific enolase and/or chromogranin A) was variably positive in the examined cases. The electron microscopic examination was diagnostic for neuroblastoma in all examined cases.

Conclusion: A reliable cytologic diagnosis of neuroblastoma may be based on the combination of neuropil, moulded clusters and thin cytoplasmic processes connecting adjacent cells in fine needle aspirates. Unequivocal rosettes as well as ganglion cell differentiation were uncommon findings. In doubtful cases electron microscopy was the most valuable ancillary method.

Fine needle aspiration (FNA) cytology and imaging studies in the preoperative diagnosis of hibernoma

F Remotti, W Ryd, JM Meis-Kindblom, LG Kindblom

Dept. of Pathology, Sahlgren University Hospital, Gothenburg, Sweden

Hibernoma is a rare, benign tumor with features of brown fat. The radiographic and morpologic distinction of hibernoma from liposarcoma, lipogranuloma, and other lesions with multivacuolated cells may be quite difficult.

Design: 11 FNA cases suggesting the diagnosis of hibernoma were retrieved and correlated with the histology of the resection specimens, ultrastructure, and preoperative imaging studies.

Results: In 7/11 cases the FNA diagnosis of hibernoma was confirmed by histologic and ultrastructural examination. The remaining 4 cases were lipomas with regressive changes. The hallmarks of hibernoma by FNA included: clusters of uniform, round cells with finely vacuolated and partly granular cytoplasm; central small, round, smoothly contoured nuclei; and individaul cells surrounded by delicate capillaries. Mature fat, atropic muscle, and macrophages were also observed; there was no myxoid matrix. Radiographically, plain films revealed a higher density than purely well differentiated lipomatous lesions. Angiograms showed high vascularity with rapid passage of contrast from the arterial side to draining veins; CT and MRI revealed higher attenuation compared to fat as well as prominent contrast enhancement.

Conclusion: 1) The imaging features of hibernoma may be misinterpreted as liposarcoma or another malignant neoplasm. 2) Since the FNA features of hibernoma are characteristic, clearly deviating from those of well differentiated and myxoid/round cell liposarcoma as well as lipogranuloma, a correct preoperative diagnosis is possible. 3) Before rendering a diagnosis of hibernoma by FNA, one should bear in mind that brown fat may be a normal finding in some anatomic sites (neck, supraclavicular, mediastinal, retroperitoneal) and that hibernoma-like areas may rarely be seen in some types of liposarcoma.

The HMGIC gene is amplified, rearranged and overexpressed in a subset of human sarcomas

JM Berner, LA Meza-Zepada, A Forus, O Myklebost

Dept. of Tumor Biology, The Norwegian Radium Hospital, Oslo, Norway

Amplified segments of the long arm of chromsome 12 are frequently observed in human sarcomas[1, 2]. In most cases there are separate amplified regions around the *MDM2* and *CDK4* genes[3-5], overexpression of which might inhibit cell cycle control by the *p53*- and *pRB*-mediated pathways, respectively. Recently the gene for a human architectural transcription factor, *HMGIC*, close to *MDM2*, was found to be the target for translocation in benign mesenchymal tumors. We find recurrent amplification of *HMGIC* at higher levels than flanking sequences, indicating that inclusion of *HMGIC* in amplicons is also selected for[6]. In three samples only the 5' part of *HMGIC* was amplified, and in several other samples rearrengement of the gene was observed. Expression analysis showed transcripts of aberrant sizes, lacking 3' sequences. 3' RACE of several samples revealed replacement of exons 4 and 5 ectopic sequences, resulting in loss of the carboxy terminal acidic domain of *hmgic*, whereas the DNA-binding domains were left intact. This truncation of *HMGIC* resembles that reported for translocations of *HMGIC* in benign tumors, including lipomas, and it is striking that the gene was frequently amplified or rearranged in well differentiated liposarcomas, the malignant counterpart of lipomas. It seems conceivable that the resulting high levels of either full length or truncated *hmgic* could be relevant for the etiology of these tumors.

Fluorescent in situ hybridisation (FISH) in sarcoma research and diagnosis

A Forus[1], F Pedeutor[2], O Myklebost[1]

[1]Dept. of Tumor Biology, The Norwegian Radium Hospital, Oslo, Norway, [2]UMR 65649, CNRS UNSA, Université de Nice-Sophia Antipolis, France

Detailed knowledge of specific chromosomal aberrations in certain subtypes of sarcomas has made molecular techniques increasingly valuable for diagnosis. Whereas routine karyotyping in most cases will detect these aberrations, this usually requires open biopsies and considerable time for propagation of cultures. In cases where chromosomal analysis is important for the initial treatment of the patient, a more rapid technique would be valuable. FISH analysis of interphase nuclei allows specific diagnostic questions to be asked, and can be done in a couple of days on cells prepared from cytological samples. For this technique, genomic probes flanking the translocation breakpoint in question are needed, and after hybridisation to fixed nuclei, the probes are detected by fluorescence microscopy. Because of the proximity of the two probes, normal chromosomes will be observed as two close fluorescent spots, whereas a translocated chromosome will result in random distribution of the two spots within the nucleus. Because sensitivity may be a problem, in most cases cosmids are used, containing close to 50 kilobasepairs of genomic sequence, thus giving a sufficiently strong signal. FISH techniques may be more robust than e.g. detection of translocation transcripts by PCR-based methods, in that sample integrity is less critical, and variant translocations may also be detected. FISH may also be used for the detection of cryptic translocations and for determination of the chromosomal origin of marker chromosomes. For these purposes chromosomal "paints" are often used, which are probes that detect entire chromosomes. Detection of loss or gain of subchromosomal sequences is also possible by FISH, either by the rather demanding comperative genomic hybridisation (CGH) technique, or, when the relevant sequences are known in advance, by interphase FISH.

Free microvascular flap reconstruction in soft tissue sarcoma

E Tukiainen

Dept. of Plastic Surgery, Helsinki University Hospital, Helsinki

Modern methods of microvascular tissue transfer make extensive tumor resections possible. In large, vital tissue defects, such as exposed brain or dura, open chest or abdominal cavities, integrity can be achieved with free microvasular flaps. In extremity resections open joints, exposed tendons, vessels or nerves (often reconstructed with grafts as well) can be covered with free flaps. This makes limb salvage possible. Microvascular flaps are harvested far from the tumor area. The flap obliterates dead space of the wound thus enhancing would healing, and make early radiation therapy possible, if indicated.

67 (65 patients) free flap reconstructions were performed 1987–1996. The tissue defects were located at head and neck in 6 patients, in trunk in 16, in upper extremity 13 and in lower extremity in 30 patients. The age of the patients varied from 5 to 80 years. Most tumors were high grade malignant.

A latissimus dorsi flap (muscular or musculocutaneus) was commonest (35 cases). In full-thickness thoracoabdominal defects, tensor fasciae latae free flaps proved most suitable (11 cases). Smaller muscular flaps (rectus abdominis 5, gracilis 2) were used when a thin flap was needed. Bony defects were reconstructed with fibula (4) or iliac crest flap (1). In 3 cases the amputated remnant extremity (2 fore arm, 1 lower leg) was used to cover the large defect after extended fore-quarter amputation or hemipelvectomy.

1 free flap was lost because of vessel thrombosis, and the lower leg had to be amputated. In 2 cases the extremity had to be amputated postoperatively, because the histologic examination showed inadequate margins.

Microsurgical reconstruction is most efficient and least time consuming in units where microsurgery is routine in everyday practice. The use of microvascular flap reconstruction is safe, it adds a new dimension to sarcoma surgery and often offers a chance of extensive radical resection and limb salvage in cases, which can no be treated with traditional surgical methods.

Has survival in children with bone sarcoma in Sweden improved?

T Möller[1], H Anderson[1], G Andersson[1], S Garwicz[2], T Wiebe[2]

[1]Regional Tumour Registry and [2]Dept. of Pediatrics, Lund University Hospital, Sweden

In the period 1982–1991, 99 cases of bone sarcoma <16 years were reported to the Swedish national cancer registry (compulsory reporting); 43 cases of Ewing sarcoma, 54 of osteosarcoma and 2 other bone sarcomas. The VSTB register (voluntary reporting) included during the same time 41 Ewing sarcomas, 46 osteosarcomas and 2 other bone sarcomas. The SSG register (study register) included for the period 1987-91, 14/22 of the Ewing sarcomas, 26/30 of the osteosarcomas and 0/2 of the other bone sarcomas. All cases in the VSTB- and SSG-registers were also found in the cancer registry.

The 5-year survival was calculated for two periods: 1982-86 and 1987-91. Survival for all cases with *Ewing sarcoma* was ≈50% for both periods. For *osteosarcoma* survival increased from 50% in the first period to 70% in the second (p=0.06).

There were no survival differences in cases not reported to the VSTB- and SSG-registers except for osteosarcomas diagnosed 1982-86 for which the 5- year survival for those not in the VSTB register (n=7) was substantially better than for those included (n=17), 100% versus 32% (p=0.002).

Evaluation of treatment response in osteosarcoma

M Winderen, E Stenwig, M Aas, G Saeter, J Høie, G Folleråas, Ø Solheim

The Norwegian Radium Hospital, Oslo, Norway

We investigated patients with osteosarcoma with dynamic scintigraphy before and after preoperative chemotherapy treatment according to the SSG VIII protocol. Changes in scan findings were compared with histopathologic response in the primary tumor. Of 17 patients 15 were evaluable, 1 patient did not have a preoperative scan, and 1 a wrong field of view was chosen.

Sex	n	age (years) median (range)	tumor localization femur	tibia	humerus
Female	12	17 (6–21)	6	4	2
Male	5	19 (17–23)	3	2	

200 scintigrams were obtained during the first 400 seconds after intravenous injection of 7–10 MBq Tc-99m-MDP per kilo bodyweight. Regions of interest were drawn around the tumor and a reference area, preferably the opposite normal bone, and a time/activity curve was produced. Three criteria on the curves were evaluated: 1. the earliest phase, whether an initial activity peak occurred, which was the rule preoperatively, 2. the slope of the curve, 3. the tumor to non tumor ratio (T/NT) at the end of the dynamic study. We found:

Change from 1 to 2 investigation

Histopat response[a]	n	peak disapp.	curve slope	T/NT change median (range)[b]
IV	1	1	1	45
III	9	7	5	59 (41–111)
II	5	1	0	91 (61–173)

[a] Grading according to the SSG guidelines
[b] Percent of the first investigation

Our observations indicate that dynamic scintigraphy the first 6 minutes after injection of bone-seeking tracers may contribute to the evaluation of treatment response.

Extraskeletal osteosarcoma—the Gothenburg experience

M Dalén[1], B Gunterberg[1], P Bergh[1], Ö Berlin[1], LG Kindblom[2], J Meis-Kindblom[2]

Depts. of [1]Orthopedics and [2]Pathology, Sahlgren University Hospital, Gothenburg, Sweden

Extraskeletal osteosarcoma is a rare malignancy which accounts for about 1% of all soft tissue sarcomas and most often occurs in middleaged and elderly patients. We reviewed 10 patients with extraskeletal osteosarcomas, treated at Sahlgren University Hospital.

Patients and methods: 5 men and 5 women (mean age 53 years) with extraskeletal osteosarcomas involving the thigh (5), abdomen (2), breast (2) and head and neck region (1) were treated. Preoperative investigations included plain radiography, sonography, scintigraphy, CT, angiography and in most cases biopsy. All patients had surgery, 5 patients had adjuvant chemotherapy postoperatively.

Results: 8 patients died of tumor related disease 9-26 months after diagnosis. 1 patient died of cardiac failure 13 years after diagnosis. He had been operated on 11 times because of a grade III recurrent tumor. The remaining patient is alive without evidence of disease.

Conclusion: Extraskeletal osteosarcoma is a highly malignant tumor. Despite adequate surgery and adjuvant chemotherapy, the prognosis is poor.

Giant-cell tumor of the axial skeleton

B Gunterberg[1], B Stener[1], P Bergh[1], Ö Berlin[1], LG Kindblom[2], J Meis-Kindblom[2]

Depts. of [1]Orthopedics and [2]Pathology, Sahlgren University Hospital, Gothenburg, Sweden

Only approximately 15% of giant cell tumors (GCT) occur in the axial skeleton, where treatment is difficult with few options. We investigated the outcome in our patients.

Patients and methods: 14 (9 women) patients were treated. The average age at diagnosis was 32 (15-57) years. 9 patients had vertebral tumors and 5 had sacral tumors. All patients had pain with an average duration of 7 months. 11 patients had neurologic deficits. Intralesional curettage was done in 8 patients, intralesional resection in 3 and extralesional resection in 2 patients. 5 patients received radiotherapy, 1 as only treatment, 2 after a primary operation, and 2 after a recurrence.

Results: 4 patients developed a local recurrence, 2 after intralesional curettage of a vertebral tumor before referral and 2 after intralesional curettage (1 vertebral, 1 sacral) in our centre. All were reoperated and radiotherapy was added in 2 of these cases. 1 vertebral tumor recurred twice in spite of this and had additional surgery. Follow-up time was average 13 years. All patients were without evidence of disease. 2 patients had neurologic disability as a consequence of surgery and 2 had moderate back pain. The remaining 10 patients had no complaints.

Summary and conclusions: Intralesional surgery, sometimes supplemented with irradiation, seems to be able to control GCT of the axial skeleton in a substantial number of cases. 4/14 tumors recurred but appear to be controlled (1 has a short follow-up time). 40 Gy adjuvant irradiation did not prevent recurrence of 2 vertebral tumors. There seemed to be an equal chance for cure of a GCT in the axial skeleton as in the extremities, where modern treatment includes power curettage, phenol treatment and bone cement. These options are hard to apply in the axial skeleton in a truly antitumoral way.

Clear cell chondrosarcoma of bone—new observations on a rare entity

LG Kindblom[1], JM Meis-Kindblom[1], F Bertoni[3], P Bacchin[3], F Remotti[1], B Gunterberg[2], G Stenman[1]

Depts. of [1]Pathology and [2]Orthopedic Surgery, Sahlgren University Hospital, Gothenburg, Sweden, [3]Rizzoli Institute Bologna, Italy

Clear cell chondrosarcoma comprises only 1-2% of all chondrosarcomas of bone; there are approximately 80 cases reported. Studies with longterm follow-up as well as ultrastructural, molecular and cytogenetic studies are sparse or lacking.

Design: A series of 18 cases diagnosed and treated at Sahlgrenska University Hospital and the Rizzoli Institute were analyzed.

Results: The M:F ratio was 4:1 and the median age 40 (20–60) years; 9 involved the proximal femur. In addition to characteristic clear cell chondrosarcoma foci, the tumors had areas resembling osteoblastoma, chondroblastoma, chondromyxoid fibroma, ABC, conventional chondrosarcoma, osteosarcoma, chordoma, metastatic clear cell carcinoma or melanoma. Ultrastructurally the clear cell features corresponded to abundant glycogen deposits and clear zones with a paucity of organelles; tumor cells, which had chondroblastic features, produced osteoid as well as a chondroid matrix. Immunohistochemistry revealed: vimentin + (100%); S100 protein + (85%); EMA focally + (10%; cytokeratins and HMB45, both negative. Ki67 values were <10% (median 1%) and p53 immunoreacitivity negative. Cytogenetic analysis of 1 case revealed a clone showing an interstitial deletion of 2q as the sole anomaly. Longterm follow-up (median 10 yrs) revealed no metastses and 2 local recurrences (both treated by curettage).

Conclusions: 1) Long-term follow-up confirms the low malignant potential of this chondrosarcoma variant as do the low Ki67 values, p53 negativity, and diploid karyotype. 2)

Morphology, Ki67 and p53 do not predict local recurrence which is influenced by the primary surgery. 3) The tumor cells have predominantly chondroid features, but they may produce osteoid, refuting the notion that osteosarcoma is the only malignant tumor which produces neoplastic osteoid.

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

S Crnalic[1], L Boqvist[2], R Löfvenberg[1]

Depts. of [1]Orthopedics and [2]Pathology, University Hospital, Umeå, Sweden

Orthotopically transplanted tumor xenografts might resemble the clinical situation and the biological behaviour of the tumor. With the aim to establish a new human osteosarcoma spontaneous metastasis model, histologically intact tumor tissue was transplanted into the tibia of nude mice.

Methods: Solid tumor pieces of subcutaneously growing human osteosarcoma xenografts from the 32nd serial passage were implanted into the proximal tibia in 31 nude mice. At 2, 4, 6, and 8 weeks after transplantation the animals were killed and examined macroscopically and microscopically for local tumor growth and metastases.

Results: Tumors radiographically and histologically similar to primary human osteosarcoma were found in all mice at the site of the inplantation. Lung metastases were observed in all mice, local and distant lymph node metastases in 15, and liver metastases in 6 mice. The tumor tissue of the metastases showed histologic appearance similarity to that observed in the donor patient's tumor, corresponding subcutaneous xenografts and orthotopically transplanted intratibial tumors.

Conclusion: This tumor model seems suitable for further studies on local tumor growth, formation of metastasis and antitumor therapy.

Immunohistochemistry of growth factors and growth factor receptors in chondrosarcomas

S Inerot[1], P Bergh[1], S Benassi[2], K Scotlandi[2], P Picci[2]

[1]Dept. of Orthopedics, Sahlgren University Hospital, Gothenburg, [2]Laboratorio di Ricerca Oncologica, Istituti Ortopedici Rizzoli, Bologna

Chondrosarcomas are traditionally treated with surgery alone. The prognosis of high grade chondrosarcomas is often poor. Chondrosarcomas may show more or less differentiation into cartilaginous tissue. As capable of forming cartilage chondrosarcomas display some of the effects of the growth process. Growth factors and their receptors are important mediators of growth.

Materials and methods: Tissue specimens were obtained fresh from the operating room, frozen, in liquid nitrogen and stored at -80 °C until processing. For comparison some benign cartilage tumors and tumorlike conditions were also sampled. Normal epiphyseal and articular cartilage served as references. The patient material included 27 chondrosarcomas, 5 chondroblastomas, 1 osteochondroma, 1 synovial chondromatotis and 1 reactive cartilage proliferation in osteoarthrosis. Antibody directed against PDGF-BB, TGFß-1, TGFß-2, IGF1, IGF2, aFGF, bFGF, EGF, TGFa and their corresponding receptors were obtained from commercial suppliers.

Results: Generally chondrosarcomas showed positive staining for IGF1, aFGF, bFGF, PDGF-BB, TGFß-1, TGFß-2 and the corresponding receptors. High grade chondrosarcomas often showed more staining than low grade tumors. Chondroblastomas, osteochondroma, synovial chondromatosis and reactive cartilage proliferation generally were less positive.

Conclusions: The results imply the possibility of self stimulation by autocrine mechanisms, so called autocrine loops, previously implied in Ewing sarcomas. The production of growth factors by the tumor cells remains to be established. A study with RT-PCR methodology is underway to investigate this.

Superfibronectin—a cellmigration-inhibitor—a new concept for antimetastatic treatment in multiple malignant tumor types?

Ö Berlin[1], B Gunterberg[1], S Inerot[1], P Bergh[1], M Dalén[1], R Pasqualini[2], E Ruoslahti[2]

[1]Section of Orthopedic Oncology, Sahlgren University Hospital, Gothenburg, [2]Burnham Institute (La Jolla Cancer Research Foundation), San Diego

Pasqualini et al. have recently presented the first evidences that superfibronectin (sFN), a polymeric form of fibronectin, may have antimetastatic effect on human osteosarcoma, melanoma, and carcinoma cells in experimental and spontaneous metastasis assays. sFN is a polymeric fibrillar form of fibronectin produced in vitro by incubation of fibronectin with a recombinant fibronectin fragment (III-1c). Multimers are formed in a similar fashion to the fibronectin matrix produced in vivo. The authors propose that sFN prevents metastasis by paralysing adherence and/or migration mechanisms of tumor cells in the host.

We have studied the effect of sFN in an experimental osteosarcoma model with spontaneous metastasis formation[3]. In a pilot study of 5 nude mice in the experimental group 20.000 KRIB osteosarcoma cells were injected orthopically in the proximal tibia. A dose of 200 microliters of superfibronectin (100 ml of III-1c) was given intraperitoneally twice a week for 6 weeks. In comparison to a control group of 12 mice we noted that all animals in both groups developed local tumors, but metastasis formation was less pronounced in the lungs of the mice in the experimental group (20% versus 50%). The result are promising enough to extend the experiments to a larger series of mice and to give

more frequent treatment. No severe side effect of the treatment was noted among the nude mice.

Nature Medicine 2: 1197-1203, 1996.

Risk of transmitted diseases in Tampere bone bank

M Hirn[1], T Krusius[2], J Pajamäki[1], P Halonen[1], O Auvinen[1], M Järvinen[1]

[1]Tampere Bone Bank, University Hospital, Tampere and [2]Finnish Red Cross Blood Bank, Finland

The basic aim of a bone bank is to provide safe and appropriate material especially for bone tumor surgery and revision arthroplastics. Every donation includes a risk because of window-period of transmitted diseases. The risks in bone donation is discussed comparing bone donors with blood donors in Finland.

Patients and methods: In 1996, 146 Tampere bone bank donors and almost 200,000 Finnish blood donors were tested. Serological tests include HIV antibodies, hepatitis C antibodies, hepatitis B surface antigen (HBsAg), hepatitis B core protein antibodies (anti-HBc), alanine aminotransferase and syphilis. Blood donors were also tested for HTLV-I and -II. Living bone donors were retested 2 months after donation for HIV and hepatitis B and C.

Results: The seroprevalence of HIV in Finnish blood donors has been 1:200.000. Since 1986 not a single case of HIV infection due to blood transfusion is known to have occurred in Finland. There has never been a HIV positive bone donor in Tampere bone Bank. The window-period with the new 3rd generation antibody tests is 3 weeks. The prevalence of new blood donors with positive hepatitis B or C serology was less than 0.1%. Among bone bank donors the same figure was 1.4%. The window-period of hepatitis may vary between 24-128 days. The seroprevalence of HTLV in Finnish blood donors has been 1:80.000. We have not tested bone donors for HTLV-I and -II because with blood products there seems to be no transmission when stored more than 10 days.

Conclusion: Retesting of living bone bank donors gives good security for HIV. The risk is highest for hepatitis B and C. However, with thorough donor selection and screening tests, allograft bone is a safe alternative for filling bone defects.