Scandinavian Sarcoma Group

22nd meeting, Reykjavik, May 7–9, 1996

Editor: Thor Alvegård and Anders Rydholm
University Hospital
S-221 85 Lund
Sweden

Soft tissue and bone sarcomas in Iceland 1955-1995

G Baldursson[1], A Karlsdottir[1], B A Agnarsson[2], K R Benediktsdottir[2], J Hrafnkelsson[1], H Sigurdsson[1]

[1]Departments of Oncology, [1]University Hospital, Landspitalinn, and [2]University of Iceland, Reykjavik, Iceland

According to figures from the National cancer registries in the Nordic countries the incidence of all soft tissue sarcomas is highest in Iceland, especially in the capital area of Reykjavik. The reasons for this is unknown but referral pattern, autopsy figures or geographic factors may be of importance. Possible explanations will be discussed. The incidence of bone sarcomas, on the other hand, is similar to that in the other countries. We evaluated incidence, diagnostic and treatment policy and prognostic factors for soft tissue and bone sarcomas in Iceland during a 40-year-period which is unique for a whole nation.

Patients and methods: 171 soft tissue sarcomas were reported to the cancer registry (excluding sarcomas in internal organs such as uterus and gastrointestinal tract, dermatofibrosis protuberans, Kaposi sarcoma and mesothelioma). The average age-standardized incidence was 1.8/100.000 for men and 1.6/100.000 for women. Malignant fibrous histiocytoma, liposarcoma and leiomyosarcoma comprised more than half of the tumors diagnosed. All tumors were examined by microscopic slides by two independent pathologists (BAA and KRB). All cases were graded using both a three (I-III) and four (I-IV) scale system.

107 bone sarcomas were reported to the cancer registry during the period with chondrosarcoma (38 cases) and osteosarcoma (21 cases) being commonest. The age-standardized incidence is 1.0/100.00 for women and 1.6/100.000 for men.

Results: Prognostic factors for survival were assessed by Cox's multivariate analysis and included: age, sex, tumor localization, histopathological subtype, tumor size malignancy grade, year of diagnosis and DNA ploidy status. The strongest prognostic factors for soft tissue sarcomas were malignancy grade, tumor size, and year of diagnosis. There has been a more than 50% reduction in mortality risk during the period. We did not find DNA ploidy status as a prognostic factors for the soft tissue sarcomas. Exact prognostic figures for the bone sarcomas are not available at this time.

Conclusion: During the last two decades the prognostic procedures have changed dramatically with the advent of fine needle aspiration, CT scans and more recently the MRI technique. Concurrently the surgical treatment has changed to better margins, more limb sparing procedures and the treatment and follow up has been more centralized. A close collaboration with the SSG has enabled us to discuss all complicated newly diagnosed cases and several have been sent to Lund for treatment. This cooperation has had a very positive impact for both doctors and patients with more favourable survival experience and better quality of life of our patients.

Prognosis in soft tissue sarcomas—the French sarcoma experience

J M Coindre

Institut Bergonié and University of Bordeaux II - Bordeaux - FRANCE

The French medical care system is liberal with both academic and private practices, and therefore a centralized management for rare tumors is difficult to organize. Patients with a soft tissue sarcoma (STS) are frequently referred to the Cancer Centers with locally advanced tumors, local recurrences or metastases. The French Federation of Cancer Centers Sarcoma Group was founded in the early 1980's with the intention of defining prognostic factors and improving treatment of adult STS.

In a first step, we defined a grading system which strongly correlated with overall survival (OS) and metastasis-free survival (MFS) (1). Reproducibility of this grading system was tested (2). We recently compared our system with the NCI grading in a subgroup of 410 patients (3). In the French system there were more grade 3 tumors and fewer grade 2 tumors and the system showed a higher predictive value for OS and MFS in multivariate analysis.

In a second step, we initiated a cooperative data base with collegial pathology review, and from 1980 to 1989, we collected 694 patients admitted it the participating Cancer Centers for the management of the first tumoral event. 546 patients with a non-metastatic and a locally controlled STS were studied (4). Initial treatment consisted of complete tu-

mor resection with amputation in only 4%. Adjuvant radiotherapy was delivered in 58% of patients and adjuvant chemotherapy in 31%. Unfavorable characteristics with an independent prognostic value for distant metastasis were grade 3, no adjuvant chemotherapy, size 10 cm and deep tumor location: and for local recurrence no adjuvant radiotherapy, "poor" surgery (local excision) and deep location. Combination of grade, depth and tumor size were used to define groups of patients according to the metastatic risk. Adjuvant chemotherapy appeared beneficial in terms of overall survival and metastasis-free survival only in grade 3 tumor patients.

Our data base has been expanded to about 1,300 patients, and the next step will be a study of prognostic value according to histologic types.

References:

1. Trojani M, Contesso G, Coindre JM, et al. Soft-tissue sarcomas of adults; study of pathological prognostic variables and definition of a histopathological grading system. Int J Cancer 1984, 33, 37-42.
2. Coindre JM, Trojani M, Contesso G, et al. Reproductibility of a histological grading of soft tissue sarcomas of adults. Cancer 1986, 2, 306-9.
3. Guillou L, Coindre JM, Bonichon F, et al. A comparative study of the NCI and FNCLCC grading systems in a population of 410 adult patients with a soft tissue sarcoma. Annual Meeting of the United States and Canadian Academy of Pathology. Washington DC, March 23-29, 1996.
4. Coindre JM, Terrier P, Bui NB, et al. Prognostic factors in adult patients with locally controlled soft tissue sarcoma. A study on 546 patients from the French Federation of Cancer Centers Sarcoma Group. J Clin Oncol 1996, 14, 869-77.

Monitoring neoadjuvant chemotherapy in patients with high-grade bone sarcoma using perfusion—preoperative assessment of response with emphasis on perfusion-sensitive techniques

H-J van der Woude, J L Bloem, A H M Taminiau, P C W Hogendoorn

Leiden University Hospital, Leiden, The Netherlands

Monitoring preoperative chemotherapy in patients with high-grade bone sarcoma has critical consequences for strategy and timing of surgery and radiation therapy. Evaluating the most cost-effective, non-invasive diagnostic measures aids in the design of prospective trials in the treatment of those patients.

We assessed the capabilities, expected benefits and limitations of conventional radiography and various novel perfusion-sensitive imaging techniques in predicting response to neoadjuvant chemotherapy in patients with high-grade bone sarcoma. Conventional radiography, color Doppler ultrasonography (CDUS), three-phase bone scintigraphy and native and dynamic contrast-enhanced magnetic resonance imaging (MRI) were applied to monitor chemotherapy in patients with osteogenic or Ewing's sarcoma. Imaging data were always compared to the histologic response, assessed on macrosections of the resected specimens.

Plain radiographs were unreliable in predicting response to chemotherapy in patients with Ewing's sarcoma. Using a combination of native (without contrast) MRI parameters, based on changes in tumor volume and extramedullary tumor appearance, a fair agreement between the response assessed with MRI and histologic examination was found.

Tumor (neo) vascularization and perfusion appeared to be principal targets in monitoring chemotherapy. Persistent intratumoral flow with decreased resistive index, assessed with CDUS, indicated poor histologic response after two cycles of chemotherapy in bone sarcomas with an associated soft-tissue mass (p=.03). Histopathologic response could not be predicted before or after the first cycle of chemotherapy using CDUS. Three-phase bone scintigraphy did not allow accurate discrimination between good and poor responders on the basis of quantitative changes in perfusion and blood-pool phase. Fast dynamic contrast-enhanced MRI proved to be valuable for the identification and localization of (even small clusters of) residual viable tumor prior to surgery at well-known sanctuary sites. A short-time interval of < 6 sec between arterial and tumoral enhancement strongly suggests residual viable tumor. In contrast to CDUS, MRI is not hampered by size of the tumor, which makes it a particularly useful tool in (small) intraosseous tumors. The high temporal resolution of the dynamic MRI technique used also allowed distinction between viable tumor and zones of reactive changes.

In conclusion, (fast dynamic) MRI is superior in monitoring efficacy of therapy in patients with intraosseous tumors and in preoperative locoregional staging, whereas color Doppler US seems a promising modality in tumors with an associated soft-tissue mass.

Current concepts and developments in bone tumor surgery with emphasis on advances in pelvic surgery

F H Sim[1], M I Connor[2]

[1]Department of Orthopaedic Surgery, Mayo Clinic, Rochester, MN, [2]Jacksonville, FL, USA

While management of malignant tumors of the pelvis remains a challenging problem, the outlook has improved with recent advances in orthopedic oncology. These include improved imaging modalities, effective neoadjuvant chemotherapy and improvements in methods of reconstruction.

Patients and methods: In a review of 60 patients, there were 23 iliosacral (P1,4), 25 acetabular (P2), and 12 ischiopubic (P3) lesions. Most of the resections were done with a wide margin and disruption of femoral sacral continuity. The techniques of reconstruction varies with the location and ex-

tent of resection and is influenced by the patient's age and activity demands. The methods of reconstruction include arthrodesis, pseudarthrosis, allograft, and prosthetic replacement.

Results: In our series, reconstruction included 10 iliosacral, 14 iliofemoral, and 3 ischiofemoral arthrodeses. 10 of the patients, primarily those in whom an iliosacral lesion extended into sacrum, had a local recurrence.

Conclusion: Our experience indicates that if a satisfactory margin can be achieved, salvage of the limb is justified from both the oncological and functional standpoint.

Differential diagnosis, chemotherapy response evaluation and prognosis of osteosarcoma

F Bertoni, P Bacchini

Surgical Pathology-Rizzoli Orthopaedic Institute, Bologna, Italy

Osteosarcoma (OS) of bone is now divided into several varieties according to clinical, radiographic, and histological appearance and its location in the central or superficial part of bone. Furthermore, the advent of chemotherapy makes the subtyping of OS even more important. Some varieties (central low grade, parosteal, jaw) have a good prognosis with only surgery. If these tumors are included in therapeutic trials, the results will be erroneous. Some subtypes (teleangiectatic) are more sensitive to chemotherapeutic agents than others.

The OS can be graded according to the most malignant appearing area and typified according to the predominant type of tissue produced (chondroblastic, osteoblastic, fibroblastic). Improved survival in the treatment of high grade OS has resulted from the use of contemporary chemotherapy.

A direct relationship between the percentage of tumor necrosis in the primary OS and the ultimate prognosis has been emphasized in the literature. Pathologists have tried to standardize "objective" criteria for microscopic evaluation of tumor necrosis after neoadjuvant chemotherapy. This is by no means an exact science - but it gives a good hint as to definition of good and bad responders.

DNA copy number changes studied by comparative genomic hybridization (CGH) in sarcoma

S Knuutila

Department of Medical Genetics, Haartman Institute, University of Helsinki, Helsinki, Finland

CGH is a new and powerful technique for the study of DNA gains, amplifications and losses in tumors. In CGH, differentially labelled tumor and normal DNA are cohybridized to normal human metaphase spreads and detected with two different fluorochromes. Differences in the tumor to normal fluorescence intensities along the metaphase chromosomes reveal over- or underrepresentations of DNA sequences in the entire tumor genome. Analysis of fluorescence intensity ratios along the chromosomes by a digital image analysis system provides a "copy number karyotype" of the tumor highlighting all chromosomal regions with an aberrant DNA sequence copy number in a single hybridization. Thus chromosomal regions with a consistently increased copy number, especially those undergoing high-level amplification, may reflect sites of activated dominant oncogenes, whereas regions with a consistently decreased copy number may indicate regions containing putative tumor suppressor genes.

Our CGH studies of osteosarcoma, parosteal osteosarcoma, chondrosarcoma, osteochondroma, Ewing's sarcoma, liposarcoma and lipoma have revealed recurrent novel gains and losses. Our poster entitled "DNA gains and losses in sarcomas - a CGH study" presents a more detailed description of these changes.

Genetics of osteosarcoma

S Knuutila

Department of Medical Genetics, Haartman Institute, University of Helsinki, Helsinki, Finland

Cytogenetic and molecular genetic changes in osteosarcoma are poorly known. No specific chromosomal abnormalities have been found so far. The aberrations are complex, even chaotic with numerous structural and numerical aberrations. The aberrations seem, however, not to be random. Some of the structural aberrations, such as 1p36, 7q11, 12p13, 17p11 and 19q13 are frequently involved (Academic dissertation by Maija Tarkkanen).

Comparative genomic hybridization shows that geneticalIy osteosarcoma is highly complex. Several recurrent high-level amplifications have been found, the most important being 12q12-22 and 17p11-12. The former area is known to harbor the MDM2-SAS locus, which undergoes amplification in 14–27% of cases; the latter is not known to locate any cancer genes.

Knowledge of molecular changes in osteosarcoma is scanty. Alterations of Rb and p53 gene are detected in one third to half of the cases. The prognostic significance of the alterations in these suppressor genes cannot be explained yet. Amplifications of MDM2, CHOP, SAS, GLI, A2MR and CDK4, all mapped to 12q12-22 are observed frequently.

Surgical procedure and margin in osteo- and Ewing's sarcomas—the Scandinavian Sarcoma Group experience

O Brosjö

Oncology service, Department of Orthopedics, Karolinska Hospital, Stockholm, Sweden

Since 1990, new pre- and postoperative chemotherapy protocols have been used in Sweden, Norway and Finland in the treatment of osteosarcoma (SSG VIII) and Ewing's sarcoma (SSG IX). This study analyzed local recurrence in relation to surgical procedure and margin.

Methods: Type of surgery was recorded as local excision (including rotational plasty) or amputation. Surgical- and pathological reports were retrospectively evaluated and surgical margin was assessed as adequate, i.e. wide and radical or inadequate, i.e. intralesional, marginal and contaminated wide.

Results: From 1990 to February 1996, 99 patients with osteosarcoma and 66 with Ewing's sarcoma have been treated. In osteosarcoma, the rate of local excisions is increasing. From 1990-93, the rate of local excisions was 0.4 compared to 0.7 since 1994. Only 3 local recurrences have been reported since 1990. In Ewing's sarcoma, there is a trend toward less ablative surgical procedures, 8/66 in SSG IX compared to 12/51 in SSG IV (1984-90). 3 local recurrences (2 marginal and 1 wide surgical margin) have been reported after 35 local excisions.

	SSG VIII	SSG IX
Local treatment (local recurrence)		
Local excision	54 (2)	35 (3)
Amputation	45 (1)	8 (0)
Radiation		23 (2)
Total	99 (3)	66 (5)
Surgical margin (local recurrence)		
Adequate	84 (2)	28 (1)
Inadequate	11 (1)	13 (2)
Total	95 (3)	41 (3)

Conclusion: After efficacious preoperative chemotherapy in osteosarcoma it seems possible to increase the rate of local excisions and still having a low local recurrence rate. In Ewing's sarcoma, surgery with inadequate margin should be supplemented with local radiation.

Limb salvage surgery in osteosarcoma

R Capanna[1], G Bacci[2], F Bertoni[2], C Forni[2], D A Campanacci[1], P Caldora[1], M Del Ben[1]

[1]Centro Traumatologico Ortopedico, Florence, [2]Istituto Ortopedico Rizzoli, Bologna, Italy

Between 1983 and 1995, five neoadjuvant protocols were used. In the first protocol (1983-86) MTX (7.5 gr/m^2 i.v.) and CDP (125 mg/m^2 i.a.) were given preoperatively, while 3 cycles of ADM, MTX, CDP (in good or fair responders) or 5 cycles of ADM and BCD (in poor responders) were delivered postoperatively. In the second protocol (1986–1989) MTX, CDP and ADM were used preoperatively: 3 more cycles of the same drugs were administered postoperatively in good responders while ADM, IFO, MTX, CDP and VP16 were used in poor responders. The third protocol (1990–1991) had a similar schedule but: 1) patients were randomized preoperatively between CDP i.a. vs i.v.; 2) MTX dose increased from 8 to 10 g/m^2; 3) ADM total dose decreased from 480 to 390 mg; 4) ADM was delivered together with CDP, while VP16 was omitted in poor responders; 5) Postoperative treatment was shorter (2 months). In the fourth protocol (1991-92), preoperatively the combination MTX-CDP (i.v.)-ADM-IFO was compared vs the regimen MTX-CDP (i.a.)-ADM: 3 cycles of IFO, MTX, CDP plus ADM were delivered postoperatively. In the fifth protocol, (1993-95) preoperative chemotherapy started with MTX (week 0) followed by CDP-ADM (week 1), MTX (week 4), IFO-CDP (week 5), IFO-ADM (week 8); postoperatively ADM, MTX, CDP, IFO were delivered as a single drug therapy for a short period (10 cycles) in good and a longer one (14 cycles) in poor responders.

Results: Among 548 cases there were only 22 local recurrences (4%). The results obtained in each of these five different protocols are reported in the following table:

Protocol	cases	Necrosis (>90%)	Limb salvage surgery %	Adequate surgery %	Disease free surv % (2yr)	Local recur. %
1st	127	48	72	90	55	5
2nd	144	77	86	89	85	3
3rd	98	54	80	95	66	6
4th	60	80	86	96	73	2
5th	128	73	97	95	87	5.5

The local recurrence rate depended on: 1) the type of surgery (amputation = 1.1%; resection = 4.6%); 2) necrosis (>90% = 2.2%; <90% = 7.5%); 3) surgical margins (adequate = 2%; inadequate = 32%).

Ewing's sarcoma—differential diagnosis of small cell tumors, chemotherapy response evaluation and prognosis

A Llombart-Bosch

Department of Pathology, University of Valencia, Spain

Ewing's sarcoma (EWS) is rare, even by standards of childhood neoplasms. The highest specific age rate per 10^6 children is 8 for boys and 5 for girls at age 13. The histopathologic diagnosis is difficult. Several variants of small round cell tumors (SRCT) mimick EWS. Moreover, histologically EWS belongs to a category of SRCT with neuroectodermal features in which pPNET represents the differential counterpart of conventional EWS. Between these two categories a number of transitional forms may be recognized (atypical EWS). The phenotypic expression of diversity in the microscopical, immunohistochemical (neural markers, HBA/71 positivity) and electron microscopical configuration is supported by a common genotypic character in which t(11;22)(q24;q12) and t(21;22)(q22;q12) are the most frequent reciprocal translocations. Activation of genes EW1, FL1 and ERG results as a consequence of these chromosomal rear-

rangements.

Histologically EWS/pPNET should be distinguished from other SRCT of bone such as small cell osteosarcoma, mesenchymal chondrosarcoma, primitive sarcoma of bone, and primary non-Hodgkin's lymphoma. A rare entity is EWS with endothelial features.

The prognostic factors are based mainly on the histology and anatomical location, together with the tumoral stage. Among the first, necrosis extension and infiltrative pattern in soft tissue extension of the tumor indicate a poor prognosis. Other microscopical features are of negligible value. The anatomical location of the primary neoplasm, central versus peripheral, is mandatory for the clinical outcome. Thoracic ES/pPNET (Askin's tumor) and pelvic locations account for poor prognosis, whereas those affecting distal extremities show excellent clinical response.

Several assays have been undertaken in order to obtain additional information of prognostic value, such as flow cytometry, glycoprotecin P detection, "trk receptor" analysis and post-chemotherapy evaluation of residual neoplasms, in a way similar for osteosarcomas. At present, however, no statistically valid predictive factors have been obtained from these studies.

Cytogenetic and molecular genetic features of Ewing sarcoma

F Mertens

Department of Clinical Genetics, University Hospital, Lund, Sweden

Ewing sarcoma (EWS) belongs to a family of developmentally related neoplasms known as peripheral primitive neuroectodermal tumors (pPNET). These tumors are of presumed neural crest origin and include, apart from ES, peripheral neuroepithelioma, Askin tumor, and esthesioneuroblastoma. The cytogenetic hallmark of pPNET is a balanced translocation t(11;22) (q24;q12) that has been detected in all types of pPNET. Most cytogenetic and molecular genetic data derive from studies on EWS. Of 104 cytogenetically aberrant EWS, 88 (85%) have had a t(11;22), in 15% of the tumors as the sole anomaly. Frequent secondary changes occuring in addition to the t(11;22) include gain of chromosomes 8 (34%), 12 (14%), and 2 (12%) and an unbalanced t(1;16) (12%) leading to loss of the long arm of chromosome 16 and gain of the long arm of chromosome 1. The clinical and biologic significance of the secondary changes are unknown.

Molecular genetic investigations have disclosed that the t(11;22) fuses the *EWS* gene in 22q12 with *FLI1* in 11q24, resulting in an oncogenic hybrid protein consisting of the amino terminal part of the EWS protein and the DNA binding domain of FLI1. The *EWS/FLI1* fusion may be detected in 85-90% of all ES. In 5-10% of the cases a variant fusion of *EWS* with *ERG* in 21q22 is present and <5% have a t(7;22)(p22q12) resulting in fusion of *EWS* with *ETV1*. *FLI1*, *ERG*, and *ETV1* all belong the the *ETS* family of transcription factor encoding genes, and the three different hybrid proteins are thought to have similar phenotypic effects. Some target genes, the expression of which becomes inappropriately activated or repressed, have been indentified, but their role in tumorigenesis is unknown.

POSTERS

The Scandinavian Sarcoma Group Register of musculoskeletal tumors

H. Bauer, T.A. Alvegård, T. Möller, Ö. Berlin, C. Blomqvist, O. Brosjö, N. Egund, I. Elomaa, M. Erlanson, P. Gustafson, M. Karlsson, L-G. Kindblom, A Kivioja, R. Klepp, O. Monge, A. Rydholm, G. Saeter, Ø. Solheim, H. Strander, C. Trovik, T. Wiklund,

The Scandinavian Sarcoma Group, Lund University Hospital, S-221 85 Lund, Sweden, tel +46-(0)46-177555, fax +46-(0)46-188143, e-mail evy.nilsson@onk.lu.se

2288 patients with primary malignant tumors of the extremities or trunk wall were registered between March 1, 1986 and December 31, 1994. Data was reported from 2 institutions in Finland, 3 in Norway, and 5 in Sweden. There are 740 bone tumor (BT) patients and 1544 soft tissue sarcoma (STS) patients. The accrual rate has been approximately 80 BS and 180 STS per year. The data is continuously reevaluated for use in different studies. Hence, all surgical data on STS patients from 1986-91 have been reassessed for studies of local recurrence. Similarly, all Ewing's sarcoma and osteosarcoma patients have been reviewed as part of SSG treatment protocols II, IV, VIII, and IX. Verification of patient data from children and young adults with soft tissue sarcoma is almost completed. The SSG pathology board continuously reviews all histologic slides from patients with Ewing's sarcoma and osteosarcoma and has started review of all soft tissue sarcomas. Review of synovial sarcoma (115 cases) is completed and that of MFH (637 cases) is underway.

The patient data forms were changed as of January 1, 1995 to make data entry simpler. The Register, without patient identification, will now be made available to all SSG Institutions who have entered patients. The Register will be demonstrated at the Poster session.

Histopathologic peer review of Central Registry soft tissue sarcoma

M. Åkerman[1], L-G Kindblom[2], O Myhre-Jensen[3], J Meis-Kindblom[3], E Stenwig[4], H Willén[1], M Virolainen[5], P Lilleng[6], B Bjerkehagen[4], L Walaas[7], T Halvorsen[8]

[1]University Hospital, Lund, [2]Sahlgren Hospital, Gothenburg, [3]Municipal Hospital, Aarhus, [4]Norwegian Radium Hospital, Oslo, [5]University Hospital, Helsinki, [6]Haukeland Hospital, Bergen, [7]Rikshospitalet, Oslo, [8]Regional Hospital, Trondheim

In March 1996, 2126 soft tissue sarcoma had been registered by the Scandinavian Sarcoma Group. A continous histopathologic peer review of primary sarcomas by a Scandinavian review panel of histopathologists started in September 1995. Three different review diagnoses were applied; agreement with the primary diagnosis, another type diagnosis, and exclusion (no type diagnosis but disagreement with the primary diagnosis or other reason). The protocol not only included the review diagnosis but also malignancy grade (four grade scale), presence of necrosis and vascular invasion, mitotic rate, and mode of growth (pushing or infiltrating). Three review meetings have been held since September 1995. 109 synovial sarcomas out of 127 registered and 137 malignant fibrous histiocytomas (MFH) out of 698 registered have been re-examined.

Results: 11 of 109 synovial sarcomas were excluded, no specific review diagnosis was suggested. 39 of 137 MFH (28%) were excluded. 16 were re-diagnosed as leiomyosarcoma, 5 as liposarcoma, 1 each as pleomorphic sarcoma with myogenic differentiation, synovial sarcoma and malignant mesenchymoma, and 15 for other reasons (no type diagnosis suggested and primary wrong registration).

Comments: Technically insufficient material (including immunohistochemical stainings) and lack of pertinent immunohistochemistry or electron microscopy were the main reasons for the lack of a review diagnosis.

DNA gains and losses in sarcomas—a CGH study

S Knuutila[1], G Armengol[1], S Asko-Seljavaara[2], C Blomqvist[3], T Böhling[4], I Elomaa[3], E Karaharju[5], A H Kivioja[5], M L Larramendy[1], J Nevalainen[6], J Szymanska[1], M Tarkkanen[1], E Tukiainen[2], J Valle[4], M Virolainen[3], T Wiklund[3]

Departments of [1]Medical Genetics and [4]Pathology, Haartman Institute, University of Helsinki, [2]Departments of Plastic Surgery, [3]Oncology and [5]Ortohopaedics and Traumatology, Helsinki University Central Hospital, Helsinki, Finland, [6]Department of Clinical Medicine, University of Tampere, Tampere, Finland

Comparative genomic hybridization (CGH) allows the study of DNA copy number changes and makes it possible to assign these to chromosomes. We have performed CGH studies on the following tumor subtypes: osteosarcoma, parosteal osteosarcoma, chondrosarcoma, osteochondroma, liposarcoma, lipoma and Ewing´s sarcoma. In general, osteosarcoma and liposarcoma showed the highest numbers of changes. Gains were more frequent than losses. High-level amplifications were seen only in osteosarcoma, parosteal osteosarcoma and liposarcoma. The recurrent high-level amplifications were 1q22, 1q24, 3q26, 12q12-13, 12q13-15, 17p11-22, 19, and Xp21.

Gains (+) and losses (-) observed in more than 20% of the cases studied were as follows

Osteosarcoma (11 cases) (1)
+1q21-31, -2q34-qter, -6q16-qter, -8p12-pter, +8cen-q13, +8q21.3-23, -10p, +11q14-23, +Xcen-p21, +Xq25-qter
Parosteal osteosarcoma (6 cases) (2)
+2p15-pter, +2cen-q14, -5q22-31, +11p11.2-13, +12q13-15, -13, +14, +15q21-qter
Ewing's sarcoma (18 cases) (3)
+1q21-22, +8q13-24, +12
Chondrosarcoma (23 cases) (4)
+1cen-q24, +14q23-qter, +17p, +20q, +20p
Osteochondroma (16 cases) (5)
no changes observed
Liposarcoma (14 cases) (6)
+1q21-24, +8cen-q21.2, -9p21-pter, +12q14-21, -13q21-qter, +19q, +20q
Lipoma (12 cases) (7)
+4q26-28, +13q21-31, 18q12-qter

Treatment of spontaneous lung metastases from KRIB human osteosarcoma cells growing intratibially in nude mice

M Winderen[1], K Breistøl[2], I Kjønniksen[3], Ö Berlin[4] and Ø Fodstad[2]

[1]Department of Nuclear Medicine and [2]Department of Tumor Biology, The Norwegian Radium Hospital, Oslo, Norway, [3]Department of Pharmacy, The National Hospital, Oslo, Norway and [4]Department of Orthopaedics, Sahlgren Hospital, University of Gothenburg, Gothenburg, Sweden.

The v-Ki-*ras* oncogene transformed human osteosarcoma cell line (KRIB) transplanted orthotopically into the tibial bone of athymic mice, gives subsequent seeding of tumor cells and metastases to the lungs (1). The model, which is representative for the major clinical problem with incurable lung metastases, was used with bone seeking tracers; ^{99m}Tc-MDP for imaging and organ uptake studies, and with ^{153}Sm-EDTMP for therapeutic purposes.

Methods: 1x10^{4}KRIB-cells was injected in the tibia of nude mice. After 14 days, animals were treated intravenously with 400 (n=9), 800 (n=5) or 1600 (n=7) MBq/kg ^{153}Sm-EDTMP. Disease-free latency was defined as the period between tumor cell injection and symptoms caused by tumor growth. Five serial sections of the lungs, and of areas suspect of increased uptake on bonescans, were examined for metastasis formation by histopathological methods.

Results: The control (n=7), and treatment animals, developed palpable tibia tumor after a mean period of 35, 42, 44 and 47 days respectively. A moderate tumor uptake was seen on the tibial bone scans, while no lung lesions with increased uptake of ^{99m}Tc-MDP could be demonstrated, even in lungs with high tumor burden. No significant osteoid formation in the lung tumor lesions and no skeletal metastases could be demonstrated upon histopathologic examination.

Conclusion: Treatment with the bone-seeking agent ^{153}Sm-EDTMP gave a dose-dependent delay in tumor growth in the KRIB spontaneous lung metastasis model, both of the primary tibial tumor and of the lung metastases. The model is interesting for investigating mechanisms of metastases, and for evaluating therapeutic strategies with radionuclides like the unspecific agent ^{153}Sm-EDTMP, or with more specific targeting like monoclonal antibodies labeled with radionuclides, toxins or cytotoxic agents.

Reference: 1.Berlin, Ö et al. Development of a spontaneous metastasis model of human osteosarcoma transplanted orthotopically into bone of athymic mice. Cancer res. (1993) 53: 4890-4895.

Amphotericin B, carboplatin and radiation in human osteosarcoma xenografts in nude mice—in vivo interactions

S Crnalic[1], L-Å Broström[1], P Bergström[2], R Henriksson[2], R Löfvenberg[1]

[1]Department of Orthopaedics and [2]Oncology, Umeå University Hospital, Umeå, Sweden

It has been shown that AmB can increase intracellular accumulation of carboplatin and augment the cytotoxic effect of this drug *in vitro*. The purpose of the present investigation on human osteosarcoma xenografts in nude mice, was to study in vivo the possible interactive effects of AmB and carboplatin in combination with radiation.

Materials and methods: A human osteosarcoma was transplanted bilaterally to the flanks in nude mice. One of the two tumors in each animal was irradiated with a single dose of 12 Gy following treatment with AmB (5 mg kg^{-1}), or carboplatin (20 mg kg^{-1}), or AmB (5 mg kg^{-1}) plus carboplatin (20 mg kg^{-1}), respectively. Tumor growth was compared with non-treated tumors.

Results: A significant reduction of tumor growth was observed after irradiation. Carboplatin in itself reduced tumor growth and also added to the effect of radiation. An unexpected interaction was seen where AmB obviously decreased the effect of either carboplatin or radiation alone or the two given concomitantly.

Conclusion: Our findings contradict some earlier in vitro studies and imply that the interactive effect in general and especially with regard to AmB can not be universally applied to all experimental situations.

Expression of P-glukoprotein in human osteosarcoma and malignant fibrous histiocytoma xenografts in nude mice

S Crnalic[1], L-Å Broström[1], P Bergström[2], R Henriksson[2], R Löfvenberg[1]

Departments of [1]Orthopaedics and [2]Oncology, Umeå University Hospital, Umeå, Sweden

Multidrugresistance has been associated with amplification of a group of genes termed MDR genes in human and rodent cultured cell lines. This group of genes encode a group of membrane glycoproteins termed P-glycoproteins. This study was performed with the aim to establish an in vivo model for testing multidrug resistance.

Materials and methods: The expression of P-glycoprotein was observed in human osteosarcoma and malignant fibrous histiocytoma (MFH) xenografts in serial passages in nude mice using immunohistochemical analysis. Murine monoclonal antibodies C219 and C494 obtained from Signet lab were used.

Results: P-glycoprotein was found in both tumors and was more homogenously expressed in the peripheral parts of the tumor, where higher cellular activity and more intense tumor growth were observed. In the later passages the immunostaining showed a more similar pattern to the primary tumors.

Conclusion: Our observations indicate that this experimental tumor model might be useful in the future studies on multidrugresistance.

Effect of radiation on cell cycle in human osteosarcoma xenografts measured by in vivo labelling with iododeoxyuridine

S Crnalic[1], L-Å Broström[1], R Stenling[3], R Henriksson[2], R Löfvenberg[1]

Departments of [1]Orthopaedics, [2]Oncology and [3]Pathology, Umeå University Hospital, Umeå, Sweden

The delay of the progression of cells through the phases of the cell cycle after irradiation may be related to the radioresponsiveness of tumor cell populations. The purpose of the present study was to analyse the effect in vivo on irradiated human osteosarcoma xenografts.

Materials and methods: Human osteosarcoma xenografts transplanted to the flanks of nude mice were irradiated (single dose 4, 8, 16 Gy) locally under air breathing conditions. Cell cycle perturbations induced by radiation were analysed using flow cytometry and immunohistochemistry in detection of in vivo incorporated iododeoxyuridine (IdUrd).

Results: The irradiation induced delay of the G2-phase of the cell cycle. The number of IdUrd labelled cells accumulating in the G2-phase after irradiation was time- and dose-dependent. The percentage of IdUrd labelled cells undergoing apoptosis were higher in the irradiated tumors compared with controls.

Conclusion: Our findings may indicate that osteosarcoma xenograft cells irradiated in the S-phase are damaged to such an extent that they cannot achieve mitosis (G2-delay) or that they die in radiation induced apoptosis.

Targeted internal radiotherapy in patients with advanced osteosarcoma using 153Sm-EDTMP

Ø S Bruland[1], A Skretting[2], M Winderen[3], G Sæter[1], M Aas[3]

Departments of [1]Oncology, [2]Medical Physics and Technology, [3]Nuclear Medicine, the Norwegian Radium Hospital, Montebello, N-0310 Oslo, NORWAY

Most osteosarcomas (OS), including metastases, produce osteoid, some even producing abundant primitive bone matrix. We explored the use of a bone seeking therapeutic radiopharmaceutical, ^{153}Sm-EDTMP, as a new treatment modality in relapsing OS-patients. 10 patients with OS, presenting with either locally recurrence or metastatic disease after all conventional treatment modalities had failed, were subjected to ^{153}Sm-EDTMP treatment consisting in i.v. infusions of 25-60 MBq/kg body weight on 1 to 3 occasions, usually 6 weeks apart when hematological parameters were restored. All patients had been heavily pretreated with chemotherapy.

In all 3 patients who had pain before treatment, the pain was relieved. One patient, bedridden with paraparesis and impaired bladder function due to a vertebral lesion, had no neurological symptoms, and no metastases 6 months after the last radionuclide treatment. Subsequently he experienced increasing pain, and died 2 months later from purulent meningitis. In 5 other patients significant growth delays were observed lasting for up to 18 months. We observed dramatic decline of serum alkaline phosphatase in the 5 patients with osteoblastic lesions, as evidence of tumor response. One patient with widespread metastatic OS to bones, lungs and soft tissues showed progressive tumor growth despite good uptake of the radiopharmaceutical in numerous metastatic lesions. 3 other patients had low tumor uptake of ^{153}Sm-EDTMP and progressed rapidly.

The absorbed radiation doses were calculated using attenuation corrected conjugated view techniques by combined use of CT-information and whole body scans obtained with a dual head gamma camera. The dose levels may reach 80 Gy in bony parts of the tumor following a single course of the treatment, and the average tumor doses exceed 30 Gy. Repeated scanning showed that the biological halflife of ^{153}Sm-EDTMP in OS-lesions corresponded to the physical halflife of ^{153}Sm. ^{99m}Tc-MDP scintigraphy essentially corresponds to ^{153}Sm-EDTMP scans, and can be used to single out patients with a favourable dosimetry.

We conclude that targeted radionuclide therapy using ^{153}Sm-EDTMP may give considerable palliative effect in patients with osteoblastic OS. An attractive treatment strategy, which is now beeing explored, is to use, already in the primary treatment of osteoblastic OS, 153Sm-EDTMP as a boost technique to conventional external radiotherapy and as an adjunct to chemotherapy.

Neo-adjuvant chemotherapy, conformal radiotherapy and intra-arterial ^{153}samarium-EDTMP as primary treatment of high grade osteosarcoma of the spine

O Monge[1], M Følling[2], M Hordvik[3], R Hafslund[4], P Lilleng[5], A Walløe[6], Ø Bruland[7]

Departments of [1]Oncology, [2]Nuclear Medicine, [3]Radiology, [4]Radiophysics, [5]Pathology and [6]Orthopaedic Surgery, University of Bergen, Haukeland Hospital, N-5021 Bergen, and 7Department of Oncology, The Norwegian Radium Hospital, N-0310 Oslo, Norway

We report a patient with a high grade osteosarcoma of the thoracic spine in which the primary multimodal management involved the administration of intra-arterial therapeutic dose of the bone seeking isotope ^{153}Sm-EDTMP as targeted radionuclide therapy. The patient was a 40 year old woman that noticed a rapidly growing soft tissue tumor in her right thigh concurrently with back pain. The subcutaneous tumor in the thigh was removed with a wide excision in February 1995. The tumor was a metastatic high grade osteosarcoma of osteoblastic type. Imaging indicated a destructive tumor in the body of the 4th thoracic vertebra with a large paravertebral soft tissue component extending along several vertebrae and in the mediastinum. Our diagnosis was primary locally advanced/extracompartmental osteosarcoma of the spine with a solitary (resected) soft tissue metastasis. A partial response was achieved with first line chemotherapy that included 6 courses of high dose methotrexate (12 g/m^2) and 3 courses cisplatinum/doxorubicin. Although further response was seen after 3 courses of second line chemotherapy with ifosfamide/etoposide, it was considered impossible to completely resect the residual vertebral tumor and the paravertebral soft tissue component. Instead, radical radiotherapy was given with conformal technique with 8MV photons according to a 10-field treatment plan with shielding of the spinal cord in most radiation fields. The patient was given 1.50 Gy daily to the original tumor volume with 5 fields and 1.50 Gy to the residual tumor 6 hours later as a daily concurrent boost with another 5 fields to a total dose of 66 Gy in 44 fractions in 37 days. The mean dose to the spinal cord was only 32 Gy (about 48% of the target dose) with a steep dose gradient. Another 3 courses of ifosfamide/etoposide was given alternating with the radiotherapy. After completing chemoradiotherapy, diagnostic bone scan (99mTc-MDP) was enhanced by selective injection in a branch of the intercostal artery supplying the tumor, as compared to the i.v. route. On October 26, 1995 the primary treatment was completed by giving a therapeutic dose of 2.0 GBq (37 MBq/kg) ^{153}Sm-EDTMP via the selective intra-arterial route. Except for temorary grade 4 leucopenia and thrombocytopenia, the treatment was without complications. The

patient is without evidence of disease and without signs of myelopathy in March 1996. To our knowledge, this is the first reported case of intra-arterial administration of a therapeutic dose ^{153}Sm-EDTMP in a human.

Dose intensity in SSG VIII osteosarcoma chemotherapy

M Nilbert, T A. Alvegård, A Gustavsson for the Scandinavian Sarcoma Group

Dept of Oncology, University Hospital, Lund, Sweden

SSG VIII is a Scandinavian multicentric, prospective study including chemotherapy and surgery for osteosarcoma patients (1). 111 patients entered the study 1990–1995. The preoperative chemotherapy consists of 2 cycles of Methotrexate (MTX) (8 or 12 g/m^2), Cisplatinum (90 mg/m^2) and Adriamycin (25 mg/m^2 for 3 days). Postoperatively, patients with histopathological tumor response grades III and IV continue with the preoperative regimen for an additional 3 cycles, whereas patients with tumor response grades I and II recieve 5 cycles of Ifosfamide (1.5 g/m^2 for 3 days) and VP-16 (600 mg/m^2, 72 hour infusion). We evaluated the SSG VIII material for dose intensity (DI; mg/m^2/week) according to Hryniuk (2). The recieved dose divided by the intended dose per unit time represents DI, which is expressed as the average for all drugs included.

Results: 93 patients were evaluated for the preoperative chemotherapy; 41 recieved 8 g of MTX and 52 recieved 12 g. The mean DIs were 0.82 and 0.83, respectively. There were no great differences in DI for the individual drugs (MTX, Cisplatinum and Adriamycin). No correlation was found between average or individual-drug preoperative DI and histopathological tumor response. There was, however, a positive correlation between the total doses for each drug and tumor response. 79 patients were evaluated for the postoperative chemotherapy; 57 patients with tumor response grades III and IV continued the same regimen with a mean DI of 0.69 and 22 patients with response grades I and II recieved Ifosfamide and VP-16 with a mean DI of 0.97.

Conclusions: In contrast to previous investigations we found no correlation between DI and histopathologic tumor response. Postoperatively, DI was difficult to maintain (with the same regimen) in the good responder group, mainly due to hematologic toxicity. The poor responders, however, recieved the alternative postoperative regimen with a high DI, which indicates that the latter was more tolerable.

References:

1. The treatment of osteosarcoma, SSG VIII/1990. Scandinavian sarcoma group & Oncologic tumor centre, Lund University Hospital.
2. Hryniuk VM: The importance of dose intensity in the outcome of chemotherapy. In: DeVita VT, Hellman S, Rosenberg SA, eds. Important advances in oncology. Philadelphia: JB Lippincott, 1988:121-142.

Dose intensity and early and late toxicity in osteosarcoma chemotherapy. The Lund experience from SSG II and VIII

M Nilbert[1], A Gustavsson[1], T. A. Alvegård[1], T Wiebe[2], G Baldursson[3]

Depts. of [1]Oncology and [2]Pediatrics, University Hospital, Lund, Sweden and the Dept. of [3]Oncology, Landspitalinn, Reykjavik, Island.

In Lund 25 patients with non-metastatic osteosarcoma have been treated according to the SSG II (1) and VIII (2) protocols, which include preoperative chemotherapy, operation and two alternative postoperative regimens depending on histopathological tumor response. We evaluated dose intensity (DI) according to Hryniuk and toxicity according to the WHO criteria.

SSG II: 16 patients entered the study 1982-1989. The mean age was 18 (range 10-33) years. Preoperatively, all patients recieved methotrexate with a mean DI of 0.92. Postoperatively, 13 patients with tumor response grades I or II recieved 2-3 cycles of adriamycin, cisplatinum, bleomycin, cyclofosfamide and dactinomycin with a mean DI of 0.71. 2 patients recieved the alternative, methotrexate containing regimen, and 1 patient was excluded from analysis. Grades III and IV anemia occurred in 10% of the phases, neutropenia in 62%, trombocytopenia in 14% and elevated transaminases in 30%. Nefrotoxicity was seen in 1 patient who required temporary dialysis and ototoxicity occurred in 7 pediatric and 1 adult patient after median 1 cycle cisplatinum. Cardiomyopathy developed in a 17-year-old girl after a total adriamycin dose of 600 mg/m^2.

SSG VIII: 9 patients entered SSG VIII 1990-1995. The mean age was 16 (range 2-39) years.

Preoperatively, all patients recieved 1-2 cycles of methotrexate, cisplatinum and adriamycin with a mean DI of 0.80. Postoperatively, 5 patients continued this regimen with a mean DI of 0.66, 1 patient recieved ifosfamide and VP-16, and 3 were excluded from analysis. Grades III and IV anemia occurred in 21% of the phases, neutropenia in 42%, trombocytopenia in 23% and elevated transaminases in 31%. CNS toxicity was seen in one patient after methotrexate administration. 3 pediatric patients developed ototoxicity after cisplatinum administration and cardiomyopathy developed in a 4 -year-old girl after a total adriamycin dose of 325 mg/m^2.

Conclusion: Hematologic toxicity, especially neutropenia, was in SSG II and VIII the major reason for dose reductions and/or prolonged treatment intervals. Liver toxicity of short duration occurred i 1/3 of the phases. Ototoxicity, usually with mild symtoms, was detected in 11 patients. Cardiomyopathy developed 1 year after adriamycin treatment in 2 patients.

References:

1. Combination chemotherapy in osteosarcoma, SSG II/1982. Scandinavian sarcoma group & Oncologic centre, Lund University Hospital, Sweden.
2. The treatment of osteosarcoma, SSG VIII/1990. Scandi-

navian sarcoma group & Oncologic centre, Lund University Hospital, Sweden.

Treatment of high-grade osteosarcoma localized outside the extremities—the Norwegian Radium Hospital/National Hospital experience

G Sæter, A E Stenwig, K Talle, J Høie, G Folleräs, Ø P Solheim, Ø S Bruland, M Boysen.

The Norwegian Radium Hospital (NRH) and The National Hospital, Oslo, Norway.

From 1981, 104 patients (pts) with high-grade osteosarcoma were treated at NRH, 28 of these had non-extremity tumours. The median age in the latter group was 38 (12-87) years, and 3 pts had distant metastases at diagnosis. The primary tumor sites were the jaw (11), pelvis (7), ribs (5), vertebral column (2), skull (2) and scapula (n1). Of 24 pts with initially localized disease who have completed primary treatment, 19 pts had surgery, 11 of these had additional chemotherapy and 4 had additional radiotherapy. Surgical margins were intralesional in 8 pts, marginal in 6 and wide in 5. Wide or marginal surgery was obtained most commonly in the mandible and thoracic wall (10/14), and never in the pelvis, vertebral column or skull (0/7). The 14 pts who received aggressive chemotherapy (SSG protocols) were significantly younger (median 30, range 12-45), and only 6 pts received both protocolled chemotherapy and at least marginal surgery. At 3 years, metastasis free (MFS) and overall survival (OS) were 46% and 36%, and the local control rate for operated pts at 2 years was 41%. Pts with wide or marginal surgery had significantly higher local control rate than pts with intralesional surgery. Although surgery and chemotherapy had no detectable impact on MFS or OS when analysed separately, pts who had protocolled chemotherapy and at least marginal surgery had better OS. It is concluded that although the clinical behaviour of high-grade osteosarcomas appears similar irrespective of primary tumor site, patient characteristics and surgical considerations in pts with non-extremity tumors indicate that novel treatment approaches are needed.

From limb salvage to joint sparing surgery—report of four cases of osteosarcoma around the knee

O Brosjö[1], H Bauer[1], V Söderlund[2], Y Wahlqvist[3]

Oncology service, Departments of [1]Orthopedics, [2]Radiology and [3]Pediatrics, Karolinska Hospital, Stockholm, Sweden

When clinical and radiological evaluation after preoperative chemotherapy in osteosarcoma indicate a response grade III-IV, a joint sparing surgical procedure with adequate surgical margin can sometimes be performed.

Patients and methods: Since January 1994, we have treated 13 patients with stage IIB osteosarcoma around the knee. After preoperative chemotherapy according to SSG VIII protocol, 4 patients (age 7-16 years) were judged as candidates for a knee-joint sparing local excision. The location of the osteosarcoma was distal femur and proximal tibia (2 cases each). The tumor excision was done under fluoroscopic control and after studies of preoperative MRI. Reconstruction was performed with massive, intercalary allografts fixed with locked, intramedullary nail and/or compression plates.

Results: There were no pre- or postoperative complications. The surgical margin was wide in all 4 cases. The histologic tumor response was grade III-IV in all cases. The postoperative chemotherapy was uneventful in all cases. At follow-up, 2 patients are still walking with crutches 4 months after surgery. A-13-year old girl (NED), operated 2 years ago due to a tumor in the proximal tibia, is now fully weightbearing without any pain and with normal motion. One patient, operated due to a tumor in the femur at age 7, died in lung metastases but without local recurrence. The distal femur osteotomy did not heal with callus formation.

Conclusion: Local excision of osteosarcoma around the knee and reconstruction with a mega knee prosthesis is a well known procedure. However, after preoperative chemotherapy and evidence of grade III-IV tumor response, some patients will probably benefit of a knee-joint sparing local excision. The use of massive, intercalary allografts seems encouraging.

Reliable diagnosis of Ewing sarcoma without open biopsy

P F M Choong[1,6], H Willén[2], B Carlén[2], F Mertens[3], N Mandahl[3], K Jonsson[4], T A Alvegård[5], M Åkerman[2], A Rydholm [1]

Departments of [1]Orthopedics, [2]Pathology, [3]Clinical Genetics, [4]Radiology, [5]Oncology, University Hospital, Lund, Sweden, Department of [6]Orthopedics, St. Vincent's Hospital and The Peter MacCallum Cancer Institute, Melbourne, Australia

Open biopsy is a standard procedure for managing bone tumors. In poorly compartmentalized areas such as the foot, hematoma formation from open biopsy may lead to contamination of areas which may otherwise be unengaged by tumor. An alternative technique which is routinely used at our institution is fine needle aspiration biopsy. This is performed as an outpatient procedure and a preliminary cytological report can be available within 30 minutes. Tissue is also procured for immunocytochemistry, electron microscopy, cytogenetics and molecular genetics. We believe this versatile approach may enhance the accuracy of diagnoses, is less traumatic to the patient, expeditious and cost effective.

We present a case of Ewing sarcoma of the foot which was diagnosed by fine needle aspiration cytology, and confirmed by electron microscopy and cytogenetic analysis.

The use of femur in the reconstruction after hemipelvectomy

G Folleråsˡ, O Reikeråsˡ, C Trovik²

[1]Orthopaedic Department, Rikshospitalet, Oslo,
[2]Orthopaedic Department, Bergen, Norway

Patient: A-48-year old man had pain in the left hip. Plain radiographs, CT and MRI disclosed a tumor in the left hemipelvis with a soft tissue component into the pelvis. The femoral vessels and nerve were not involved. An open biopsy close to the sciatic nerve was done. The hip joint was accidentally opened during the procedure. The histology was a low-grade chondrosarcoma.

Operation: In October 1993 we removed the biopsy tract including the sciatic nerve, and performed a hemipelvectomy through the sacral foramina, and included the hip and proximal femur. The femoral vessels and nerve were conserved. A distal femoral amputation was done. The femur was transposed proximally and fixed to the sacrum using screws. The post-op course was uneventful.

Result: He had a prosthesis, and walked very well. He preferred to sit without his prosthesis. Sitting created some problems with pressure on the stump. A special made chair with a lowered sitting cushion on the left side solved these problems.

Conclusion: Walking was better than with an ordinary hemipelvectomy prosthesis. Sitting was more difficult, but the problems were solved by a special chair. Considering all aspects, we think that this reconstruction was of benefit to the patient.

^{99}Tcm-MIBI scintigraphy in the evaluation of chemotherapy response in Ewing's and osteosarcoma

V Söderlundˡ, S A Larsson², H Jacobssonˡ, H C F Bauer³, O Brosjö³

Departments of [1]Radiology, [2]Hospital Physics and [3]Orthopedics, Karolinska Hospital, Stockholm, Sweden

Technetium-99m methoxyisobutylisonitrile (MIBI) accumulates in mitochondria in most tumors. We analyzed whether MIBI scintigraphy could be used to evaluate the preoperative chemotherapy response.

Patients and methods: 12 patients with osteosarcoma and 1 with Ewing´s sarcoma underwent planar examination with MIBI before and after preoperative chemotherapy. The scintigraphic activity of the tumor was assessed as a quotient between ROI:s of the tumor and the contralateral side and corrected for the normal background tissue activity. Tumor response was assessed histologically in the resected specimen in 12 patients and clinically in 1 (dead preoperatively).

Results: There were 5 patients with histological and 1 clinically poor response (grade 1 and 2), 8 with good response (5 grade 3 and 2 grade 4). The reduction in tumor MIBI-uptake correlated with the histological response grade:

Number of patients	6	5	2
Histological response grade	1-2	3	4
Average reduction if MIBI-uptake (%)	52±37	74±28	84±5

Discussion: All tumors showed a reduced MIBI accumulation after chemotherapy. Since there was a corresponding histological response, the reduction indicates true monitoring of tumor response. It is too early to conclude the clinical value of MIBI in therapy response evaluation but the figures are encouraging. Although MIBI-uptake was reduced 50% in the poor responders, the reduction seems to be proportional to the response grade. The variation would probably be reduced by tomographic examination (SPET). Variation in the groups is too large to allow individual evaluation. If MIBI accumulation is correlated to the tumor response throughout the therapy cycles, it may be possible to early identify poor responders for change of therapy regime.

Limb saving surgery with prosthetic replacement of the proximal humeus

J-M Björkenheim, A Kivioja, H Ervasti, J Kinnunen

Department of Orthopaedics and Traumatology, University Central Hospital, Helsinki, Finland

From 1984 to 1994, 10 patients with primary malignant bone tumors of the proximal humerus were reconstructed with a prosthetic replacement of the resected proximal humerus. The criterion for entry in the study was a primary malignant bone tumor that necessitated radical resection and reconstruction. The mean age at the time of the operation was 37 (21-72) years. Reconstructions included 1 Neer II, 2 Link, and 7 isoelastic Mathys custom made prostheses. The soft tissue was meticulously reconstructed including the deltoid and rotator cuff muscles. Pre- and post-operatively the patients were treated according to the standards outlined by the Scandinavian Sarcoma Group. The rehabilitation was dependent on the degree of soft tissue resection. The patients were followed-up on average for 54 (4-120) months. The functional outcome mainly depended on the amount of resected deltoid and rotator cuff muscles. According to the evaluation criterias adopted by the Musculosceletal Tumor Society, the results were excellent or good in 9, and poor in only 1 patient. However, when the outcome was related to the functional assessment scoring system by Constant, there were no good or even satisfactory results. Nevertheless, with the improvement of preoperative imaging modalities and more accurate histological staging, combined with effective neo-adjuvant chemotherapy and radiation, limb saving surgery with prosthetic replacement of the proximal humerus, turned out to be a good and secure way to treat these problem cases. This was clinically seen as a low recurrency rate with reasonable functional outcome.

Function after limb saving surgery and amputation for malignant bone tumors—evaluation of POFA (Postoperative Functional Assessment) of SSG

H Ervasti, A Kivioja, E Karaharju

Department of Orthopedics and Traumatology, Helsinki University Central Hospital, Helsinki, Finland

A standardised system of reporting the functional result after surgery for extremity tumors has been modified through years and the complicated initial system of Enneking (1987 and 1989) has been simplified (Enneking 1993) and adopted by the Musculosceletal Tumor Society (MSTS). The Scandinavian Sarcoma Group (SSG) has revised the system further (Post Operative Functional Assessment, POFA, 1993). We compared these systems in 62 patients.

Patients and methods: 62 patients treated during 21 years (1974-1995) because of a primary malignant bone tumor were included. 25 were amputees (mean age 27 yr) and 37 were limb salvages (mean age 34 yr). The follow up of amputees was 9 years and that of limb salvages was 4 years. There were no amputations of the upper extremity but there were 9 patients with humeral endoprosthesis reconstruction. All patients were clinically evaluated.

In this study the initial system of Enneking is called type I, the new system of Enneking (1993) is called type II and the POFA is called type III. The 7 parameters of type I are motion, pain, stability, deformity, strength, functional activities and emotional acceptance. In type II there are factors pertinent to the patient as a whole (pain, functional activity and emotional acceptance) and factors specific either to the upper extremity (positioning of the hand, manual dexterity and lifting ability) or the lower limb (use of external supports, walking ability and gait). Type III is similar to type II but without scoring emotional acceptance. A numerical score and percent rating was calculated (Total score/Maximum score = % Rating). The descriptive terms of the initial system were converted to numerical ones (excellent=5, good=3, fair=1, poor=0). For statistical analysis the Student's T-test was used.

Results: After ablative surgery the rating was 57% in type I, 64% in type II and 63% in type III. After limb saving surgery the rating was 61% in type I, 62% in type II and 63% in type III, respectively. Sports activities were multiple and variable after ablative surgery, when the external prosthesis could even be thrown away during physical activity (squash, slalom). Patients who had limb saving surgery had more pain than amputees. The emotional acceptance of amputation was better than that of limb saving surgery. The amputees managed functionally worse, when motion, strength, stability and deformity were scored according to old Enneking system (type I), and the difference was clearly statistically significant comparing with the modern Enneking system and the POFA.

Conclusion: The amputees managed worse when motion, stability, deformity and strength were measured, but they had less pain and their emotional acceptance was better than that of limb salvages. The functional result of both groups was equal using POFA and it was very similar using any analysis.

Limb salvage in juxtaarticular primary bone tumors

B Kulinsky, J G Petersen, B Lund

Department of Orthopedics, Rigshospital, Copenhagen

We evaluated the outcome after limb salvage in juxtaarticular primary bone tumors.

Patients and methods: Between March 1989 and August 1995, 15 consecutive patients were treated. They suffered from osteosarcoma (5), parosteal (juxtacortical) sarcoma (2), chondrosarcoma (3), Ewing's sarcoma (1), giant-cell tumor (4). There were 8 women and 7 men (mean age was 38 (7-78) years). The tumors were localised in the distal femur (12), proximal tibia (2) and proximal femur (1). The follow-up is 28 (2-82) months. Before therapy, all patients underwent complete physical examination, CT, bone-scan, chest radiographs and bone biopsy. Patients with Ewing's-, osteo- and parosteal sarcoma were treated with adriamycin and cisplatin followed by wide radical excision and installation of a Kotz prosthesis. 2 patients with giant cell tumors had a Kotz prosthesis after wide excision, because the tumor had spread through the cortex. 3 patients with giant cell tumors, initially treated before 1989, were reoperated with a Kotz prosthesis.

Results: 4/5 patients with osteosarcoma, grade 3, died within 19 (13-29) months postoperatively from pulmonary metastases. 1 patient with chondrosarcoma died 2 months after surgery from general weakness. One limb salvage failed in a girl, who suffered from osteosarcoma. She developed spasm in the femoral artery postoperatively and got a hip exarticulation. One patient was revised in 2 stages because of deep infection. One child was reoperated because of progressively malrotation of the leg. 4 patients had to undergo reoperation because of loosening of the tibial/femoral component. Patients with several reoperations had a poor function: they had pain, walked with a stick and had a stiff knee (3/14).

Conclusion: Limb salvage should be the treatment of choice for patients with juxtaarticular bone tumors.

Dose intensity and early and late toxicity in Ewing sarcoma chemotherapy. The Lund experience from SSG IV and IX

M Nilbert[1], A Gustavsson[1], T A Alvegård[1], T Wiebe[2]

Depts of [1]Oncology and [2]Pediatrics, University Hospital, Lund, Sweden

In Lund 22 patients with Ewing sarcoma have been treated according to the SSG IV (1) and IX (2) protocols. We evaluated dose intensity (DI) according to Hryniuk and toxicity according to WHO in this material.

SSG IV: 14 Ewing sarcoma patients were 1984-1990 treated according to the SSG IV protocol, which includes cyclofosfamide, adriamycin, methotrexate, vincristine, bleomycin and actinomycin D. The mean age was 16 (range 8-27) years. 12 patients had localized disease at diagnosis and 2 had tumor infiltration in the bone marrow. Preoperatively, all 14 patients recieved 1-2 cycles with a mean DI of 1.0. Postoperatively, 8 patients were treated with an additional 2-4 cycles with a mean DI of 0.92. The remaining 6 patients recieved other postoperative regimens and were therefore excluded. Grades III and IV neutropenia occurred in 67% of the phases and was thus the most common type of toxicity. Grade III anemia was recorded in 3% of phases, grades III and IV trombocytopenia in 8% and elevated transaminases in 3%.

SSG IX: From 1990 to date 8 Ewing sarcoma patients have entered the SSG IX study, which includes ifosfamide, adriamycin, vincristin and cisplatinum. The mean age was 20 (range 14-27) years. All but 1 had localized disease. Preoperatively, 8 patients recieved 1-4 cycles with a mean DI of 1.0. Postoperatively, 7 patients recieved an additional 2-3 cycles with a mean DI of 0.84. Treatment induced hematologic toxicity was the most frequent type of toxicity; grades III and IV anemia occurred in 32% of the phases, neutropenia in 86% and trombocytopenia in 33%. Elevated transaminases were observed in 2% of phases. 2 patients developed ototoxicity with a hearing deficit after cisplatinum administration.

Conclusion: The SSG IV and IX therapies have in this material been administered with a high preoperative DI. Postoperatively, DI fell mainly because of hematologic toxicity, which inforced prolonged treatment intervals. Hematologic toxicity was the most common type and was somewhat more pronounced in the SSG IX study, which may indicate a need to add bone marrow stimulatig factors such as e.g. G-CSF in this regimen

References:

1. Combined modality therapy in Ewing's sarcoma, SSG IV/ 1983. Scandinavian sarcoma group & Oncologic centre, Lund University Hospital, Sweden.
2. Combined modality therapy in Ewing's sarcoma, SSG IX/ 1990. Scandinavian sarcoma group & Oncologic centre, Lund University Hospital, Sweden.

Extraskeletal myxoid chondrosarcoma (EMC)—a reappraisal of prognostic factors in 117 cases

J Meis-Kindblom[1], P Bergh[2], F Remotti[1], B Gunterberg[2], L-G Kindblom[1]

Departments of [1]Pathology, and [2]Orthopedic Surgery, Sahlgren University Hospital, Gothenburg, Sweden

Because EMC is rare, its clinical course and prognostic factors are not well defined, nor have potential prognostic markers been studied. 117 EMC cases diagnosed between 1971-1990 were retrieved from the Sahlgren University Hospital and the Soft Tissue Registry of the AFIP in Washington, DC and statistically analyzed.

Results: The M:F ratio was 2:1; median age 52 years; and median tumor size 7 cm. 80% were located in the extremities (18% distally). Most excisions were intralesional or marginal. Median follow-up was 9 years (99 cases). Estimated median survival, intervals to local recurrences and metastases were 18, 8 and 12 years, respectively. Cellular chondroblastoma-like foci were identified in 29%. Pleomorphism, cellularity, necrosis, mitoses, tumor interface, vascular invasion, and Ki67, p53, bcl-2 and PCNA values did not correlate with survival. Older age, larger tumor size, and location in the proximal extremity/limb girdle were independent adverse prognostic factors. Metastases adversely affected survival, despite longevity following metastases.

Conclusions: Though EMC patients have a long survival, they also have a high rate of metastases and local recurrences. Cellular EMC variants exist. Histologic grading, proliferation markers, bcl-2 and p53 have no clear prognostic value in EMC. Significant prognostic factors are tumor location, age, tumor size, and metastases.

Dedifferentiated chondrosarcoma of bone—the Gothenburg experience.

F Remotti[1], P Bergh[2], L-G Kindblom[1], J Meis-Kindblom[1], Ö Berlin[2], B Gunterberg[2], S Inerot[1]

Departments of [1]Pathology, [2]Orthopedic Surgery, Sahlgren University Hospital, Gothenburg, Sweden

Dedifferentiated chondrosarcoma is defined as a low grade chondrosarcoma juxtaposed to a high grade sarcoma.

Results: 10 patients (9M:1F) with dedifferentiated chondrosarcoma were diagnosed (9 treated) at the Sahlgren University Hospital from 1978-1995. Mean patient age was 52 (28-71) years. Tumors were located in the pelvis (7), humerus, (1) femur (1) and sternum (1). The dedifferentiated component was classified as osteosarcoma (5; 1 teleangiectatic), fibrosarcoma (4) and MFH (1). 7 patients were treated primarily with hindquarter amputation, 2 with local resection, and 1 with forequarter amputation. 3 patients received adjuvant chemotherapy. All 9 patients with adequate follow-up died of disease (median survival 0,5 (0,3-9) years). Proliferative activity (Ki67 immunostaining) was low (<1%) in the well differentiated cartilaginous component (10 cases) and high (>50%) in the dedifferentiated component (7). p53 immunostaining was seen in both the well differentiated component (1) and the dedifferentiated component (4).

Conclusions: Dedifferentiated chondrosarcoma has a uniformly poor prognosis independent of the dedifferentiated component's histology. Detection of p53 in the well differentiated component supports the concept of a single neoplasm with tumor progression ("dedifferentiation") along with cytogenetic findings of a single case in the literature.

Characterisation of 1q21-q22 amplifications in human sarcomas by CGH and molecular analysis

A Forus[1], A Geurts van Kessel[2], Ø Fodstad[1], O Myklebost[1]

[1]Department of Tumor Biology, Norwegian Radium Hospital, Oslo, Norway, [2]Department of Human Genetics, University Hospital, Nijmegen, The Netherlands

Comparative Genomic Hybridisation (CGH) analysis is a powerful tool for detection of genomic imbalances in tumor cells. Gains or losses of chromosomal sequences can be detected in a single-step in situ hybridisation procedure. Tumor DNA and normal DNA are labelled with different fluorochromes, mixed in defined ratios, and hybridised to normal metaphase spreads. Subsequently, the intensities of the different fluorescent signals along the chromosome can be measured. A change in fluorescent ratio reflects the copy number changes within the original tumor. Furthermore, CGH allows subchromosomal localisation of the amplified or deleted sequences. Using this technique, we have identified and mapped regions of DNA amplification in 68 human sarcomas of various histological subtypes. Half of the tumors analysed had amplified regions, most frequently affecting the chromosomal segments 12q13-14 and 1q21-q22 (14/64 and 17/64 samples, respectively). Amplification occurred most frequently in liposarcomas. Some sarcoma subgroups had a normal copy number of all genes tested. The 12q13-14 amplicon contains the MDM2 and CDK4 gene, overexpression of which can inhibit two of the main tumor suppressor genes, namely p53 and RB. We are now analysing the extent of the 1q21-q22 amplicons, in search for a minimal common region. This region may harbour important growth regulatory genes, providing a selective advantage to the tumors on overexpression.

Genetic analysis in the differential diagnosis of lipomatous tumors

L-G Kindblom, A Peydro´-Mellquist, JM Meis-Kindblom, H Sjögren, E Röijer, G Stenman

Department of Pathology, Gothenburg University, Sahlgrenska Hospital, Gothenburg, Sweden

The differential diagnosis within and between lipomatous and myxoid soft tissue tumors is frequently problematic. Recent cytogenetic analysis of lipomatous tumors has revealed specific translocations of diagnostic importance in several subgroups, including a t(12;16)(q13;p11) in myxoid liposarcoma. We assessed the occurrence of the t(12;16) and/or its molecular consequences (FUS/CHOP gene fusion) in a series of 19 lipomatous tumors and 5 myxoid MFH/myxofibrosarcomas using cytogenetics, Southern blot and RT-PCR.

Results: The t(12;16) was identified in 3 myxoid/round cell liposarcomas, and was detected by RT-PCR and/or DNA analyses in 8 myxoid/round cell liposarcomas. One chondroid lipoma, 2 pleomorphic lipomas, 2 well differentiated liposarcomas, and 4 pleomorphic liposarcomas failed to reveal CHOP rearrangements as did all of the myxofibrosarcomas.

Conclusions: The FUS/CHOP hybrid transcript is specific for myxoid and round cell liposarcomas, supporting the notion that round cell liposarcoma represents progression of myxoid liposarcoma to a higher grade tumor. The absence of the FUS/CHOP hybrid gene in other lipomatous neoplasms and in myxofibrosarcoma has diagnostic potential. There is a variant of pleomorphic liposarcoma with round or small cell features that is genetically unrelated to the myxoid/round cell group.

Gene amplification and p53 mutation and expression patterns in 123 bone and soft tissue tumors

G Stenman[1], A Peydro´-Mellquist[1], JM Meis-Kindblom[1], E Röijer[1], P Söderkvist[2], B Gunterberg[2], L-G Kindblom[1]

Departments of [1]Pathology and [2]Orthopedic Surgery, Gothenburg University, Sahlgrenska Hospital, Gothenburg, Sweden

Recently, a cluster of genes at 12q14-15, including A2MR, GLI, CHOP, SAS, CDK4, HMGI-C and MDM2, was found to be amplified in sarcomas. We determined the frequency of amplification of these genes by Southern blot, and assessed the p53 status by immunocytochemistry, SSCP- and DNA sequence analyses in a large, well characterized series of 123 sarcomas.

Results: Amplification of MDM2 was detected in 8 cases, including 2 MFH, 2 fibrosarcomas, 3 osteosarcomas, and one liposarcoma; 1 MFH and 3 osteosarcomas also showed amplification of SAS and CDK4. In addition, 2 osteosarcomas had amplification of GLI and/or CHOP, and 1 osteosarcoma and i fibrosarcoma had amplification of HMGI-C. p53 overexpression was detected in 39% of the cases, and included predominantly high grade tumors. p53 mutations were identified in 21 of 34 cases analyzed.

Conclusions: Amplification of 12q14-15 derived sequences is relatively rare in sarcomas and is predominantly found in certain tumor subsets. Amplification in 12q14-15 may involve two different regions containing CDK4/SAS and MDM2. p53 expression and mutation occur primarily in high grade sarcomas and may well reflect late tumor progression. MDM2 amplification and p53 overexpression seem to be unrelated genetic events.

Ultrasound guided biopsy of soft tissue tumors

M Court-Payen, B Bjerregaard, G Lausten, L Ingemann-Jensen, B Skjoldby

Departments of Ultrasound, Pathology, Orthopaedics and Radiology, Herlev University Hospital, Copenhagen,

Denmark

We have used ultrasound guided large-needle biopsy and fine-needle aspiration in the diagnostic work-up of soft tissue tumors since 1991. We compared the results of 1.2 mm trucut needle biopsy, 2.0 mm trucut needle biopsy and fine-needle aspiration.

From January, 1994, to January, 1996, 54 patients with suspected malignant soft tissue tumors were examined using all three types of biopsies. The tumors were located in the extremities (48) and on the trunk (6). In 2 patients rebiopsies were performed and 1 patient had two tumors biopsied. Extirpation of the tumor or follow up showed 13 malignant (M) and 41 benign (B) tumors.

In 18 (4M and 14B) fine-needle aspirates the material was insufficient, compared with 14 (4M and 10B) 1.2 mm needle biopsies and 3 (2M and 1B) 2.0 mm needle biopsies. Using the 1.2 mm needle there were 3 false negatives, and with the 2.0 mm needle there was 1 false negative. There were no false positives. The combination of the 1.2 mm needle and fine needle aspiration biopsies yielded insufficient material in 5 cases and there were 2 false negatives. Combining the 2.0 mm needle and fine needle aspirations biopsies showed only 2 cases with insufficient material and 1 false negative (well differentiated liposarcoma).

Our preliminary results show that ultrasound guided needle biopsies are valuable in the preoperative diagnostic work-up of soft tissue tumors. A 2.0 mm trucut biopsy in association with fine-needle aspiration is recommended as a valuable complement to clinical examination and proper imaging techniques.

Fine-needle aspiration cytology of rhabdomyosarcoma. Is a reliable type diagnosis possible to render?—a retrospective study of 23 cases

M Åkerman, H Willén, B Carlén,

University Hospital, Lund

We investigated wether it was possible to distinguish embryonal, alveolar and pleomorphic rhabdomyosarcoma (rms) in fine-needle aspirates (FNA).

Material and methods: 34 FNA from 23 patients with rhabdomyosarcoma diagnosed 1980-1995 (19 from primary tumors and 15 from recurrencies and metastases) were re-evaluated.

Electron microscopic examination of the aspirate was performed in 10 tumors and immunocytochemistry in 7, respectively. The diagnosis of rhabdomyosarcoma was based on histopathologic examination of the primary tumor in 22 patients; in addition to routine stainings immunohistochemistry was performed in all and electron microscopy in 15 patients. 8 tumors were embryonal rms (1 of them the spindle cell type), 13 were alveolar rms and 1 a pleomorphic rms. Surgery was not performed in 1 patient, the diagnosis was established by electron microscopic examination of the aspirate.

Cytologic reexamination: In most FNAs the yield was rich and the smears composed of a mixture of more or less cell-thight clusters and dispersed cells. Stripped nuclei were common. Generally the embryonal rms were composed of small-medium-sized, pleomorphic rhabdomyoblast-like cells, including multinucleated tumor cells, mixed with rounded, primitive cells. Prominent nuceoli were a common find. The embryonal rms of spindle cell type was characterized of fairly uniform atypical spindly cells.

All alveolar rms, however, appeared as small round cell tumors predominatly composed of primitive cells with rounded nuclei and scanty often vacuolated cytoplasm. Small pear-shaped rhabdomyoblasts were observed in most aspirates. Occasional multinucleated cells were seen. The pleomorphic rms looked like a pleomorphic sarcoma with numerous giant cells and bizarre cells. Scattered highly atypical cells were rhabdomyblast like with deeply eosinophilic cytoplasm in the wet-fixed smear.

Adjunctive methods: Immunohistochemistry (desmin, D33, Dako) was strongly positive in all examined cases while the electron microscopic examination was non-diagnostic in 4 aspirates (necrosis or primitive cells without clear rhabdomyoblastic differentiation)

Conclusion: The light microscopic examination strongly suggested rhabdomyosarcoma in all but one of the primary tumors. Immunocytochemistry was the most valuable adjunctive diagnostic method. Alveolar rhabdomyosarcoma could be confidently diagnosed as such provided the yield was rich and the cells preserved.

The Gothenburg–Rizzoli joint study on synovial sarcoma

P Bergh[1], Ö Berlin[1], B Gunterberg[1], L-G Kindblom[2], J Meis-Kindblom[2], P Bacchini[3], F Bertoni[3], F Gherlinzoni[3], P Picci[3]

Departments of [1]Orthopedics, [2]Pathology, Sahlgren University Hospital (SUH), Gothenburg, Sweden, [3]Rizzoli Institute (RI), Bologna, Italy

We performed a retrospective joint study of 122 patients (Sahlgren 64, Rizzoli 58) .

Results: Mean age was 39 years, mean tumor size 7 cm. 55 tumors were located proximally in the extremities, 51 distally, 13 in the trunk and 3 in the head and neck. 44 had microscopically poorly differentiated areas (PDA). 65 patients had local surgery and 55 amputation; 2 were inoperable. The final surgical margins were wide/radical in 106 cases, intralesional/marginal in 14. 38 patients developed local recurrences, and 64 metastases. 57 patients had no evidence of disease, 4 were alive with disease, 59 were dead of disease (DOD) and 1 died of other causes. Prognosticators for *local recurrence* were: larger size; for *metastases*: older age, larger size, PDA and necrosis; for *DOD:* older age, larger size and PDA. Patients with primary treatment outside a tumor center had a significantly higher risk for local recurrences,

metastases and DOD. Local recurrences (analyzed as a time dependent variable) were associated with a 4-fold increased risk of DOD.

Conclusions: Our findings are of therapeutic and prognostic significance: a low risk group of synovial sarcomas characterized by young age (< 25 years), small tumor (< 5 cm), lack of PDA and necrosis, and adequate primary surgical treatment could be identified.

High tissue urokinase plasminogen activator levels predict metastasis and local recurrence in 69 soft tissue sarcomas

P F M Choong[1,4], M Fernö[2], M Åkerman[3], P Gustafson[1], H Willén[3], E Långström[2], T A Alvegård[2], A Rydholm[1]

Departments of [1]Orthopedics, [2]Oncology, [3]Pathology, University Hospital, Lund, Sweden, Department of [4]Orthopedics, St. Vincent's Hospital and The Peter MacCallum Cancer Institute, Melbourne, Australia

The proteolytic enzyme, urokinase plasminogen activator (uPA), appears to have an important role in the local and systemic invasiveness of soft tissue sarcomas. We analysed the expression of uPA in soft tissue sarcoma using a luminescent immunoassay technique and examined the relationships between uPA levels and tumor characteristics and behaviour.

Patients and methods: We evaluated 69 patients (37 men, 32 women; median age 66 (26-92) years with surgically treated soft tissue sarcomas (MFH 43, leiomyosarcoma 8, liposarcoma 5, synovial sarcoma 4, others 9) of the extremities and trunk wall. The median follow-up for survivors was 4.5 (2.5-6.5) years. 11 patients developed local recurrences only, 21 developed metastases only and 5 had both. The median uPA level was 1.4 (0.04-10.6) ng/mg protein.

Results: Increasing uPA levels correlated with increasing malignancy grade, DNA non-diploidy, tumor necrosis, local recurrence, and metastasis. Moreover, storiform-pleomorphic MFH and leiomyosarcoma had higher uPA levels than other tumors. A cut-off value ol 0.25 ng/mg protein was identified above which local recurrence and metastasis more frequently occurred.

Conclusion: High uPA levels appears to reflect the malignant phenotype in soft tissue sarcoma.

19p+ marker chromosome correlates with relapse in 69 malignant fibrous histiocytomas

P F M Choong[1,6], N Mandahl[2], F Mertens[2], H Willén[3], T A Alvegård[4], A Kreicbergs[5], F Mitelman[2], A Rydholm[1]

Departments of [1]Orthopedics, [2]Clinical Genetics, [3]Pathology, [4]Oncology, University Hospital, Lund, Department of [5]Orthopedics, Karolinska Hospital, Stockholm, Sweden, Department of [6]Orthopedics, St. Vincent's Hospital and The Peter MacCallum Cancer Institute, Melbourne, Australia

A recurrent aberration involving 19p13 has been reported in malignant fibrous histiocytoma. This study examined the relationship between 19p13 aberrations, usually leading to addition of unknown material (19p+), ring chromosomes and clinical outcome in these tumors.

Patients and methods: We examined 69 MFHs. 19 had 19p+ and 24 had ring chromosomes. After a median follow-up of 3 (1.5-11) years 24 patients developed metastases and 27 patients developed local recurrence. 10 patients had both local recurrence and metastasis.

Results: Local recurrence was more common in association with 19p+. Metastasis was more common with 19p+ tumors in high risk patients (tumor size > 5 cm and grade III-IV, n=48). There was an inverse trend between relapse and the presence of ring chromosomes.

Conclusion: 19p+ may be an independent marker of unfavourable outcome in MFH.

Microscopic invasiveness at the tumor border correlates with outcome in soft tissue sarcoma

P F M Choong[1,5], M Åkerman[2], H Willén[2], K Jonsson[3], P Gustafson[1], T A Alvegård[4], A Rydholm[1]

Departments of [1]Orthopedics, [2]Pathology, [3]Radiology, [4]Oncology, University Hospital, Lund, Sweden, Department of [5]Orthopedics, St. Vincent's Hospital and The Peter MacCallum Cancer Institute, Melbourne, Australia

Growth characteristics may reflect tumor behaviour. We examined whole transverse tumor sections (macrosections) to ascertain if growth patterns at the border correlated with outcome.

Material and methods: 70 macrosections were examined. Infiltrative (n 37) growth was any penetration of tumor into host tissue. A pushing pattern (n 33) was tumor expansion without penetration into adjacent host tissue. The median age was 73 (24-94) yr. There were 5 trunk, 17 upper and 48 lower limb tumors, 24 were subcutaneous and 46 deep. 61 tumors were high grade (III-IV). There were 47 MFH, 12 leiomyosarcomas, 3 liposarcomas, 2 synovial sarcomas, and 6 others. Treatment included intralesional surgery + postoperative radiotherapy (2), marginal surgery (9), marginal surgery + postoperative radiotherapy (8), wide surgery (38), myectomy (13).

Results: 2/9 low grade and 35/61 high grade tumors were infiltrating. There was no correlation between invasiveness and size or depth of the tumor. Outcome was analysed in all patients (n 44) who were followed for >20 months (median 46 (20-124) months). 8/22 patients with infiltrating and 1/22 with pushing tumors developed local recurrence. Of 35 widely excised tumors, 5/16 infiltrating and 0/18 pushing developed local recurrence. 11/22 patients with infiltrating and 5/22 with pushing tumors developed metastases.

Surgical margin in soft tissue sarcoma: Assessment by frozen gross sections

C Trovik[1], H C F Bauer[1], P Lilleng[4], O Brosjö[1], A Kreicbergs[1], J Lindholm[3], V Söderlund[2]

Departments of [1]Orthopedics, and [2]Radiology, Karolinska Hospital, [3]Department of Pathology, Danderyd Hospital, Stockholm, [4]Department of Pathology, Haukeland Hospital, Bergen

After local resection of soft tissue sarcoma, we routinely freeze the whole specimen immediately postoperatively and gross sections are taken for macroscopic evaluation of surgical margin. After photography, samples for microscopy are taken from areas of interest. The method improves margin assessment by preventing the retraction of soft tissues thereby facilitating the identification of areas of interest for microscopic evaluation. Two groups of patients, referred for extended surgery after intralesional or marginal surgery outside the tumor center, were studied. In the frozen gross-section group, residual tumor was diagnosed in 7 out of 11 specimens. In a standard formalin fixed group, tumor was only found in 3 of 13 specimens.

The histologic details are well preserved after freezing. We recommend, however, that some representative tumor tissue is taken before freezing for special analysis, e.g. chromosome analysis.

Resistance to chemotherapy in vitro of biopsy material from sarcomas

O Brodin, P Nygren, L Scheibenpflug, M Hedman, M Nistér

University Hospital, Uppsala, Sweden

It has been claimed that only a few drugs are efficient in soft tissue sarcomas, mainly doxorubicin, ifosfamide, etoposide and dacarbazin. Combined treatment with doxorubicin, cyclofosfamide, vincristine and dacarbazin brings about response in 40-50% of the patients. We studied the resistance to chemotherapy in cells from sarcomas, to find out if the FMCA assay, semiautomized dye inclusion method, produce data in accordance with what is known about drug effects in sarcomas.

Methods: From resected sarcomas or biopsy material, a small representative sample was taken out by the pathologist and sent to the laboratory for sterile processing to single cell and small aggregates. The cell-solution was distributed to a 96-well plate, a few control wells without drugs and the other with chemotherapy drugs in standarized concentrations. After incubation for 3 days, survival was investigated by a dye inclusion test. From the survival data the drug/cell relationship were categorized as low resistance, intermediate, and high resistance.

Results: Data have been obtained of 14 drugs in 38 patients (35 soft tissue and 3 Ewing sarcomas), most of them tested in 2 concentrations. However, the material was not sufficient to test all drugs in all patients. There were striking differences between different tumors, with respect to resistance pattern. In more than half of the tumors doxorubicin, etoposide and one of the metabolities of Ifosfamide demonstrated low resistance, while in e.g. 5-Fu, prednisolon and cytosinearabinoside less than half demonstrated low resistance. Taxol was in this study the most efficient drug, with two thirds of the tumors in the low resistance group.

Conclusion: The FMCA test has until now, except in exceptional cases, been used to chose chemotherapy. Our findings indicate that the drugs most efficient clinically seem to be the best ones also according to the FMCA method. A clinical study in which the choice of second line treatment will be determined by the test is now discussed.

Monotherapy with high dose Ifosfamide in sarcomas

K Engström[1] B Gunterberg[2], I Turesson[1]

Departments of [1]Oncology, [2]Orthopedics, Sahlgren University Hospital, Gothenburg, Sweden

We studied the efficiency and tolerance of high-dose Ifosfamide (HDI) in primary as well as in heavily pre-treated tumors.

Patients and methods: 21 patients, mean age 41 (19-67) were treated between 1993-1995. 4 of them had primary tumors. HDI 14 g/m^2 was administrated in dose of 2 g/m^2 i.v. over 4 hrs followed by 2 g/m^2/day x 6-7 days by continuous i.v. infusion. Mesna in equivalent doses an sodiumbicarbonate supplementation were given. All patients received G-CSF in 10 days after HDI.

Results: 84 cycles were administrated with a mean number of 4 cycles per patient. The max. number of cycles was 9 which were given in 3 periods to one patient. Of the 21 patients 20 were evaluable for response: 2 CR, 5 PR, 9SD, and 4 PD. Hematological toxicity was mild. Renal tolerance was good in patients with normal renal function. 5 patients (age 22, 60, 61, 64 and 67) had CNS toxicity. 3 of them continued the treatment without bolus inj. and experienced no significant CNS-toxicity.

Conclusion: Tumor response is good in heavily pre-treated patients. The treatment is well tolerated and hematological toxicity is not dose-limiting using G-CSF. CNS-toxicity may be dose-limiting in elderly patients.

Spontaneous bone healing in a patient with destructive hemangioendothelioma

S Friesland[1], J-O Fernberg[1], U Falkmer[1], C Silfverswärd[2], O Brosjö[3], V Söderlund[4], H Strander[1]

Departments of [1]Oncology, [2]Pathology, [3]Orthopedics, and [4]Diagnostic Radiology, Karolinska Hospital, Stockholm, Sweden

A previously healthy 51-year-old male photographer had a

trauma involving the right forearm. Radiographs showed lytic destructions in the metacarpal bones and radius. Scintigraphs showed a pathological uptake in the destructions but no other abnormalities. Radiographs 2 months later showed no progression. Cytology was inconclusive and an open biopsy was performed. The diagnosis was multifocal hemangioendothelioma (later reviewed with the same diagnosis by pathologists at the Mayo Clinic). Therapy was discussed and after consideration radiotherapy was suggested instead of amputation. Start of therapy was delayed as the patient went abroad on a business trip.

Radiographs 2 months later showed regression with sclerosis. The sclerosis was even more pronounced at 6 and 12 months. After 18 months the destructions had healed completely. The patient is now free from disease after 3 years. To our knowledge there are no reports of spontaneous regression in this disease. An interesting possible etiology has been found. As a child the patient used to play in a shoe-shop where an X-ray machine had been introduced to facilitate shoe fitting. The patient demonstrated the machine to his friends by putting in his right arm repeatedly.

The role of "embolization" and amputation in extensive soft-tissue hemangioma

M Dalén[1], S Inerot[1], P Bergh[1], Ö Berlin[1], B Gunterberg[1], P Svendsen[2], G Wikholm[2], M Geijer[2], L Angervall[3]

Departments of [1]Orthopedics, [2]Radiology, [3]Pathology, Sahlgren University Hospital, Gothenburg, Sweden

Extensive, deep seated soft-tissue hemangiomas are often unresectable and require other treatment. The role of instillation therapy, sometimes combined with local surgery, and amputation was studied.

Patients and methods: 29 patients (11 male, 18 female) with involvement of the upper extremities (8), lower extremities (19) or trunk (2) were treated. Pain and swelling were the most common complaints. All tumors were large, some unmeasurable. Plain radiograms, CT and MRI were part of the work-up. MRI proved to be the most valuable diagnostic modality but only moderately useful for posttreatment evaluation. 27 patients were treated with Sotradecol® injections one or more times. 8 had local surgery in addition. 2 patients with hemangioma in the entire lower limb and pelvis were amputated.

Results: Most patients experienced relief of symptoms after Sotradecol® treatment. However, several had recurrent pain and required additional injections. One patient who had hemipelvectomy was cured, and one who had transfemoral amputation was improved.

Conclusion: Preliminary results indicate that Sotradecol® injections are beneficial in the symptomic treatment of extensive hemangioma; results improve when local surgery can be added. Amputation may be the ultimate alternative in desperate cases.

Ultrasonic surgical aspiration for cervical chordoma

B Gunterberg, P Bergh

Department of Orthopaedics, Sahlgren University Hospital, Gothenburg, Sweden

Chordoma of the cervical spine may be difficult to excise with an adequate margin because of the proximity of vital structures. We describe the benefits of ultrasonic surgical aspiration.

Patients and methods: 2 patients, with 6 and 8 cm large tumors, originating from the C_3 and C_{3-5} vertebrae were operated on. After excision of the bulk of the tumor the remaining portions were removed with a Cavitron Ultrasonic Surgical Aspirator (CUSA, system 200, Valleylab. Inc. Boulder, Co.) The handpiece consists of a hollow titanium vibrating suction device with coaxial saline irrigation. The tip oscillates longitudinally at 23 kHz with a stroke of 0,3 mm. The tissue is fragmented and aspirated. After macroscopical removal of the tumors reconstruction was done with tricortical bone blocs and titanium plates. Radiotherapy was added in one case.

Results: The tumors were easily removed. The vertebral arteries were skeletonized free of tumor as well as the dura without damage. Tumor tissue invading bone was easily fragmented and aspirated. No complications attributable to ultrasonic surgical aspiration occurred.

Conclusions: CUSA is a valuable tool for intralesional removal of chordoma. The system combines fragmentation, irrigation and aspiration in one instrument. It selectively fragments moist tissue as well as hard, calcified, tissue but spares collagenrich structures.

Is revascularization possible in allografts? A long-term follow-up with plain films, quantitative computed tomography, bone scans and magnetic resonance imaging

A Kivioja[1], J Kinnunen[2], S Bondestam[3], O Korhola[3], E Karaharju[1]

[1]Department of Orthopaedics and Traumatology, Töölö Hospital, [2]Division of Diagnostic Radiology, Tölöö Hospital, [3]Department of Radiology, Meilahti Hospital, Helsinki University Central Hospital, Helsinki

We reviewed 3 women and 5 men clinically and radiologically. They had been operated between 1970 and 1977 because of aggressive or low-grade malignant bone tumors. 7 patients had received osteoarticular massive allografts either of the distal femur (6) or proximal tibia (1), and 1 patient a segmental (intercalary) allograft of the tibia. At follow-up after mean 19 years plain films showed excellent fusion in all 8 patients with both periosteal and primary bone formation. No statistically significant difference was found between bone mineral content of allograft and host bone. Bone scan was used as an adjunct to MRI findings. 5 patients un-

derwent MRI of the allografts. In all grafts there were juxtafusional zones, which showed homogenous bone marrow signal intensity (SI) on both T1 and T2 sequences. The homogenous SI zone was isointense to that of the host bone in the distal femoral grafts for a mean length of 2.6 cm from the original junction between living and allograft bone equalling one fifth of the total length of the graft. In the tibial intercalary graft the SI of the homogenous zones (5 cm proximally and 1 cm distally, two fifthts of the total length) was lower at T1 and higher at T2 than that of the host. The femorotibial grafts had a 92% length of homogenous and equal SI and showed no additional contrast enhancement (CE) with gadolinium. The tibial segmental grafts showed slight uniform CE. The distal femoral grafts with total knee prosthesis showed CE for 4.5 cm distal to the junction. One distal femoral graft showed no CE and in the fifth graft examined with MRI there was contrast enhancement through the grafts very irregularly.

It seems that the late results of allografts are good concerning graft strength. This may be due to revascularization which can occur through the whole length over 10 cm long bone grafts.

Giant cell tumors in Jutland—a 25-year follow-up study

M T Davidsen, J Keller, A G Jurik, O S Nielsen, O Myhre-Jensen, O Sneppen

Centre for Bone and Soft Tissue Sarcomas, University Hospital of Aarhus, Denmark

From 1970 to 1995, 49 patients (29 men and 20 women) were treated for giant cell tumors at our center. All the patients came from Jutland which represents about 2 million citizens (2/5) of the whole country. Mean age was 35 (6-62) years. Half of the tumors were located around the knee. The patients were followed for 32 (3-150) months.

Results. Curretage were performed in 26 patients, 15 of these had the cavity filled with bone chips, 9 with gentamicin-cement. Excision was performed in 16 patients: 8 cases were reconstructed with fibular graft and 6 patients had an arthroplasty. 7 patients were amputated. There was local recurrence in 10 cases.

Curretage and chips (15)	Cement (9)	Excised (16)
Local recurrence 5	2	3

Conclusion. We found a good tumor control when patients were treated with cement or fibular graft, but bad tumor control when treated with curretage and bone-chips.