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Lectures

The past and the future of the Scandinavian Sarcoma Group

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Background: Musculoskeletal sarcomas call for multidisciplinary management by a "tumor team" of specialized orthopedists, radiologists, pathologists, tumor biologists, cytologists, radiotherapists, and oncologists. Only a few such teams existed in Scandinavia during the 1970s. With the inception of the Scandinavian Sarcoma Group (SSG) in 1979 (founded by Ø P Solheim, the Norwegian Radium Hospital, Oslo during the first SSG meeting at Lysebu, Holmenkollen, Oslo, November, 2–3, 1979), several other new teams were started, each with regional responsibility for centralized treatment of sarcoma patients.

The past: During the past 20 years 17 treatment and research protocols were introduced by the SSG regarding management and treatment of musculoskeletal tumors (SSG I–XIII, ISG/SSG I–IV). A total of 990 articles have been written by members of the Scandinavian Sarcoma Group in the period of 1979–1999. This publication represent research from the various Scandinavian tumor center and the SSG research program. 10 members wrote their Ph.D. theses of on issues relevant to sarcoma in this period.

The future: Our knowledge of sarcoma biology has increased significantly during recent years and this has already had an impact on diagnostic precision and prognostic predictability. For the future there is also need for larger trials with fast accrual operating with successful international collaboration, i.e. the Italian Sarcoma Group and other collaborative groups. The SSG tumor biology and morphology group has to work closer together in the future for molecular subclassification of soft tissue tumors. United tumor response grading system for osteo- and Ewing's sarcoma has to be developed. Research and treatment protocols for other than extremity and trunk localized sarcomas, i.e. retroperitoneal sarcoma, has to be developed. The SSG Central Register has to improve further in regard to reporting, follow-up and review of data in the register. Several articles and doctors thesis are in preparation regarding prognostic factors, referral patterns, and importance of surgical margin for musculoskeletal tumor based on the SSG Central Register.

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Needle core biopsy in diagnosis of adult soft tissue tumors

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Accurate diagnosis is essential for management of soft tissue tumors (STT), and an adequate tissue sample is necessary to assess malignancy, subtype and grade. Excisional biopsy is used for small superficial lesions. For deeper masses, open incisional biopsy has disadvantages which are avoidable by closed (needle) biopsy, which can be of various types.

Methods: This presentation reviews the advantages of needle core biopsy (NCB) as used in diagnosis and grading of STT in a specialized multidisciplinary soft tissue tumor unit.

Results: The minimum clinical data required are age, sex, site size and duration of the tumor and its anatomical plane. Reactive lesions and benign tumors are common (20% of 424 STT). Most pseudosarcomas occur in the subcutis, whereas deep tumors are usually malignant. Assessment of malignancy is difficult for well-differentiated fibroblastic and fatty lesions. For some sarcomas, diagnosis is obvious. Further categorization, especially of spindle cell, myxoid and small round cell tumors, requires immunohistochemistry, electron microscopy and genetic studies. Over 95% accuracy can be obtained for benign vs malignant diagnoses, 82% for subtyping of sarcomas and 85% for grading. Results are comparable between specialist centers, and better than from non-specialist practitioners.

Conclusion: NCB is safe, simple, repeatable, quick, inexpensive and reliable in specialist hands. Open incisional biopsy is needed only when NCB fails.

Imaging surface lesions of bone

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Imaging has a fundamental role in all aspects of the management of musculoskeletal tumors from detection and diagnosis to ultimately, where possible, a cure. An intriguing group of lesions arise on the surface of bone and present a challenge to both the radiologist and pathologist.

Terminology for these lesions in the literature is confusing but they can be categorized in two ways. First, as with other musculoskeletal tumors, by their site of origin be it cortical, subperiosteal, periosteal, parosteal or paraosseous (1, 2). Second, by aetiology be it neoplastic (benign or malignant), post-traumatic and inflammatory. The term juxtacortical is imprecise and best used for those lesions where the site of origin cannot be determined.

In detection and diagnosis the radiograph remains the imaging method of choice due to its low cost and wide availability. CT can be helpful in demonstrating the integrity or otherwise of the cortex and the presence of matrix mineralization. Although MR imaging may not reveal the latter feature it has largely superceded CT in the staging of the primary lesion due to its superior ability to reveal medullarly invasion and relationships with other critical structures. This presentation concentrates on the radiological diagnosis of surface lesions of bone and highlights the pitfalls. Features distinguishing between parosteal osteosarcoma and posttraumatic reparative conditions in the hands and feet are stressed.

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Outcome of limb salvage—objective or subjective assessment?

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The best way to evaluate outcome in orthopedic oncology patients hasn't been established. Existing systems are inadequate. The Enneking System, endorsed by the International Society of Limb Salvage Musculoskeletal Tumor Society (ISOLS-MSTS) has had world wide acceptance. Nevertheless it is not scientifically sound. Among its problems, it is a nonparametric system that is used in a quantitative, parametric fashion. Furthermore, it mixes subjective and objective measures, and many of the categories lack a word correlate to the numerical score. Clearly, we need a better system.

Objective measures are desirable. Quantitative techniques may be more scientifically valid. They may also be more suitable for cross-cultural evaluation and communication. Gait analysis is one such method that has potential for our specialty. It may incorporate measures of stride, gait, strength, and oxygen consumption. Each gives useful information. Comparison of results achieved for different reconstructive procedures highlights the relative advantages and disadvantages of operations in an objective, functionally important way. It has allowed us to prove several things.

1. Patients with endoprostheses use less energy than above knee amputees.
2. van Nes rotationplasty patients perform nearly as well as below knee amputees.
3. Internal hemipelvectomy patients with stable, mobile hips have better gait symmetry and use less energy walking than patients who were less effectively reconstructed, and
4. The relationship between gait parameters and ISOLS score can be quantified and expressed as an easy to use formula.

The analyses are time-consuming, expensive, and not available in most centers. Therefore, it is not practical for gait analysis to be the standard for the evaluation of tumor patients. Nevertheless, it is crucial for all alternative measures to be validated against objective m easures such as gait analysis.

Subjective measures, and self reporting by patients have been advocated as the most effective method to judge outcome in orthopedics, but there are few studies in oncology patients. Instruments such as the AAOS-MODEMS tool and the SF-36 enjoy widespread use and need to be validated for musculoskeletal tumor patients. We have identified potential problems with such systems. For example, patients have individual goals, needs and priorities that influence their perceived quality of life. These may vary over time as their disease status changes. This minimizes their ability to assess quality of Life (QOL) fully, and to respond to changes in the patients' disease status and function.

The existing systems lack the breadth, depth, or reproducibility for use in the orthopedic oncology population. Integration of objective and subjective measures hold the greatest promise to define outcome. It is imperative that cooperative groups work together to validate such a system.

Diagnosis, treatment and prognosis of retroperitoneal sarcomas

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The management of retroperitoneal sarcomas continues to represent a challenge for the treating surgeon as it is frequently not possible to deliver therapeutic radiation doses to the tumor bed for the control of residual microscopic disease. To date no study has shown that chemotherapy is beneficial in retroperitoneal sarcoma. Thus, a properly executed surgical resection continues to be the most important therapeutic modality. The objective of the present study is to iden-

tify important diagnostic and prognostic factors relevant to clinical outcomes in retroperitoneal sarcoma.

Methods: An analysis was performed of 284 consecutive patients with retroperitoneal sarcoma seen at the Brigham and Women's Hospital and Dana Farber Cancer Institute of which 201 patients were treated since 1994.

Results: Of 284 patients with retroperitoneal sarcoma 176 (62%) were seen for newly diagnosed primary sarcoma, 40 (14%) had locally recurrent sarcoma and 68 (24%) had metastatic disease at diagnosis. The most common histologic types included: leiomyosarcoma/GIST in 40%, liposarcoma in 20%, malignant peripheral nerve sheath tumor in 7%. The multivariate analysis showed that high-grade and intermediate-grade histology was associated with a five-to-six-fold increased risk of death compared with low-grade histology. In addition to grade, gross positive margin of resection and microscopic positive margin of resection were important independent prognostic factors for survival.

Conclusions: The histologic grade and the margin of resection are prognostic for survival in retroperitoneal sarcoma. Although a complete surgical resection remains the most important therapeutic intervention for long-term survival, a novel effective non-toxic adjuvant therapy for minimal microscopic residual disease would represent a significant therapeutic advance. The thiazolidnedione, troglitazone, represent a promising new non-toxic differentiation agent for the adjuvant treatment of retroperitoneal liposarcoma.

Retroperitoneal sarcomas

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The diagnosis of a retroperitoneal tumor is usually made by ultrasound or CT scan. After exclusion of lymphoma, germ cell tumor, metastases, paraganglioma, tumors of kidney or adrenal gland, a variety of mesenchymal tumors should be considered. Neurogenic tumors, mostly benign, are suspected when in close relation with the paravertebral space and foramina. The other soft tissue tumors should be considered malignant until proven otherwise. Liposarcoma, leiomyosarcoma and malignant fibrous histiocytoma are the most frequent types. CT or MRI images should be carefully studied for necrosis, fat density and topography. Even a small area with fat density suggests liposarcoma and should alert surgeon and pathologist about possible dedifferentiated liposarcoma where a well differentiated liposarcoma co-exists with a high grade sarcoma. The imaging also reveals the relation of the tumor with bone, vessels, muscles and organs. In many perirenal tumors it is possible to distinguish between a perirenal location within Gerota's fascia and a pararenal location allowing conservation of the kidney. CT thorax is indicated in search for metastases although the incidence is less than 10%.

Spinal cord involvement and encasement of the major vessels at the root of the mesentery constitute irresectability and legitimize an incisional biopsy, which is contra-indicated in resectable tumors. The benefit of neo-adjuvant therapy is not proven although an occasional patient with a high-grade sarcoma might benefit. Surgery remains the major therapeutic act and should aim at complete resection of the tumor surrounded by a layer of normal tissue such as colon and muscle fascia but non-existent medially at the great vessels. A difficult dissection correlates with high grade.

A major problem for radiotherapy remains the large treatment field dictated by the large volume of most of these tumors. In our center radiation therapy is given for high-grade sarcomas, and when residual tumor is left. Adjuvant chemotherapy is not indicated. Local recurrence remains a major problem but warrants further surgery and radiation in case of low grade sarcomas.

The M.D. Anderson Sarcoma Center experience in the treatment of musculoskeletal sarcomas

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I shall cover two areas: 1) 123 patients with primary, high-grade osteosarcoma of the extremities treated by primary chemotherapy and varied postoperative chemotherapy; and 2) 79 patients with soft-tissue sarcomas treated with dose-intensive chemotherapy, to illustrate the role of medical oncology in the context of our multidisciplinary sarcoma center.

Materials and Methods: 123 patients with extremity osteosarcoma received IV adriamycin and IA cisplatinum. Postoperative chemotherapy was essentially unchanged in our first group of patients, high-dose methotrexate added for poor responders in a second group, and ifosfamideadded in a third group. 79 patients with soft-tissue sarcomas received dose-intensive AI (adriamycin-ifosfamide).

Results: For good responders with osteosarcoma, 5-yr continuous disease-free survival (CDFS) was 78%. For poor responders without change in chemotherapy, CDFS was 13%. High-dose methotrexate improved CDFS to 34%. Ifosfamide improved CDFS to 67%. For patients with soft tissue sarcomas, the response rate was 65%.

Conclusions: Primary chemotherapy for patients with osteosarcoma followed by tailored postoperative chemotherapy improved CDFS. Dose-intensive AI increased the response rate for patients with soft-tissue sarcomas.

Microarray-based analysis of gene expression. New tools for the diagnosis of problem cases?

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The Genome Project has two main results, the raw sequence of all the chromosomes, and that of the individual genes. In addition to the large number of genes that have been cloned by traditional research projects, massive general approaches have yielded huge numbers of short, anonymous gene fragments, "expressed sequence tags" or ESTs. This gives an enormous potential for detailed information on the gene expression pattern of cells and tissues, which will revolutionize histological diagnosis.

Thousands of cloned sequences can be arrayed on single microscope glass slides by robotic devices, and the expression levels in tumors of all genes represented by these "DNA microarrays" can be analyzed simultaneously. This is done by the hybridization of fluorescently labeled probes representing the entire mRNA population of the tumor to the microarrays, in competition with a probe from a reference tissue. The resulting expression fingerprints can be classified by computer-aided comparison to various preestablished histotype-specific expression patterns. Expression patterns can be correlated with prognosis and therapy response, but the interpretation of the enormous data sets that will result from studies of clinical series will be the most important challenge in the near future. Facilities for microarray production and analysis are currently being set up at our institute.

History of radiology in SSG and imaging response to chemotherapy

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In the early days of SSG Dr. Kristian Talle enjoyed himself at the joint meeting of diagnostic radiology. In these days CT was revolutionizing in the preoperative assessment of bone and soft tissue tumors and especially so in the assessment of response to chemotherapy when combined with bone scintigraphy.

The era of MR-imaging started in 1986 in Scandinavia but although imaging techniques have improved, conventional radiographic techniques remain of fundamental importance in analysis of bone tumors.

There is a wide-spread demand for imaging techniques which allow assessment of response to chemotherapy following the first and second course of treatment in Ewings and osteosarcomas. It is the opinion of the imaging group in SSG that neither dynamic gadolinium contrast MR imaging nor Doppler sonography are appropriate for such assessment in centres with only a few patients per year. New macromolecular MR contrast media and new ultrasound technology using microbubbles are or will be available during 1999 and may improve measurement of tissue perfusion.

Imaging response to chemotherapy: The Birmingham experience

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In the past two decades the prognosis for patients with a primary sarcoma of bone has been dramatically improved with the introduction of chemotherapy. This in turn has increased the surgical options such that limb-salvage surgery has become more sophisticated with introduction of CT, MR imaging and most recently PET scanning. Much of the recent research in the imaging of bone tumors has concentrated on attempting to accurately assess the response of the primary tumor to chemotherapy as this has been shown to be an independent major prognostic parameter for relapse-free and overall survival in both osteosarcoma and Ewing's sarcoma. Conventional radiographs are not reliable for monitoring tumor response. Similary, angiography is considered obsolete in this respect. The use of scintigraphy for this purpose appears confined to research units and is hampered by low spatial resolution. CT has been largely superceded by MR imaging where dynamic contract enhanced studies are more helpful than static studies. There are, however, significant limitations with this technique due to the heterogeneous nature of sarcomas. These drawbacks and the logistical and financial implications of offering such a service will be presented. The raison d'être for assessing response to chemotherapy is to allow changes in treatment regime if the sarcoma is failing to respond. However, alteration of the chemotherapy would bring into question the validity of the multinational studies that most of these patients are entered into.

The past and future of the SSG Register

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In 1986, SSG initiated a register of sarcoma patients referred to tumor centers in Finland, Norway, and Sweden. The aim was to create a large database of patients treated during a limited time period according to uniformally accepted guidelines, to assess how SSG treatment guidelines were implemented, and to permit multicenter studies of rare tumor entities.

Patients: Data was reported from all sarcoma centers in Norway and Sweden. Patients have been reported from the Helsinki University Hospital 1986–93 and from Turku and Tampere University Hospitals regularly since 1994. 1031 patients with bone (BS) and 2121 with soft tissue sarcoma (STS) of the extremities or trunk wall diagnosed 1986 to 1997 were registered.

84% of BS patients but only 58% of STS patients were referred to a SSG center before open biopsy or surgical treatment. Only 1/3 of patients with subcutaneous STS were re-

ferred as compared to 2/3 of those with deep lesions.

Discussion: The principal of referring BS patients to SSG centers before surgery or biopsy is closely adhered to in Scandinavia. The referral practice in STS is less well established, especially in parts of Norway and in Finland. The referral practice in the Scandinavian countries compares favorably to that of the USA.

Accrual of new patients, validation of reported data, and continuous follow-up will be ensured as the SSG Register is used for clinical studies of musculoskeletal neoplasia. Projects based on the SSG Register, such as on local recurrence of STS and on synovial sarcoma, will provide a quality assured basis for creating treatment protocols for safe diagnostics, surgical treatment and adjuvant chemo- and radiotherapy.

The SYT-SSX1 variant of synovial sarcoma is associated with high tumor proliferation rate and poor clinical outcome—a Scandinavian Sarcoma Group study

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Introduction: Cytogenetically synovial sarcoma is characterized by the translocation t(X:18)(p11.2;q11.2); a fusion between the SYT gene on chromosome 18 and SSX1 or SSX2 on the X chromosome, resulting in a new chimeric gene; SYT-SSX1 or SYT-SSX2.

Patients and methods: The study was based on a series of 33 patients with primary synovial sarcoma without metastases at diagnosis. The type of fusion transcript was determined by RT-PCR and sequence analysis in all 33 cases, based on specimens from the primary lesion. Proliferation rate was analyzed using anti-Ki-67 antibodies. The median follow-up period was 4 years.

Results: There were 13 patients with SYT-SSX1 and 19 with SYT-SSX2 fusion transcript. One case was excluded from further analysis, because of an insertion of 57 base pairs. The hazard ratio (HR) with respect to metastases free survival for patients with SYT-SSX1 versus SYT-SSX2 was 7.4 (95% CI 1.5–36, log-rank p=0.004). There was a significant association between high tumor proliferation and SYT-SSX1 (p=0.02).

Conclusions: Our findings suggest that the SYT-SSX fusion transcript, determines the proliferation rate and is an important predictor of clinical outcome in patients with synovial sarcoma.

Local recurrence in soft tissue sarcoma

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To elucidate the consequences of a local recurrence and evaluate current Scandinavian treatment regimens, the SSG central register has initiated three studies.

559 patients diagnosed 1986–1991 with extremity or trunk wall localized tumors, no metastasis at diagnosis and a median follow-up for survivors of 7 years. All were operated for primary tumor at a SSG center and none had adjuvant treatment. The overall estimated 5-year metastasis-free survival rate was 0.72. Multivariate analysis showed that malignancy grades III–IV and large tumor size were the most important risk factors. Local recurrence was associated with an increased risk of metastases but we could not prove any causal association between the two.

458 adult patients with primary, high malignant, deep-seated tumors, reported 1986–1993 were chosen. Among 180 patients with intralesional/marginal margins, 65% received postoperative radiotherapy compared to 10% among 189 patients with myectomy/wide margins. Median follow-up was 6.5 (0.5–11) years. 215 patients are alive. There were 34% local recurrences among patients with intralesional/marginal margin and no radiotherapy compared to 24% among patients with a wide margin and no radiotherapy ($p = 0.01$). Adding radiotherapy to the treatment regimen of patients with inadequate margins reduced the local recurrence rate to 25%. 60 resections could be classified as myectomies. The local recurrence rate was 27% among these patients and no advantage could be demonstrated for myectomies compared to other wide margins.

Among 1224 patients, surgically treated 1987–1995, 205 had 284 local recurrences.169 patients were surgically treated for their first local recurrence. An intralesional or marginal margin was achieved in 110 of these patients, 59 of whom were also given radiotherapy. The second local recurrence rate was 0.50 if the first local recurrence was treated with only surgery with a marginal margin, compared to 0.28 if treated with surgery with a marginal margin with adjuvant radiotherapy or with a wide margin ($p = 0.0008$). In extremity STS, the total amputation rate for local recurrences was 0.22 (31 of 142), higher than for primary tumors 0.09 (96 of 1065) ($p < 0.0001$). The average cost of treating a patient with a local recurrence was ~ USD 20.000.

The SSG morphology group—reflections on the past 20 years

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The spirit in which SSG was created 20 years ago has made it an important means by which morphologists have been able to communicate their views and experience on diagnos-

tic and scientific issues regarding musculoskeletal tumors to colleagues in surgery, oncology, radiology, cytogenetics, molecular tumor biology, and epidemiology. Likewise it has been a forum for pathologists to learn from these colleagues with different types of expertise.

Since the SSG began 20 years ago, a growing group of Scandinavian pathologists with a particular interest in soft tissue and bone tumors have met on a regular basis to discuss scientific and diagnostic issues and to review cases reported to the SSG Registry which have caused diagnostic problems. The morphologic review of cases has been the basis for analyses with the aim to define morphologic and clinical prognostic factors for specific sarcomas and to provide meaningful clinical and morphologic information with regard to grading. The morphology group within the SSG has also formulated practical guidelines for the handling of surgical specimens and for the morphologic diagnosis of soft tissue and bone tumors, has participated in the design of numerous treatment protocols and treatment evaluation programs, and has organized specialty and multidisciplinary scientific and practical diagnostic seminars. In 1995, a more formalized peer-review committee with 10–11 pathologists representing Sweden, Norway, Finland, and Denmark was created. Since then, the committee has met regularly in Gothenburg, Sweden, four to five times per year. To date, the committee has reviewed more than 1200 sarcomas in detail from the SSG Registry, representing approximately one fourth of all cases.

From the 20 years experience it can be concluded that:

Morphologic re-evaluation of the diagnosis and assignment of malignancy grade in all sarcomas within the SSG Registry is essential for studies which attempt to correlate the clinical and morphologic factors with prognosis.

The rarity and extremely wide morphologic spectrum of soft tissue sarcomas as well as its simulators make the morphologic diagnosis of soft tissue tumors particularly demanding. A multidisciplinary, center-based approach to their diagnosis involving integration of clinical, radiographic, molecular biologic and genetic information with the histologic findings is therefore essential not only for diagnostic accuracy in the individual case but also to obtain and maintain diagnostic expertise in the area.

The application of guidelines for the handling of surgical specimens and the use of standardized forms or protocols for reporting the diagnosis improve the quality and utility of the pathologic diagnosis.

The creation of a SSG peer review committee has helped to standardize sarcoma diagnoses in Scandinavia, provided the opportunity to review a large series of rare tumors in a short period of time, provided young pathologists on the committee with a unique opportunity to gain diagnostic expertise in soft tissue sarcomas, and has facilitated the development of a system whereby contributing pathologists receive feedback and instructive or educational information regarding their cases.

Micrometastases in patients with osteosarcoma

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Currently it is not possible to identify, with certainty, individual patients belonging to the different prognostic subgroups of high-grade osteosarcoma (OS). Hence, new tools for initial staging, monitoring effect of chemotherapy, and follow up are warranted. Recently we have developed a method to detect microscopic disease, viz. tumor cells present in clinical samples from peripheral blood and bone marrow aspirates. The principle is based on the use of superparamagnetic monodisperse particles with a diameter of 4.5um, coated with polyclonal anti-mouse IgG (Dynabeads M-450). Such immunobeads are pre-incubated with different tumor-associated murine monoclonal antibodies (Mabs). TP-1, TP-3 and 9.2.27 are Mabs previously shown to react with OS cells but not with cells in normal peripheral blood and bone marrow. Mononuclear cell suspensions are obtained from samples of heparinized peripheral blood and bone marrow aspirates by Lymphoprep®-gradient centrifugation. Following incubation with the immunobead variants, cells reactive with the Mabs can be isolated with a strong magnet, and the number of positive rosettes are counted in a microscope. The lecture will highlight findings in a pilot study, involving 31 OS-patients in various clinical stages and phases during the course of their disease. A few patients had repeated sampling; at surgery and after having completed the adjuvant chemotherapy. At primary diagnosis approximately 60% of the patients had positive findings in their bone marrow, whereas only 15% of the samples from peripheral blood showed any reactivity. All 5 patients presenting with overt metastases at the time of primary diagnosis had numerous rosettes in their bone marrow, 3 of which also had rosettes in peripheral blood. The patients with relapsed metastatic OS usually had positive bone marrow samples, and findings in peripheral blood only among those with extensive metastases. Also patients with primary tumors only had initially in the range of 60% reactivity in bone marrow, but usually a much lower number of rosettes. Only one of fifteen had findings in peripheral blood. Interestingly, neither of two young patients with Ewing sarcoma, nor a patient with aneurysmal bone cyst (initially suspected to have OS) showed any rosettes in their bone-marrow/peripheral blood samples. Positive rosettes were never observed in samples from ten healthy donors and twelve patients with non-sarcoma malignancies (breast and prostatic carcinoma as well as non-Hodgkin's lymphoma, non of whom undergoing chemotherapy). These results indicate that false positives do not seem to be a problem under these circumstances. Options to verify and characterize the malignant phenotype of the isolated rosettes will be discussed. In one of the OS-patients, relapsing with numerous bone and lymph node metastases, a very high number of rosettes were disclosed. These were inoculated into the abdominal wall of Balb\c nude mice. The xenograft that subsequently developed had retained its OS-

morphology, and retro-peritoneal lymph node metastases were also observed. This tumor line has successfully been transferred into new animals. Furthermore, purged rosettes from two other relapsing patients have successfully been expanded as a monolayer cell cultures *in vitro*. We believe that this technology may become useful as a diagnostic and prognostic tool in the clinical management of OS.

Chemotherapy in Ewing's sarcoma

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The Scandinavian Sarcoma Group has during 15 years treated 140 patients with Ewing's sarcoma. Two different protocols have been used.

Patients: SSG IV included 52 patients between 1984 and 1990 and SSG IX 88 patients since 1990.

Results: After 5 years local recurrences were seen in 19% of patients (M0+M1) in SSG IV group and 10% in SSG IX group. Distant metastases developed 57% of M0-patients in SSG IV group and 33% in SSG IX group. Tumor-related survival (overall) of M0-patients was 49% in SSG IV and 70% in SSG IX, and metastasis-free survival 45% and 58%, respectively. Histologic good responders to chemotherapy had a better survival rate than histlogic poor responders (SSG IV $p < 0.02$ GI–II vs GII–IV and SSG IX $p < 0.003$ GI–III vs GIV).

Conclusion: We conclude that SSG IX gave a better local control and survival rates than SSG IV.

Presentation of an Italian–Scandinavian treatment protocol for non metastatic (ISG/SSG III) and high-risk Ewing's family tumors (ISG/SSG IV)

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For the Italian/Scandinavian Sarcoma Group

The outline of the following two protocols will be presented:

The **ISG/SSG III** trial is an Italian/Scandinavian joint, multicenter, and prospective study for the evaluation of combination chemotherapy, surgery, and/or radiotherapy in patients with non metastatic, standard risk, localized Ewing's family tumors. The study is not randomized and it is open to any specialized cancer center that is part of ISG/SSG network, and which fulfills all the protocol criteria and complies with the other requirements for inclusion in the study. The aims and general protocol design are the following:

1. Evaluation of event free survival in patients with localized ES or PNET treated with a multimodal protocol characterized by:
   - High intensity dose of chemotherapy and accelerated radiotherapy.
   - An induction phase using all six drugs active in the Ewing's family tumors: Ifosfamide (Ifo), Etoposide (Eto), Vincristine (V), Actinomycin-D (Act), Adriamycin (Adm), Cyclophosphamide (C).
   - A different treatment in the maintenance phase, based on tumor response to induction chemotherapy. Patients with a poor response will receive high doses of Busulphan (Bu) and Melphalan (M) with reinfusion of peripheral blood stem cells (PBDSC).
2. Evaluation of the percentage of patients with a good histologic response after induction chemotherapy with 6 drugs (V, Adm, Act, C, Ifo, Eto) followed by surgery.
3. Evaluation of the percentage of patients with good radiologic response after induction chemotherapy with 6 drugs (V, Adm, Act, C, Ifo, Eto).
4. Correlation in between the histologic responses to prognosis.
5. Correlation between the radiologic response and prognosis.
6. Evaluation of the prognostic significance of: age at diagnosis, diagnosis (ES, PNET), tumor location, tumor volume, and dose intensity of the chemotherapy received.
7. Study the biological characteristics of ES: immunohistochemical, cytogentic, with their clinical correlations.

The **ISG/SSG IV** trial is an Italian/Scandinavian joint, multicenter, and prospective study for the evaluation of combination chemotherapy, surgery, accelerated radiotherapy and/or high-dose chemotherapy in patients with high–risk (solitary lung metastasis >0.5 cm multiple lung and/or pleural metastasis(-es) and only one bone metastasis) Ewing's family tumors. The aims and general protocol design are as the following:

1. Evaluation of event free survival in patients with high-risk ES or PNET treated with a multimodal protocol characterized by:
   - High intensity dose of chemotherapy and accelerated radiotherapy.
   - An induction phase using all five drugs active in the Ewing's family tumors: Ifosfamide (Ifo), Etoposide (Eto), Vincristine (V), Adriamycin (Adm), Cyclophosphamide (C).
   - Patients will receive high doses of Busulphan (Bu) and Melphalan (M) with reinfusion of peripheral blood stem cells (PBDSC) followed by total lung irradiation (TLI).
2. Evaluation of the percentage of patients with a good histologic response after induction chemotherapy with 5 drugs (V, Adm, C, Ifo, Eto) followed by surgery.
3. Evaluation of the percentage of patients with good radiologic response after induction chemotherapy with 5 drugs (V, Adm, C, Ifo, Eto).
4. Correlation in between the histologic responses to prog-

nosis.
5. Correlation between the radiologic response and prognosis.
6. Evaluation of the prognostic significance of: age at diagnosis, diagnosis (ES, PNET), tumor location, tumor volume, and dose intensity of the chemotherapy received.
7. Study the biological characteristics of ES: immunohistochemical, cytogentic, with their clinical correlations.

Overview of the SSG chemotherapy trials

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The first chemotherapy study by the Scandinavian Sarcoma Group in soft tissue sarcoma (STS) was started in 1986 (SSG I) and evaluated adjuvant single agent doxorubicin in a randomized setting in patients with high-grade STS. No improvement was noticed in overall survival or disease free survival.

In advanced disease a more dose intensified chemotherapy was hereafter (1991–1994) studied in a phase 2 study introducing ifosfamide and continous infusion etoposide with growth factor support (SSG X). The response rate in previously untreated patients was high (42%), but complete remissions were scarce. Analysis made on patients undergoing surgery after preoperative chemotherapy indicated increased survival. A recent metaanalysis of adjuvant chemotherapy for localized resectable STS in adults, including the SSG I trial, indicated better disease-free survival and possibly improved overall survival. Presently, it is tested whether such a benefit can be proven for patients with high risk prognostic criteria by giving adjuvant ifosfamide and doxorubicin treatment after primary surgery (SSG XIII). In this latter SSG study, activated July 1 1998, the adjuvant therapy is studied in a phase 2 study in selected patients with high-grade STS and other unfavourable prognostic factors including size, necrosis and vascular invasion.

Our knowledge of sarcoma biology has increased significantly during recent years and this ahas already had an impact on diagnostic precision and prognostic predictability. It is to be expected that findings in this area will bring forth additional therapeutic procedures to be used in the treatment of advanced sarcomas. For the future there is also need for larger trials with fast accrual operating with successful international collaboration.

The future of soft tissue tumor pathology—more or less entities?

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At the present time, accurate histologic subclassification is one of the most useful prognostic indicators in soft tissue sarcomas and many tumor types are associated with reproducible clinical behavior. None of the currently available pathologic grading systems reliably predicts outcome in more than perhaps 50% of cases. The continued recognition and definition of previously uncharacterized soft tissue tumors (benign and malignant), while potentially confusing or overwhelming for non-specialists, has allowed more accurate determination of tumor behavior and outcome and has helped to avoid over- or under-treatment of many lesions. Nevertheless it is clear that considerable refinement is still needed in terms of prognostication and prediction of treatment response. It is possible that molecular subclassification (making use of chip technology and gene arrays) may provide such information and could conceivably (over time) supersede histomorphologic subclassification. However, the remarkable and characteristic heterogeneity of soft tissue tumors makes this much less likely than in the common types of carcinoma. Until convincing, reproducible and widely applicable alternatives emerge, histologic assessment continues to be the most important parameter by which any patient with a soft tissue tumor is considered and, for the foreseeable future, I believe that more "entities" are likely. For patients to benefit from such classifactory sophistication, diagnosis and management in specialist centers will continue to be an important goal.

Posters

Improved quality of the central SSG registry by local audit

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Background. The central registry of the Scandinavian Sarcoma Group now includes more than 4600 cases with soft tissue or bone sarcoma reported since 1986 from the Scandinavian countries. The quality of a registry depends on the accuracy of the reported data. The Swedish part of the registry now has a status of approved national quality registry.

Aim. By local management of the SSG registry our aim was to improve the quality of the registry and to make the registry one of the tools in tumor treatment.

Method. A group with representatives from the Oncological Center of Northern Sweden and from the departments of

oncology and orthopedic surgery has met regularly. Routines have been created to improve reported data to the SSG registry: 1. Sarcoma cases reported during 1998 to the Northern Swedish Tumor Registry have been compared to the SSG registry. 2. Data are not reported to the central registry until the group corrects them. 3. Data on patients treated outside the tumor center have been requested.

Results: An increased number of cases have been reported to the central SSG registry since start of the local management. At the regular meetings more rapid and simplified corrections of data forms have been carried out. By the end of 1998 34 patients were reported to the Northern Swedish Tumor Registry. 8 of these were treated outside the tumor center. By initiative of the group 3 of these patients have so far been treated with additional surgery.

Conclusion: Local audit of the central SSG registry has improved the quality of the registry. It is now possible to use the central registry as a tool in the tumor treatment in the northern region in Sweden. Which location of sarcoma types that should be included in the SSG registry could be discussed.

Malignant fibrous histiocytoma in the Scandinavian Sarcoma Group Central Register

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Malignant fibrous histiocytoma (MFH) constitutes around 40% of soft tissue sarcomas of the extremities and trunk wall with an annual incidence of 7 cases per million in the Southern Swedish Health Care Region. During the period 1986–1993 the Scandinavian Sarcoma Group (SSG) central register received data on 618 patients diagnosed with MFH of the extremities and trunk wall.

Patients and methods: The SSG pathology review group have reviewed 551/618 patients and 387 were classified as MFH of the extremities and trunk wall. We reviewed the number of patients with MFH of the extremities and trunk wall registered in the SSG central register compared with the estimated number of new cases in Scandinavia 1986–1993. We analyzed the outcome of surgery in 374/387 patients and compared it between patients treated outside cancer centres and those who had their primary treatment at cancer centres.

Table 1. MFH of the extremities and trunk wall

	Sweden	Norway	Finland	Denmark	Iceland
Estimated no. in Scandinavia 1986–1993	462	226	262	269	14
Registered no. in the SSG register	393	165	58	2	0
No. of MFH in the SSG register after pathology review	251	107	29	0	0

Conclusion: There seems to be considerable underreporting of malignant fibrous histiocytoma of the extremities and trunk wall to the SSG central register. This is probably a result of patients not being referred to cancer centres. The rate of local recurrence is higher in tumors treated with surgery outside cancer centres.

SYT-SSX4, a new fusion gene variant in synovial sarcoma

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The synovial sarcoma specific translocation t(X;18)(p11.2;q11.2) is believed to play a causative role in tumor development. Cloning of the translocation-breakpoint revealed a fusion between the SYT gene located on chromo-

Table 2. 374 cases of malignant fibrous histiocytoma of the extremities and trunk wall treated with surgery

Primary surgery	Localization	Tumor size cm (range)	Surgical margins			Fraction of local recurrence
			marginal	wide	intralesional	
Outside cancer centre (n=121)						
subcutaneous and < 5 cm (n=60)		3 (1–5)	31	28	1	0.4
subcutaneous and > 5 cm (n=21)		8 (6–15)	12	9	0	0.4
deep any size (n=40)		8 (3–18)	22	16	2	0.6
Cancer centre (n=253)						
subcutaneous and < 5 cm (n=32)		3 (1–5)	3	8	21	0.2
subcutaneous and > 5 cm (n=37)		10 (6–28)	2	12	23	0.2
deep any size (n=184)		10 (2–30)	21	59	104	0.3

some 18 and the SSX gene located on the X chromosome. The SYT gene is evidently fused to one off two closely related genes, SSX1 or SSX2. Five variants of the SSX gene, *SSX 1–5* have been identified. The germline SYT gene is ubiquitously expressed in adult human tissues in contrast to the SSX genes, which so far have only been detected in the testis and the thyroid. The SSX-genes show strong homology especially in the 3'- and 5'- ends. Until now, only two variants of fusion genes, *SYT-SSX1* and *SYT-SSX2*, have been shown to be involved in the translocation in synovial sarcoma. We now report on a new SYT-SSX variant in synovial sarcoma, previously probably under-diagnosed, involving the exon 5 of the SSX4 gene. Several differences with regard to potential sites for post-translational modification in the exon 5 domain between SYT-SSX4 and the two other variants may have biological and prognostic implications.

Growth inhibition of human clear cell sarcoma xenografts treated with dacarbazine and docetaxel

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Clear cell sarcoma (CCS) constitutes 0.8 % of the soft tissue sarcomas in the Scandinavian Sarcoma Group registry. It is associated with tendons and aponeuroses and has melanocytic features. There are a few reports on establishment of CCS-cell lines but treatment studies on CCS-xenografts have not been published previously.

We evaluated the antitumor effect of dacarbazine (DTIC) and docetaxel (Taxotere) in CCS-xenograft model in nude mice which was established using subcutaneous transplantation of intact tumor tissue.

Methods: Tumors from the 8th passage (each group n=8) of a clear cell sarcoma tumor model (UMCCS-I) were used in the experiment and followed until day 24. Tumor growth (expressed as relative volume increase) was registered after a single i.p. injection of DTIC (200, 300 and 400 mg/kg), Taxotere (11 and 20 mg/kg) and saline solution (control group). Antitumor efficacy (growth inhibition 100%-T/C%) was calculated from the lowest T/C value (median relative volume of treated tumors over controls).

Results: No morbidity or weight loss was noted. Significant relative volume difference was noted in all the DTIC-treated groups but most pronounced in the dose of 400 mg/kg. Significant relative volume reduction was also seen in the Taxotere-treated group (20 mg/kg) compared to controls. Growth inhibition were 37–91% in the DTIC groups and 13–65 % in the Taxotere groups.

Conclusion: A single dose of DTIC and Taxotere has an antitumor effect for a limited time span in this clear cell sarcoma tumor model. Further studies using other treatment modalities are indicated in this rare tumor.

110 subfascial lipomatous tumors—MRI and CT findings versus histopathological diagnosis and cytogenetic analysis

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Purpose and methods: We have retrospectively analysed CT and/or MR images of 110 subfascial lipomatous lesions to evaluate if liposarcoma, atypical lipomatous tumors (ALT) and lipoma can be differentiated radiologically. The amount of fat in the tumors was visually graded as: none, 1–75%, 75–95% or 95–100%, and the structure of non-fatty tumor components was noted. The imagery was compared to histopathology and in 37 cases to cytogenetic findings.

Results: Only 4 of 20 liposarcomas contained fat. All 4 lesions histopathologically diagnosed as ALT contained fat assessed as less than 75% of tumor volume. The non-fatty tumor components were composed of thick irregular septa. All lesions with more fat than 75% of tumor volume were histologically diagnosed as lipoma. However, 1/3 of the karyotyped lipomas had ring chromosomes typical for ALT.

Conclusion: When a tumor is composed more or less solely of fat the diagnosis of a lipoma is most likely, nevertheless ring chromosomes can be found. In less fatty tumors the different lipomatous lesions appear to exhibit distinctive radiological features, but the overlap and heterogeneity does nor allow diagnosis based solely on imaging. When no fat is found imagery does not help differentiating lipoma or liposarcoma from other soft tissue tumors.

Solitary fibrous tumor of the soft tissue

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Solitary fibrous tumor (SFT) of the soft tissue is commonly a benign spindle cell lesion, but can rarely appear as a malignant tumor. Histologically, the tumor is often confused with other benign and malignant spindle cell tumors.

Patients and methods: 8 patients (2 women), median age 59 (18–84) years had 6 deep seated and 2 subcutaneous tumors in the trunk (2), lower arm (2), and 1 each in the thigh , back, neck and abdominal wall. All tumors were examined by FNA before surgery.

Cytology: All but 1 aspirate were representative with moderate to high cellularity, microbiopsies and dispersed spindle cells and collagen fragments. The cells had spindly nuclei, inconspicuous nucleoli and scanty uni- or bipolar cytoplasm. Numerous small cells with round or oval nuclei were present in 2 cases. Pleomorphism and atypical mitoses were absent. 4 cases examined by immunocytochemistry

were positive for antibodies for CD 31, factor VIII and CD34. Spindle cell sarcoma was suspected in 4 cases, leiomyoma, hemangiopericytoma and pseudotumor in 1 case each.

Pathology: The tumors were well circumscribed with grey-white cut surface. The median size was10 (4–23) cm. The most prominent histological features were: well circumscribed growth, admixture of high and low cellularity, monotonous spindle cell population, low mitotic rate, extensive fibrosis and rich vascularization. Storiform and/or hemangiopericytoma—like pattern and myxoid changes were common. Immunochemistry with positive CD34,CD 99, BCL-2 and vimentin and negative cytokeratins and EMA were important for the differential diagnosis. Ultrastructural analysis showed fibroblastic cells and vessels in a collagenous matrix in 7 cases. The tumors were diploid and without characteristic chromosomal pattern. The original diagnoses were SFT in 3 cases, hemangiopericytoma in 3 and monophasic synovial sarcoma in 2 cases.

Outcome: After 0,5–9 years no local recurrence or metastatic disease was observed.

Conclusion: Benign SFTs are rare spindle cell tumors, which can mimic other benign and malignant spindle cell lesions. FNA diagnosis without adjunctive techniques is difficult. Histologically, the well circumscribed growth, monotonous spindle cell tumor morphology and immunophenotype make the SFT diagnosis possible.

Fine needle aspiration of musculoskeletal tumors—diagnostic value of cell block preparation

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Cell block (CB) analysis is an established ancillary method in conjunction with traditional preparation of cytological specimens. We investigated the diagnostic value of CB in the evaluation of fine needle aspirates of soft tissue and bone tumors.

Study design: A retrospective review of CBs prepared in conjunction with fine needle aspiration (FNA) of 36 patients with soft tissue and bone tumors. 43 patients referred to the Musculoskeletal Tumor Center in Lund, Sweden from May 1997 to January 1999 were examined by FNA combined with CB. 7 CBs were insufficient for evaluation.

15 primary malignant (10 soft tissue and 5 bone) tumors and 8 metastases were examined. In addition 9 patients with benign soft tissue tumors and 4 with pseudosarcomatous proliferation or other inflammatory/reactive conditions were evaluated.

Results: In 22 patients CB confirmed the cytologic diagnosis, in 7 patients CB gave additional diagnostic information and in 7 patients CB preparation allowed accurate histologic diagnosis.

Conclusion: The advantages with a CB preparation are twofold: a better visualization of the tumor tissue pattern than is possible in FNA smear and a possibility of performing immunocytochemical and other special stains on several slides of comparable quality.

The evaluation of the cytologic smear and CB together combines cytomorphology with tissue architecture and immunocytochemistry. This increases the number of cases where an accurate cytologic diagnosis can be made.

Fine needle versus coarse needle aspiration in the diagnosis of soft tissue sarcoma

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In the primary diagnosis of soft tissue sarcoma before definitive treatment fine needle aspiration (FNA) and coarse needle biopsy (CNB) are relatively simple diagnostic methods with the following common advantages compared to open surgical biopsy: ambulatory, procedure, general anesthesia not necessary, local anesthesia rarely, minimal tissue trauma. Technical skill is necessary for optimal sampling.

In the diagnostic work-up both methods have advantages and disadvantages compared to each other.

Compared parameters	FNA	CNB
Multiple sampling (diagnose tumor heterogeneity)	+++	+
Rapid preliminary diagnosis	+++[a]	+[b]
Excellent cellular morphology	+++	+ – ++
Evaluation of tumor tissue pattern	+ – ++[c]	+++
Sample usable for ancillary diagnostics (immunostaining, electronmicroscopy, DNA-ploidy, cytogenetic/molecular genetic analyses)	+ – +++[d]	+++

[a] 10 minutes
[b] Frozen section; might impair optimal staining of ordinary sections
[c] A cellblock preparation of the aspirate, cut and stained as a "microbiopsy" may give information on tumor tissue pattern
[d] Depends on the yield. A cellblock is suitable for immunohistochemistry

In most cases FNA is sufficient when primary surgery is the treatment option (diagnostic level necessary: sarcoma or other type of malignancy, low or high grade sarcoma).

When neoadjuvant therapy followed by surgery is considered as the optimal treatment, the pretreatment evaluation must include a specific histotype diagnosis as well as a reliable malignancy grade. In this situation CNB offers better diagnostic possibilities unless the FNA yield is sufficient for various ancillary methods.

Summary: FNA and CNB complement each other and could with advantage be performed in the same seance when a specific histotype diagnosis and malignancy grade is necessary before treatment.

No independent prognostic value of urokinase plasminogen activator (uPA) and its inhibitor type 1 (PAI-1) in 85 patients with soft tissue sarcoma of the locomotor system

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Urokinase activator (uPA) and plasminogen activator inhibitor type 1 (PAI-1) are involved in the process of local and systemic invasion of malignant tumors. We analyzed the prognostic importance of the tumor tissue levels of these enzymes in 85 patients with soft tissue sarcoma (STS) of the locomotor system.

Material and methods: We evaluated 85 adult surgically treated patients with a median age of 71 (27–92) years, and with a median follow-up of 7 (3–10) years for the 36 survivors. 27 of the 85 tumors were subcutaneous. The median tumor size was 8 (2–30) cm. Malignant fibrous histiocytoma was the commonest histotype (n = 48), followed by leiomyosarcoma. 32 patients developed metastasis. The median value of uPA was 1.25 (0.03–14) ng/mg protein, and of PAI-1 1.72 (0.07–317) ng/mg protein. The prognostic value for metastasis was analyzed using uni- and multivariate analysis.

Results: In the univariate analysis increasing histopathological malignancy grade, DNA non-diploidy, high levels of uPA and PAI-1, and high-risk tumor according to the SIN-classification were associated with impaired metastasis-free survival. In the multivariate analysis, based on information from 56 patients, only histopathological malignancy grade IV (RR=3.9) and high-risk tumor according to the SIN-classification (RR=3.7) had independent prognostic value.

Conclusion: We found no independent prognostic value of neither uPA nor PAI-1 in STS of the locomotor system. Instead, histopathological malignancy grading and high-risk tumor according to the SIN-classification were independent prognostic factors.

Delayed recurrence after liver transplantation for hepatic malignant epithelioid hemangioendothelioma

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Only a few cases of hepatic epithelioid hemangioendothelioma (EHE) have been described in the literature. It occurs mainly in young patients. Herein we report the clinical course in a 22-year-old woman who was treated with liver transplantation for EHE. Initial symptoms were skin itch and abdominal pain. She had slight hepatomegaly and jaundice. CT showed multiple nodules in both liver lobes. Biopsy revealed a tumor of vascular origin which was confirmed by positive immunohistological staining for vimentin and factor VIII-related antigen. Total hepatectomy with orthotopic liver transplantation was performed. After transplantation the immunosuppression consisted of azathioprine, prednisone and cyclosporin. No extrahepatic disease was detected prior to transplantation.

At 47 months following transplantation she developed clinical signs of deep venous thrombosis in her left leg. A 3 cm tumor was found closely related to an obstructed left external iliacal vein. The tumor surrounding the vein was removed, and the histology was similar to the original tumor. At the same time two small lesions were detected in the right liver lobe and one in the left lobe. 7 months later the lesions had grown, and recurrence was documented by biopsy. The disease has since been stable for 6 months.

The etiology of EHE is unknown. A possible relation with oral contraceptive drug use has been suggested. Our patient had taken oral contraceptive steroids for an indeterminate period. Previous experience indicates that liver transplantation may offer long-term survival in these patients even in the presence of metastatic disease.

Retroperitoneal soft tissue sarcoma—the Norwegian Radium Hospital experience

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From 1980 through 1997, 150 patients (72 men) were referred to NRH with retro-peritoneal soft tissue sarcoma. The M/F ratio was 72/78 = 0.9, median age at diagnosis was 62 (17–91) years and median tumor diameter 15 (2.5–50) cm. The most common histological types were leiomyosarcoma/stromal sarcoma (35%) and liposarcoma (24%), and 61% were of high grade malignancy. Of 107 patients with initially localized disease 32% were referred with virgin tumors or after needle biopsy, 24% after marginal surgery, 34% after intralesional surgery or incisional biopsy and 10% after local or distant relapse. 89% of patients with localized disease were treated by surgery, 48% received supplemental radiotherapy and 6% received chemotherapy. Only 54% of patients with localized disease achieved non-contaminated margins at primary surgery, with higher probability for patients referred without prior surgery (74%) than for patients with initial surgery outside NRH (51%, p = 0.05).

Of 68 patients who developed distant metastases, 30 (44%) had lung lesions and 26 (38%) had liver lesions. Median follow-up for patients alive was 52 months, and projected overall tumor-specific survival (OS) for all patients was 37% at 5 years and 26% at 10 years. Patients with metastatic or multifocal disease at diagnosis had significantly poorer 5-year OS than patients with localized disease (0% vs. 55%), and in a multivariate analysis for patients with localized disease marginal or better surgical margin, low malignancy grade, female sex and age <60 were independent predictors

of a favourable outcome. In high grade tumors postoperative radiotherapy appeared to improve OS after surgical resection with non-contaminated margins (p=0.07).

Improved local control in soft-tissue sarcomas

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We compared the local recurrence rate of soft-tissue sarcomas treated at our Oncology Service over 3 consecutive time periods. Over the 3 periods, major efforts were made to comply with the guidelines of SSG, in particular with regard to the use of wide excisions and adjuvant radiotherapy.

Patients and results: From 1986–1998, 435 patients with primary Stage IA–IIB soft-tissue sarcomas were managed at our Oncology Service. 1/3 were subcutaneous and 2/3 deep-seated. 60% of the deep-seated tumors were greater than 7 cm, 50% were extracompartmental, and 80% were high grade. The 3-year local recurrence rate was estimated according to Kaplan-Meier.

	1986–90	1991–94	1995–98
Subcutaneous	*27*	*61*	*61*
wide margin (%)	59	77	87
radiotherapy (%)	19	20	8
local recurrence rate	0.14	0.13	0.00
Deep	*91*	*98*	*96*
amputation (%)	6	14	11
wide or better margin (%)	52	55	60
radiotherapy (%)	31	32	52
local recurrence rate	0.28	0.16	0.16

The results show that among subcutaneous tumors, local control improved through more wide excisions that also reduced the need of adjuvant radiotherapy. Among deep-seated tumors, surgical margin could only be improved slightly mainly because 1/2 were extracompartmental. Nonetheless, improved local control was achieved presumably by increased use of radiotherapy.

Conclusions: This retrospective study reveals improved local control of soft-tissue sarcomas at our Oncology Service during the 1990's compared to the 1980's. We believe that this is the result of the concerted efforts by the members of the orthopedic oncology network. MRI provides better preoperative planning. Safer cytological diagnosis has reduced the need of open biopsies. Improved histopathological assessment of surgical margins has been of decisive importance in identifying patients for adjuvant radiotherapy. We are considering an increased use of radiotherapy as an adjunct to surgery for deep-seated soft-tissue sarcomas.

Cytological diagnosis of skeletal lesions—analysis based on fine needle aspiration biopsy in 110 tumor patients

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We have previously shown that cytologic diagnosis based on fine needle aspiration biopsy (FNAB) is a safe and efficient method for the discrimination between benign, primary malignant and metastatic bone lesions. In this study, we address metastatic lesions specifically to assess the diagnostic accuracy and to ascertain whether FNAB permits identification of the primary lesion.

Patients and methods: Between 1990 and 1997, 444 patients were referred to the Department of Orthopedics, Karolinska Hospital for diagnosis of skeletal lesions of unknown type. Patients who had undergone prior biopsies or had been operated were not included. 119 of these patients proved to have metastatic disease or myeloma/lymphoma. 9 were excluded leaving 110 consecutive patients with metastatic carcinoma (80), myeloma (16) or lymphoma (14).

Results: A correct diagnosis was achieved by FNAB in 102 of the 110 patients (93%). In 8 cases FNAB was inconclusive (5), misleading (1), or discrepant (2) with the histopathological diagnosis. FNAB correctly diagnosed 15 of 16 patients with myeloma, 12 of 14 with lymphoma, and 75 of 80 patients with metastatic carcinoma. Furthermore, the site and type of malignancy was correctly suggested in 2/3 of the patients with metastatic carcinoma. Overall only 7 open biopsies were performed.

Conclusion: FNAB is a safe and reliable method for the diagnosis of metastatic carcinoma, lymphoma and myeloma. Time consuming and costly investigations can be limited by choosing FNAB as the initial diagnostic method in the search for the primary tumour. Hence, the choice of radiological examinations, laboratory tests and biopsies can be efficiently guided by the result of FNAB of the skeletal lesion.

Incidence of surgical treatment for breast cancer metastases in the skeleton

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The purpose of this population-based study was to evaluate the frequency and outcome of surgically treated skeletal breast cancer metastases.

Methods: The files of the Central Cancer Registry were searched. The cases found were matched with the health service records for hospitalisation at orthopedic surgery departments and copies of the medical records were acquired.

None was lost to follow up.

Results: 661 patients with carcinoma of the breast presented with a skeletal metastasis during the years 1989–1994. 20% (131/661) of the patients were operated. The indications for surgery were an impending (n=29) or a complete (n=76) pathological fracture, epidural compression (n=15) or pain (n=11). The median age for the operated group was 61 years. The median survival time after operation was 6 months and the one-year survival rate was 0.3. 85 metastases were located in the long bones, 26 in the spine, 12 in the humerus and 8 in the pelvis. The surgical reconstruction consisted of 78 osteosyntheses, 29 prostheses and 19 spinal stabilisations. Half of the operated patients were treated at a tumor centre and the other half at 5 other orthopedic surgery departments in the region. The total reoperation rate was 0.11 (range 0-0.3). The smaller units had in general the highest reoperation rates. Hip screws (4/10) and glide screw plates (3/17) were most often associated with reoperation as was location in the distal femur. The pain was improved postoperatively in 77 and the function (Zubrod scale) was improved postoperatively in 65%.

Discussion and conclusion: In this region with 1.8 million inhabitants approximately 20 patients are operated every year for skeletal metastasis of breast cancer. A higher failure rate was observed in orthopedic departments with few operated cases.

Real time MRI-guided excision and cryotreatment of osteoid osteoma in os ischii—a case report

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During the last years percutaneous CT-guided excision of the nidus and thermocoagulation has turned out to be an effective treatment with minor complications. This has also been our experience with this treatment after 15 such procedure. The disadvantages are the rather high radiation exposure, the time consuming procedure of repeated moving the patient in and out of the gantry to check the position of the instruments, and due to this a possible increased risk for infection. We therefore wanted to use real time MRI to locate and destroy the nidus, a technique which to our knowledge has not been reported previously.

Case report: A 36-year-old electrician had not been able to work during the last eight months due to intense pain in his left buttock. Plain radiographs were normal, but scintigraphy showed intense activity, and MRI and CT also indicated an osteoid osteoma in the left tuber os ischii. The patient was given spinal anesthesia, and placed in a GE Signa SP open MRI. With the patient in decubitus position a surface coil was attached and the nidus was located. A biopsy needle was placed in the centre of the lesion using a flash point system for placement of the needle. A 4 mm cylinder was cored and fixed in formaldehyde for later PAD. Then a 4 mm cryo probe (Galil Medical, Haifa, Israel) was centrally placed in the lesion. Repeated cooling to –180 °C was performed. The biopsy confirmed the diagnosis osteoid osteoma. The patient recovered well and was pain-free the day after the operation.

Discussion: Most osteoid osteoma can be removed with minimal invasive techniques. CT-guided biopsy and thermocoagulation has proven to be effective with few complications. CT scanning can be used in any part of the skeleton, but is not available for real time imaging. It gives a rather limited working-space for the surgeon, and therefore the patient has to be moved in and out of the gantry. Further the working-plans are restricted, but the most important disadvantage is the high dose of radiation in patients who are usually young. Real time MRI may be a useful alternative for treatment of osteoid osteoma.

Chondroblastoma—an easy diagnosis?

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Materials and methods: 19 patients (14 men) were either treated at the Norwegian Radium Hospital or referred to us for consultation. All were examined histologically and with conventional roentgenograms. 16 had CT and 13 MRI. Scintigraphy using technetium labelled methylenediphosphonate was performed in 15 patients and in 12 of these a dynamic study was obtained.

Results: The median age was 17 (12–48) years. 17 tumors were in the extremities, 1 in a rib and 1 in the base of the skull. The lesions were all well demarcated and lytic. Varying degrees of calcifications were found in 12. Marrow and soft tissue edema and a moderate periosteal reaction were common. Scintigraphy showed early increased blood-flow in 5 patients, less vascularity in 5 and slightly increased bloodflow in 2. Static images showed high, usually homogenious, radioactivity-uptake with diffuse uptake in the area around the tumor.

Histopathological examination revealed a characteristic picture of chondroblastoma with chondroblastlike cells with intermingled multinucleated giant cells. An immature, mostly eosinophilic chondroid intercellular substance was seen in all cases. There was a very low mitotic activity with no atypical mitotic figures. Most cases showed small necrotic areas, and calcification of chicken wire type was seen in 12 cases. All cases had secondary ossification, and foci with aneurysmal bone cysts were seen in 14 cases.

Discussion: In most cases imaging demonstrated the classical picture of a chondroblastoma. Some were however more difficult. One, with considerable soft tissue swelling and sclerotic bony changes, was initially suspected of hav-

ing a malignant lesion. Chondrosarcoma, enchondroma, osteomyelitis and a Brodie's abscess were considered. A cystic process in the distal tibia looking like a simple bone cyst on radiographs showed increased blood-flow and high homogeneous radiotracer uptake not compatible with bone cyst. Giant cell tumor was a possibility in at least 2 cases.

Conclusion: We found that the diagnosis of a chondroblastoma is usually easy, but differential diagnoses must often be considered. Scintigraphy is not specific for a chondroblastoma but give valuable additional information. Histological examination is necessary for a definite diagnosis.

Specific translocation detection in Ewing tumors by ampli-taq-gold RT-PCR

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The presence of a t(11;22)(q24;q12) translocation is one of the characteristic features of the Ewing family of tumors. Transcription across this breakpoint produces a fusion m-RNA (EWS/FLI-1) that is expressed in almost all tumors that contain the t(11;22). A reverse transcription polymerase chain reaction (RT-PCR) can be used to detect the fusion transcript.

We used Ampli-Taq-Gold DNA Polymerase in our RT-PCR to increase amplification sensitivity and specificity of low number target DNA. All fusion transcripts found was subjected to automated sequencing using BigDye™ terminator cycle sequencing. We could thus verify that our method for RT-PCR analysis was reliable.

We investigated the EWS/FLI-1 fusion transcript of 13 Ewing tumor patients using RT-PCR and sequencing, and detected 4 types of fusion transcripts. Exon combinations 7/6 (5 cases), 7/5 (5 cases), 7/7 (1 case) and 10/5 (1 case) was found in the tumors. One Ewing tumor did not express this fusion gene. The EWS/FLI-1 fusion transcript was also searched for in 7 non-Ewing small cell sarcomas, and one of them was positive for a 7/6 fusion transcript. This patient had a paratesticular embryonal rhabdomyosarcoma. We also investigated the bone marrow from a Ewing tumor patient with bone marrow metastasis, and detected the same fusion transcript in the bone marrow as in the primary tumor.

The molecular genetic detection of the EWS/FLI-1 fusion transcript is valuable in the differential diagnosis of small round cell tumors and provides an important tool for the detection of metastatic cells in Ewing tumor patients.

Leptomeningial spinal recurrence of Ewing's sarcoma diagnosed by detection of m-RNA fusion transcript EWS/FLI1 in spinal fluid

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We report rare case of diffuse leptomeningial metastasis in the spinal canal in a 16-year-old girl. She was diagnosed 15 months previously with non-metastatic Ewing´s sarcoma of the body of the 4th cervical vertebra. The primary tumor cells expressed variant 7/5 of m-RNA fusion transcript EWS/FLI1 on RT-PCR analysis. At primary diagnosis the large soft tissue component invaded the deep cervical compartment, extended into several cervical root canals and showed extradural growth into the spinal canal. She responded promptly to chemotherapy, achieved subcomplete regression of the soft tissue component, and was given radiotherapy, both according to the Scandinavian Sarcoma Group protocol SSG IX. The paralysis of both upper limbs reversed almost completely. In September 1997 she developed back pain, leg pain and sensory loss in both lower extremities. On MRI diffuse leptomeningial tumor like growth in the lumbar and thoracic level was diagnosed, i.e., distal to the radiotherapy volume. It was possible to draw only a small amount of spinal fluid that contained very few cells, too few for diagnostic purposes. Other invasive procedures in order to acquire material for morphological diagnosis was considered not feasible. However, on RT-PCR analysis of the spinal fluid, the same variant of RNA fusion transcript EWS/FLI1 as in the primary tumor, was detected. Due to the rarity of the clinical findings one might suspect other clinical conditions mimicking leptomeningial tumor growth. We consider, however, the RT-PCR findings as proof of the assumption that the leptomeningial findings represented metastatic recurrence of the patient's Ewing tumor. This case highlights the high sensitivity and specificity of RT-PCR analysis in the diagnosis of small numbers of tumor cells in patients with Ewing tumors. The clinical course suggests a need of additional local treatment in the rare subgroup of patients with high risk Ewing tumors affecting the spinal canal, e.g., intraspinal chemotherapy or prophylactic radiotherapy to the spinal axis, and also a possible role of high dose chemotherapy with CD34+ stem cell support.

Does response to chemotherapy in Ewing's sarcoma evaluated by CT and/or MR imaging correlate with histological response and survival?

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In Ewing's sarcoma response to induction chemotherapy is one of the most reliable predictors of outcome. Patients with non-resectable tumors will receive radiotherapy as definitive treatment and evaluation of response must rely on imaging alone. The aim of this joint ISG/SSG study was to evaluate if the effect of induction chemotherapy on the soft tissue component on CT and/or MRI could predict histological response and serve as a prognostic factor.

Patients and methods: A review was done of the pre- and post-chemotherapy CT and/or MR images of 55 Ewing's sarcoma patients who were treated in 1985–1996 by current protocols and with surgery as local treatment. All had a soft tissue mass at the time of diagnosis. The total disappearance or complete ossification of the soft tissue component was considered a good radiological response. This was correlated with histological response and survival.

Results: 22 patients had a good radiological response and 21 of them are alive without disease. Among the 33 patients with a poor radiological response, 12 are alive. 18 patients with a good histological and radiological response are all alive. 23 patients were poor responders by both methods and only 6 of them are alive. The total concordance radiological/histological response was 41 of 55. 3 of the 4 patients with good radiological and poor histological response are continuously disease free.

Conclusion: Complete disappearance/ossification of the soft tissue tumor during induction chemotherapy correlates well with histological response and even better with survival. Persistent soft tissue tumor is a bad prognostic factor. This method may be used to identify the poor responders in need of more intensive maintenance chemotherapy among the patients who receive radiotherapy as definitive local treatment.

Preoperative ISG/SSG I treatment for osteosarcoma—a preliminary report on dose intensity and toxicity

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118 osteosarcoma patients with localized disease have been included in the ISG/SSG I study, which includes preoperative chemotherapy using Methotrexate, Cisplatin, Adriamycin and Ifosfamide. Postoperatively the same agents are administered, but with dose escalations depending on histopathological tumor response. We have studied the preoperative treatment regarding dose intensity, fraction of total doses given and toxicity in the 84 patients who have completed the preoperative therapy.

The preoperative treatment was administered with high dose intensity, median 0.91. Likewise, the fraction of the total dose administered for all reagents was high; 0.98. Regarding the individual drugs included in the regimen nine tenths of the patients received doses >90% of the total dose scheduled for Cisplatinum, Adriamycin and Ifosfamide, and all but 1 patient received >90% of the Methotrexate dose planned.

Treatment induced toxicity other than hematologic occurred in 14 patients; liver toxicity in 5 patients, nefrotoxicity in 4, CNS toxicity in 2, delayed Methotrexate excretion in 1 and allergic reactions to Methotrexate and Mesna in 1 patient each. All toxic reactions were reversible. 1 patient died from a lung embolus during treatment. Severe pancytopenia and a varicellae infection necessetated interruption of treatment in 2 patients. Hematologic toxicity was pronounced with WHO grades III–IV neutropenia occurring in 75% of the cycles, thrombocytopenia in 42%, and anemia in 32% of the cycles. Data on dose intensity, fraction of the total administered and hematologic toxicity will be further studied in relation to histopathological tumor response and prognosis.

Pulmonary metastasectomy in osteosarcoma patients

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Many osteosarcoma patients succumb to pulmonary metastases, and the role of surgery in these patients is still poorly defined. Before the chemotherapy era a few selected patients with a limited number of slow-growing metastases were operated. As modern chemotherapy creates more patients with a limited number of metastases, surgery is now more widely applied. Pulmonary resections have been part of our osteosarcoma treatment for 25 years, and we present some of our experiences.

Of 175 osteosarcoma patients referred to us 1980–1997, 99 patients developed pulmonary metastases, of these 44 have had thoracotomies. An additional 13 patients were operated in the period 1972–1979, giving a total of 57 patients of median age 18 years (range 6–60).

Period	Number of patients
1975–80	12
1981–85	16
1986–90	13
1991–97	16

Several patients have been subjected to repeated thoracotomies; 57 individuals had 98 events of pulmonary resections.

Events	Patients
1	32
2	15
3	5
4	4
5	1

The results of any treatment regimen are presented in fractions or percentage. As the regimen is applied to a selected group in a cohort, a high cure rate may reflect effective treatment, successful selection, or both. In our opinion proper patient selection is of the utmost importance. Besides survival benefit, resections of pulmonary metastases have added knowledge regarding the importance of histological response to chemotherapy.