L1 The Scandinavian Sarcoma Group - 25 years´ experiences

T.A. Alvegård

Dept of Cancer Epidemiology and Southern Swedish Regional Tumour Registry, Lund University Hospital, Lund, Sweden
email: thor.alvegard@cancerepid.lu.se

The Scandinavian Sarcoma Group (SSG) was constituted in 1979 and is open to all Nordic oncologists (pediatric and adult), surgeons, radiologists, pathologists, and tumor biologists interested in musculoskeletal tumors. The aim of the SSG is to uphold and improve the quality of diagnostics, treatment and care of sarcoma patients by sharing information and education, and by stimulating and coordinating basic and clinical research. The SSG has approved 25 treatment and research protocols and maintains 2 patient registers: the SSG Register of Bone and Soft Tissue Sarcoma Patients and the SSG Skeletal Metastasis Register. These registers, combined with the National Cancer Registries and a new Biobank Register, will facilitate future translational sarcoma research

The SSG is part of the international sarcoma society network in cooperation with the European Musculoskeletal Oncology Society (EMSOS), the Société Internationale d´Oncologie Pédiatrique (SIOP), the European Organization for Research and Treatment of Cancer (EORTC), Connective Tissue Oncology Society (CTOS) and International Society of Limb Salvage (ISOLS).

During the past 25 years more than 1,000 scientific articles have been published by SSG members.15 members have written their Ph.D. theses on issues relevant to sarcoma.

L2 The Scandinavian Sarcoma Group (SSG) Register 1986–2002

H.C.F. Bauer, T.A. Alvegård, Ö. Berlin, M. Erlanson, A. Kalén, P. Lindholm, P. Gustafson, S. Smeland, C.S. Trovik

The Scandinavian Sarcoma Group, University Hospital, Lund, Sweden
email: evy.nilsson@cancerepid.lu.se

The SSG Register contains data on 4074 patients with bone sarcoma (BS) or soft tissue sarcoma (STS) of the trunk or extremities diagnosed between 1986 to 2001. Most BS patients were included in SSG and ISG/SSG trials and are reported elsewhere.

Soft tissue sarcoma of trunk or extremities
Approximately 200 STS patients are referred yearly to sarcoma centers in Norway and Sweden. 61 % of the patients were referred before any surgical procedure. The rate of primary referral before surgery for *deep* lesions has improved from 69 % 1986-89 to 84 % 1999–2001. Hence the referral practice for deep STS in Scandinavia is equally good as for BS (87%).

The amputation rate for STS was 13 % 1986-1989 but only 5 % 1999-2001. The surgical margins have not improved, there were 66 % wide margins 1986–1989 and 59% 1999–2001. The use of adjuvant radiotherapy is increasing. 1999–2001 40% of patients with high grade, deep-seated, STS received radiotherapy, as compared to 26% 1986-89.

The changes in referral patterns seen and the improvement in local control warrants further investigation. We plan to run the SSG Register against the Swedish and Norwegian Cancer Registries so we can account for all soft tissue sarcomas (today we miss about 10%) during the time-period. Survival analysis on such a large and complete population based material will tell us to what extent the efforts to improve primary care of sarcoma patients translates into less morbidity and better survival.

L3 The SSG Morhology review experiences

T. Böhling

Dept of Pathology, University of Helsinki, Helsinki, Finland
email: tom.bohling@helsinki.fi

Introduction In 1995 a pathologist peer-review committee was formed with the purpose to meet on regular basis to evaluate the accuracy of the morphologic data in the SSG register files; in particular those cases enrolled in the different SSG treatment protocols and in specific scientific projects.

Materials and methods The committee has met reglularly for two-day working sessions. So far the reviews have included the most common soft tissue sarcomas and osteosarcomas. In the latest meetings osteosarcomas of the SSG XIV protocol, soft tissue sarcomas of the SSG XIII protocol and chondrosarcomas of the thoracic wall have been in the main focus.

Results So far 1966 cases have been evaluated and a change in diagnosis has been made in 15–30 %, depending on sarcoma type. For example, of the 695 tumors reported to the register as malignant fibrous histiocytomas 476 (68%) were evaluated as such, 33 (5%) were considered benign, and the rest as other type of sarcoma or malignancy.

Discussion The results show that a reevaluation of all cases included in treatment and study protocols is essential to assure the diagnostic quality. Furthermore, the participation in the group has helped to standardize the diagnostic procedures in the individual centers.

Reference Meis-Kindblom J. et al. Acta Ortop Scand (suppl 285) 1999; 70 18–26

L4 The SSG Tumour biology experiences

O. Myklebost

Dept of Tumor Biology, The Norwegian Radium Hospital, Oslo, Norway
email: ola.myklebost@biokjemi.uio.no

As one of the working groups of the SSG, the Tumor Biology Group has been a meeting place for biologists and geneticists with an interest in sarcomas. The group has made and regularly updated a catalogue of genetic aberrations of sarcomas with diagnostic value and a list of the contact persons within SSG that can assist in their analyses. The pamphlet also contained recommended procedure to prepare, ship and store patient samples for molecular examinations. Although there have been a number of project collaborations between SSG researchers in this group, there has so far been no SSG-wide biology projects. This is largely due to the different research interests of the associated labs, the lack of resources to extend smaller, local studies to SSG scale. Although sample numbers are important and collaboration thus is recommended for studies of a rare and heterogeneous group of tumours, it has proven difficult to obtain tissue samples from many of the SSG partners. As a result of these factors and little SSG focus on biological studies, the Tumor Biology Group as such was dissolved in 2003, and its members merged with the other relevant working groups. One of the coming opportunities will be the EURAMOS international osteosarcoma trial, where SSG has been central in designing biological studies. A major success factor for this and future biological studies will be the support of the involved clinicians.

L5 SSG Diagnostic radiology and nuclear medicine experiences

I. Taksdal

Dept of Diagnostic Radiology, The Norwegian Radium Hospital, Oslo, Norway
email: itaksdal@klinmed.uio.no

When SSG was founded in 1979 the primary diagnostic of sarcomas was based on radiography, angiography, scintigraphy, and “primitive” computed tomography. Since then, CT has become far more sophisticated and provides information about cortex, bone structure, ossification and lung metastases. MR is an essential staging tool in showing bone marrow, soft tissues, and anatomy. Thus surgery can be planned in detail, facilitating limb salvage and reducing the risk of local recurrence. Close cooperation between surgeon and radiologist is one aspect of the multidisciplinary approach characterizing the SSG.

During the SSG radiology working group meetings different tumor entities are discussed and experiences exchanged in order to improve diagnostic quality. There is agreement on the basic diagnostic tools and examination protocols. The radiology group maintains that tumor volume calculations should be based on MR.

Today no method exists that can reliably identify tumour necrosis in response to chemotherapy. Dynamic MR, diffusion imaging, color Doppler and FDG-PET are under investigation. Dynamic skeletal scintigraphy with blood-flow phase is valuable for treatment response in osteosarcomas but less so in Ewing’s sarcoma.

With treatment remaining essentially the same over the past 20 years, early detection is perhaps the most important factor in improving survival for sarcoma patients. This can only be achieved through increased awareness and continuous information and education towards the primary health services and referring institutions.

L6 SSG surgery experiences

O. Brosjö, H.C.F. Bauer

Oncology Service, Dept of Orthopedics, Karolinska Hospital, Stockholm, Sweden
email: otte.brosjo@ks.se

Diagnostic workup With MRI, it is now almost always possible to perform a thorough preoperative planning. Fine-needle aspiration biopsy is now generally accepted at most Scandinavian centers for the diagnosis of soft tissue tumors and often also in bone sarcomas.

Surgery The limb-sparing rate in osteosarcoma had increased from only 27% in the early 1980´s to more than 90%. The over-all local recurrence rate has been lower than 10 %. In Ewing's sarcoma, two thirds have been operated and local recurrence rate has dropped to less than 10%.
In soft-tissue sarcoma we have learned that increased centralization and by using more pre- or postoperative radiotherapy, and sometimes also adjuvant chemotherapy, the local recurrence rate and amputation rate can be approximately 10%.

Reconstruction For extremity bone sarcoma, custom-made or modular endoprostheses have mostly been used. The van Ness rotationplasty is in many Sarcoma Centers considered to be the best method for children less than 10 years and with a bone sarcoma in distal femur. Soft tissue reconstruction, by using all known plastic surgery reconstructive procedures including free tissue transfer, is now commonly performed in Scandinavia and significantly reduces the postoperative complication rate both in bone- and soft tissue sarcomas.

L7 The Scandinavian Sarcoma Group: Past experiences and future directions: The SSG clinical trials

S. Smeland

Dept of Oncology, The Norwegian Radium Hospital, Oslo, Norway
email: sigbjorn.smeland@klinmed.uio.no

Since 1979 SSG has initiated 16 clinical trials of which 6 are ongoing. The first SSG osteosarcoma study, SSG II, opened in 1982 and represented a breakthrough in osteosarcoma treatment with an improvement in overall survival of more than 40% compared to historical controls. From then 4 more phase II studies have been undertaken together recruiting more than 350 patients. In parallel 4 trials in Ewing's sarcoma have been initiated with a steady improvement in survival and local control.

The first SSG trial, SSG I, was a randomized study on adjuvant doxorubicin in non-metastatic soft tissue sarcomas. After 20 years, the benefit of adjuvant chemotherapy to high-grade STS is still questioned. The use of tyrosine kinase inhibitors in the treatment of GIST has been pioneered in Scandinavia and recently a SSG chaired multi-national randomized phase II study on adjuvant imantinib to high-risk patients was opened.

There has been a development in bone sarcoma trials to more international collaboration. This aspect is truly reflected in the upcoming trial for operable osteosarcoma, Euramos 1. A European-American intergroup collaboration has been established which together cover a population of more than 500 mill people in Northern America and Europe. The development to more histology specific therapy in STS forces the same broad collaboration in STS as exemplified with the recently opened GIST protocol.

L8 SSG experiences of centralized registration of patients with surgically treated skeletal metastases

J. Keller[1], R. Wedin[2]

Depts of Orthopedic Surgery, [1]University Hospital, Aarhus, Denmark, [2]Karolinska Hospital, Stockholm, Sweden
email: keller@akh.aaa.dk

Current surgical treatment for pathologic fractures is based on retrospective analyses of single institution experience. The reported series comprise heterogeneous patient populations regarding types of primary cancer, extent of the metastatic disease and location of the lesions. Areas of uncertainty include operative methods, indications for prophylactic surgical treatment and need for postoperative radiotherapy as radiation decreases the risk of local tumour progression but increases bone-healing complications.

The Scandinavian Sarcoma Group started the Skeletal Metastasis Registry in 1999 to improve the surgical treatment of skeletal metastases. Criteria for inclusion are patients surgically treated for either impending or complete non-spinal fractures due to skeletal metastases. 9 orthopedic oncology centres from Sweden, Denmark, Norway and Finland participate and data regarding more than 600 surgically treated patients have so far been registered. Additional aims of the registry are to provide a tool for quality assessment as measured in terms of reoperation rate, operation morbidity and operation frequency for impending fractures.

L9 Surgical techniques in extremity and axial malignant tumors of bone and soft tissue. The Russian experience

M. Aliev, V. Sokolovsky, V. Teplyakov, V. Sobolevsky, E. Musaev, A. Valiev, G. Machak, T. Kharatishvili, B. Bokhian

N.N. Blokhin Cancer Center, Moscow, Russian Federation
email: machak.gennady@mail.ru

In our current protocols for high-grade bone and soft tissue sarcomas, the rate of limb-salvage procedures exceeds 80%. Post-resectional defects are usually substituted by endoprostheses, free vascularized fibula and in selected cases by distraction osteosynthesis by Ilizarov. During the last 10 years, 219 endoprosthetic reconstructions were performed: 148 (68%) in bones forming the knee joint, 34 (16%) in hip joint, 22 (10%) in proximal humerus and 2 in elbow. There were 3 intercalary, 2 total humerus and 8 total femur prostheses. The local recurrence rate is 13%. The majority of complications were related to infection (12%) or mechanical problems (8%). We used for reconstruction a free fibula in 13 patients and the Ilizarov method in 19. Surgery in pelvic tumors was resection type I (40), type II (2), type III (23) and combined (16). Sacral resections at various levels were performed in 30 patients. In spine tumors, 20 transpedicular stabilization systems were installed after decompressive procedures. 40 patients underwent transcutaneous vertebroplasty with bone cement. The neurological status and quality of life improved in most treated spine patients. Free thoraco-abdominal flaps are more often used for reconstruction after removal of locally advanced soft tissue sarcomas.

L10 Current chemotherapy protocols in high-grade bone and soft tissue sarcomas

G. Machak, N. Ivanova, B. Bokhian, M. Aliev

N.N. Blokhin Cancer Center, Moscow, Russian Federation
email: machak.gennady@mail.ru

Neoadjuvant approach is the standard treatment in high-grade bone and soft tissue sarcomas. Our current protocol for IIB osteosarcoma, MFH and high-grade chondrosarcomas, which started in 1999, consists of 4 cycles of DOX 90 mg/m^2 by 96-hour CI and CDP 120 mg/m^2 by 4-hour intra-arterial or intravenous infusion. Surgery is the standard method of local treatment. Patients who refuse surgery receive local radiation in the dose of 60 Gy. Adjuvant chemotherapy consists of alternating DOX-CDP and IFO – VP-16 cycles. Among operated patients, 61% had >90% of tumor necrosis and 19% complete necrosis. Local response was higher in the intraarterial than in the intravenous cisplatin arm (p= 0.001) with no impact on survival. In Ewing‘s sarcoma VACA, VAIA and VIDE regimens are used in young adults and high-dose VAC alternating with high-dose IFO-VP-16 in
children. Local treatment consists of surgery, radiation or both. The effectiveness of preoperative chemotherapy DOX-CDP and local hyperthermia combination is investigated in soft tissue sarcomas. Preliminary results have demonstrated that objective response and tumor necrosis >70% rates were 60% and 70%, respectively. Local failure rate is 15% and overall survival 70%. Three regimens are investigated in relapsed sarcomas: IFO-VP-16; IFO-VP-16-CARBO; and GEM-DOC.

L11 Transosseus osteosynthesis (TO) by Ilizarov in the treatment of bone tumors

V. Teplyakov, V. Karpenko, G. Machak, M. Aliev

N.N. Blokhin Cancer Center, Moscow, Russian Federation
email: machak.gennady@mail.ru

Purpose To present our experience with the Ilizarov method in cancer patients.

Patients and methods TO was used for reconstruction after resection of high-grade bone sarcomas (19), as alternative to amputation in infected implants (15), and for fixation of pathological fracture in 14 primary and 29 metastatic tumors.

Results TO allowed to substitute defects ranging from 5 to 30 cm. The average duration of distraction was 300 ± 25 days. The rate of local/systemic disease progression was significantly higher, in the resection-distraction group (15/19) than in the late implant failure group (2/15). Disease progression occurred even after extensive or complete chemotherapy induced tumor necrosis. Fracture consolidation occurred in 70% of patients with metastatic breast cancer and lymphosarcoma. Only 28% of patients with Ewing sarcoma, metastases from unknown primary, and other malignancies had consolidation.

Conclusions Due to the high risk of progression, TO is not recommended as reconstructive technique immediately after removal of high-grade bone sarcomas. TO is better indicated in late implant failures, as an alternative to amputation. In generalized tumors, potentially responsive to modern chemo-radiotherapy protocols, when fracture consolidation is expected, TO could be considered as a definitive option or a step to endoprosthetic replacement.

L12 Soft tissue leiomyosarcoma: A clinicopathologic study of 227 cases. A Scandinavian Sarcoma Group project

C. Svarvar[1], C. Blomqvist[2], T. Böhling[3], Ö. Berlin[4], B. Bjerkehagen[5], H. Domanski[6], G. Follerås[7], P. Gustafson[8], P. Lindholm[9], C. Trovik[10], E. Tukiainen[1]

Depts of [1]Plastic Surgery, [2]Oncology, [3]Pathology, University Hospital, Helsinki, Finland, [4]Dept of Orthopedics, Sahlgren University Hospital, Gothenburg, Sweden, [5]Dept of Pathology, The Norwegian Radium Hospital, Oslo, Norway, [6]Dept of Pathology and Cytology, University Hospital, Lund, Sweden, [7]Dept of Orthopedics, The Norwegian Radium Hospital, Oslo, Norway, [8]Dept of Orthopedics, University Hospital, Lund, Sweden, [9]Dept of Oncology and Radiotherapy, Turku University Central Hospital, Turku, Finland, [10]Dept of Orthopedics, Haukeland University Hospital, Bergen, Norway
email: catarina.svarvar@hus.fi

Soft tissue leiomyosarcomas are rare malignant tumors and, therefore, have not been extensively studied. This study was based on a consecutive series of cases from the Scandinavian Sarcoma Group (SSG) Register acquired during a 15-year period (1986–2001). We analyzed the clinicopathological features of 227 leiomyosarcomas of the extremities (n=157), trunk wall (n=64), and head and neck region (n=6) to determine what factors affect outcome. Patients not referred to a SSG center for treatment were excluded. Histopathologic re-evaluation of the diagnosis and assignment of malignancy grade was performed. Follow-up information was available in all cases. Cutaneous (n=37), subcutaneous (n=101) and deep-seated (n=89) tumors were included. The patients (123 females and 104 males) had a median age of 69 (20–98) years. Median tumor size was 4 (0.6–35) cm. 81% of the tumors were classified as high grade (grade 3 or 4). Patients referred with metastases and patients with metastases at diagnosis (n=19) were excluded from the survival analysis. The local treatment was adequate in 155 (75%) of 208 cases. During the follow-up period 27 (13%) of 208 patients developed local recurrence and 57 (27%) of 208 metastasized, mostly to the lungs. In both univariate and multivariate analyses large size, high grade and deep location were significantly correlated with metastasis; inadequate treatment correlated with local recurrence and high grade with decreased overall survival.

L13 Immunohistochemical profiling in 211 malignant fibrous histiocytomas confirms the prognostic value of Ki-67

J. Engellau[1], A. Persson[2], P.O. Bendahl[1], M. Åkerman[2], H.A. Domanski[2], B. Bjerkehagen[5], P. Lilleng[6], J. Wejde[7], A. Rydholm[3], T.A. Alvegård[4], M. Nilbert[1]

Depts of [1]Oncology, [2]Pathology, [3]Orthopedics, [4]Cancer Epidemiology, Lund University Hospital, Lund, Sweden, [5]Dept of Pathology, Norwegian Radium Hospital, Oslo, Norway, [6]Dept of Pathology, Haukeland Hospital, Bergen, Norway, [7]Dept of Pathology, Karolinska Hospital, Stockholm, Sweden
email: jacob.engellau@onk.lu.se

Novel prognostic markers are needed in soft tissue sarcomas in order to identify high-risk patients for adjuvant therapy. Tissue micro-array (TMA) has been introduced as a high-throughput technique that allows studies of multiple markers in large tumor materials. We used TMA for immunostaining of 211 paraffin-embedded primary malignant fibrous histiocytomas (MFH), 44 local recurrences and 18 metastases. Immunostaining for Ki-67, p53, bcl-2, CD44, cyclin A, and Pgp revealed that a Ki-67 index >20% independently predicted metastases, whereas the other markers did not. When matched primary tumors and metastasis were compared, cyclin Aand Pgp staining was up-regulated in the metastases, whereas the expression patterns in the local recurrences did not differ from the corresponding primary tumors.

In summary, Ki-67 % was the only immunohistochemical marker that correlated with metastases in this large series of MFH, which confirms previous findings. The different patterns of expression detected in the local recurrences and the metastases compared to the primary tumors, indicate that local recurrence is a consequence of residual disease, whereas
metastases rather reflect clonal tumor progression.

L14 Evaluation of intratumor versus intertumor heterogeneity in malignant fibrous histiocytomas

P. Francis[1], J. Fernebro[1], A. Laurell[1], T. Breslin[2], P. Edén[2], C. Pettersson[2], A. Rydholm[3], H. Domanski[4], C. Hegardt[1], M. Nilbert[1]

[1]Depts of Oncology, [2]Theoretical Physics, [3]Orthopedics, [4]Pathology, Lund University Hospital, Lund, Sweden
email: princy.francis@onk.lu.se

Introduction Gene expression profiles are increasingly being used for tumor sub-classification and in most cases the profiles are obtained from single tumor samples. In the case of soft tissue sarcomas (STSs), where tumors are often large and morphologically heterogeneous, one could argue that a random sample may not be representative of the whole tumor. We have therefore evaluated intra-tumor and inter-tumor heterogeneity in the gene expression profiles from malignant fibrous histocytomas (MFHs).

Materials and methods RNA was extracted from 9 different sections from a myxoid MFH and single samples from 15 different MFH and 6 myxofibrosarcomas. cDNA was synthesized and hybridized to 27k cDNA microarray slides.

Results Hierarchical clustering and multidimensional scaling (MDS) analysis of the expression profiles provided distance measurements between the various samples and showed that the intra-tumor distances between the 9 sections were minimal as compared to the inter-tumor distances.

Conclusion Our findings suggest that accurate molecular profiling can be obtained from single samples from STSs since intra-tumor heterogeneity is minimal as compared to inter-tumor variability.

L15 cDNA microarray analysis in synovial sarcoma; correlations with histopathology, cytogenetics, and fusion genes

J. Fernebro[1], P. Francis[1], P. Edén[2], C. Pettersson[2], I. Panagopoulos[3], F. Mertens[3], N. Mandahl[3], M. Nilbert[1]

[1]Depts of Oncology, [2]Theoretical physics, [3]Clinical Genetics, Lund University Hospital, Lund, Sweden
email: josefin.fernebro@onk.lu.se

Synovial sarcoma represents a subgroup of soft tissue sarcomas that are characterized by the specific X;18-chromosomal translocation. Thereby, a novel fusion protein, SS18-SSX, is formed. The fusions can be of two major types depending on which of the genes *SSX1* and *SSX2* are involved. Furthermore, the tumors occur in two histopathological forms of differentiation, monophasic and biphasic synovial sarcoma.

We have applied 27k cDNA microarray slides to 25 synovial sarcomas to determine whether the two major fusion types, SS18-SSX1 and SS18-SSX2 result in distinct gene expression profiles.

Based on histopathology, gene fusion type, and cytogenetic aberrations different gene expression clusters are obtained. The group-classifying gene list includes keratin-encoding genes and will be presented and further analyzed in order to identify which genes are up-regulated and down-regulated by the different biological characteristics in synovial sarcoma.

L16 Amplicons and their target genes in osteosarcoma – a CGH microarray analysis

S. Knuutila, J. Atiye, M. Wolf, O. Monni, T. Böhling, M. Tarkkanen, A. Kivioja, M. Serra

Depts of Pathology and Medical Genetics, Haartman Institute and HUSLAB, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland
email: sakari.knuutila@helsinki.fi

Introduction Cytogenetic and molecular data in osteosarcomas are not scanty, but no specific changes have been reported yet. We analyzed the gene copy number changes using a CGH microarray with a cDNA platform with more than 13,000 probes.

Patients For CGH microarray analysis 1 cell line and 21 untreated (but 1) osteosarcoma cases (19 conventional high grade, 2 low grade periosteal and 1 small cell) were selected.

Results Amplicons were detected in all cases. The most recurrent amplicon was 12q11–q14, seen in 9 cases, and the other recurrent amplicons were 8q, 6p, and 17 (6, 5, and 5 cases, respectively). We found numerous novel amplicons in few cases or only in a single case. The most recurrent of these novel amplicons were 14q11, 17q25, and 22q11–q13 (each seen in 3 cases). Most of the amplicons, especially the large ones at 12q, 6p, 8q and 17p were discontinuous containing amplified, non-amplified and even lost genes. However, some of the small amplicons, e.g., the amplicon at 14q11, contained only one area with approximately 10 amplified genes.

Conclusions One of the genes in the 12q amplicon, cytochrome P450 gene CYP27B1 at 12q14 is intriguing as it has an essential role in normal bone growth, calcium metabolism, and tissue differentiation. Our novel finding is that TOM1L2 at 17p was the most frequently amplified gene. This study provided an accurate demonstration of the amplicons in osteosarcoma. Some of the amplicons have not been described previously, and the earlier known 12q amplicon seems to be considerably more frequent than previously assumed.

L17 High-resolution DNA copy number analysis in sarcomas by array comparative genomic hybridization

L.A. Meza-Zepeda[1], S. Henrichson Kresse[1], J.B. Wang[1], A. Forus[1] W.L. Kuo[2], S. Gregory[3], J.W. Gray[2], O. Myklebost[1]

[1]Dept of Tumor Biology, The Norwegian Radium Hospital, Oslo, Norway, [2]The Wellcome Trust Sanger Institute, Cambridge, United Kingdom, [3]Comprehensive Cancer Centre, UCSF, San Francisco, USA
email: l.a.meza-zepeda@labmed.uio.no

Human sarcomas show recurrent amplification of specific chromosomal segments. Aberrations involving the long arm of chromosome 12 and 1 are frequently seen in this type of tumors. Our group has in the past years studied the human chromosomal region 1q21–q23, a region frequently amplified in sarcomas, as well as in a number of other tumors, including breast carcinoma, liver and ovarian cancer. For specific tumor types, over-representation of 1q21–q24 has been associated with a metastatic phenotype, resistance to aggressive treatment and poor response to chemotherapeutic agents. To identify the responsible genes that drive the complex amplification in this region we have constructed a high-density genomic microarray covering the 1q12–q25 region. The array contains approximately 400 genomic clones covering the minimal tiling-path for the region, and is being extended with about 4000 clones from the genome project, giving 1Mb global coverage and knowledge of exact sequence coverage. We have used the genomic arrays for comparative genomic hybridization of a panel of tumors with 1q amplification. Initial results show the presence of more than one amplicon, a situation previously observed in other regions frequently amplified in sarcomas. Identification of possible candidate genes is on its way.

L18 Differential diagnosis in Ewing sarcoma

M. Winderen[1], T. Bach-Gansmo[1], I. Taksdal[2], B. Bjerkehagen[3], K. Sundby Hall[4], G. Follerås[5], S. Skjeldal[5]

Depts of [1]Nuclear medicine, [2]Radiology, [3]Pathology, [4]Oncology, [5]Surgery, The Norwegian Radium Hospital, Oslo, Norway
email: mwind@online.no

A 16-year-old boy was hospitalized after a minor injury and pain in the left hip; ultrasound revealed increased fluid in the hip joint and radiographs showed a lytic lesion in the iliac bone. Fine needle aspiration was not diagnostic. Bone scintigraphy showed multiple lesions and a dislocation of the left kidney. FDG-PET confirmed all bone lesions and a large tumor in abdomen and smaller other soft tissue manifestations. CT and MR gave the same results, wide spread disease with lung metastases. Such extensive disease and almost no clinical symptoms is unusual for Ewing sarcoma and a biopsy revealed a paraganglioma. Only noradrenalin was elevated in one sample, all other catecholamines were normal. Surgery was necessary in the iliac bone due to a pathologic fracture and to prevent fracture of the ulna. Further diagnostic workup showed that ^{131}I-MIBG had significantly higher uptake than ^{111}In-octreotid. The patient have been treated with increasing doses of ^{131}I-MIBG (3,7, 3,7, 5,55 and 6,55 GBq) after removing the abdominal tumor. Dosimetric studies estimated a tumordose of 10,8 Gy /GBq injected and a bone marrow dose of 0,32Gy/GBq, giving an estimated cumulated tumor dose of 210 Gy. Control 12 month after the last dose reveals “stable disease” and no clinical symptoms.

L19 Ewing sarcoma/PNET involving the spinal cord – the importance of early oncological treatment for recovering and saving of vital functions

J.P. Poulsen[1], S. Skjeldal[2], B. Bjerkehagen[3], I .Lloret[4], R. Sørensen[5], K. Sundby Hall[1]

Depts of [1]Oncology, [2]Surgery, [3]Pathology, [4]Diagnostic Radiology, The Norwegian Radium Hospital, [5] Dept of Orthopedics, Rikshospitalet (RH), Oslo, Norway
email: j.p.poulsen@klinmed.uio.no

Case reports Two boys aged 19 and 14 were admitted with back pain, (January 03 and October 03), and lower limb pareses with loss of bladder control (Frankel B). MR showed large tumors: one extending from L2 to S3, growing through the processus spinosus in L4 with an intraspinal component, and one in the posterior part of Th3 extending into the corpus of the vertebra, compressing the spinal cord. Cytology showed highly malignant, small, round cell tumors. Acute spinal surgery for decompression would contaminate large areas with tumor cells. Instead they immediately started on high dose dexamethasone and chemotherapy according to the ISG/SSG III protocol. Both responded.

The oldest got concomitant radiotherapy starting week 14, 1,5 GY, hyperfractionated, total 42 GY. He was operated in week 26. Histology: “Small round cell sarcoma/PNET, free margins in both pedicles, marginal margins in the muscles and not free margins towards foramen vertebralis”. Poor chemotherapy response, “Picci grade I”. Neurologically he recovered (Frankel D). He finished chemotherapy with one cycle of high dose Busulfan/ Melphalan with PBSC. Treatment time was 9 months. March 04, no sign of relapse, but slight S1 root symptoms bilaterally (Frankel E).

The youngest was operated in week 19. Histology: “PNET, intralesional resection in the pedicles, no tumour in soft tissues”. Moderate chemotherapy response, “Picci grade II”. Neurologically he recovered (Frankel D). He is continuing the chemotherapy and will get radiotherapy.

Conclusions Ewing sarcoma/PNET is generally a highly chemotherapy-sensitive tumor. The responses observed in these 2 patients indicate that early, effective chemotherapy is an alternative to an acute laminectomy in the management of spinal compression due to Ewing/PNET.

L20 To treat the child to treat the teenager to treat the adult

O. Björk

Dept of Pediatric Oncology, Astrid Lindgrens Hospital, Stockholm, Sweden
email: olle.bjork@ks.se

Sarcomas in small children often occur as midline tumors in the bladder, uterus, prostate or orbita. Treatment is a challenge with risk for life threatening complications, especially infections, during the intensive chemotherapy possible in children due to excellent renal and cardiovascular function. Many children are cured but will experience late side-effects of the treatment.

To treat the teenager, often with skeletal sarcoma, is a completely different story. Already in the teenagers there are limitations to intensive chemotherapy. Impaired physical function is especially serious in this period of life. The possibility for limb salvage has indeed improved the quality of life for this age group.

Fertility is an important question for the future in both these age groups but has to be handled differently. To treat a teenager or a young child is from a psychological point of view a complete different story. The hospital ward has to be adapted to both age groups and still there is a problem with the patient that could not be called a teenager and not a adult but rather something in between. The major challenge faced by the pediatric oncologist today is to sustain the excellent survival rates without causing major late effects.

L21 Bone necrosis associated with imatinib mesylate (Gleevec®) treatment

J.O. Fernberg[1], H. Einarsdottir[2], H. Jacobsson[3]

Depts of [1]Oncology, [2]Radiology, [3]Nuclear Medicine, Karolinska Hospital, Stockholm, Sweden
email: jan-olof.fernberg@ks.se

A 61-year-old previously healthy woman, except migraine, was operated October 1999 due to a tumor in the stomach. Liver metastases were present at surgery. The tumor was found to be a GIST and chemotherapy with ifosfamide and epirubicin was instituted in February 2000.

After 6 courses of chemotherapy (June 2000), and slow tumor progression, the treatment was shifted to interferon alpha. Interferon was given for 10 months and cyclophosphamide in a low dos orally was added. The disease progressed further and when imatinib mesylate (Gleevec®) was available, treatment with 400 mg daily started in September 2001. After 4 months the patient experienced stiffness and pain in the knees and ankles.

Bone scintigraphy February 2002 showed marked activity in the knees and ankles and MRI displayed a picture of bone necrosis. The patients symptoms regressed although the changes were the same at follow up with MRI after 9 months. The patient has shown a good partial response in the liver and is still on imatinib treatment after 30 months (March 2004).

Avascular bone necrosis has been reported after chemotherapy for hematological malignancies and is associated with the prolonged use of corticosteroids. Nontraumatic osteonecrosis is more seldom seen in patients treated with chemotherapy for solid tumors. Only one previous report of bone necrosis after imatinib mesylate is known from the literature and was described in a patient with CML. Single and multiple hot spots in bone scintigraphy after chemotherapy may be originated by bone necrosis but mimicry metastases.

L22 Giant cell tumor in the extremities. The Scandinavian Sarcoma Group experience of 296 cases

G. Follerås[1], O. Brosjö[2], A. Rydholm[3], C. Trovik[4], A. Kivioja[5]

Depts of Orthopedic Surgery, [1]The Norwegian Radium Hospital, Oslo, Norway, [2]Karolinska Hospital, Stockholm, [3]Lund University Hospital, Lund, Sweden, [4]Haukeland University Hospital, Bergen, Norway, [5]Helsinki University Hospital, Helsinki, Finland
email: gunnar.folleras@klinmed.uio.no

Introduction 336 Giant Cell Tumor patients are registered in the SSG register, 296 are located in the extremities and are presented.

Patients 155 are men and 141 women. The tumor was located in the humerus (13), radius/ulna (42), femur (104), tibia (72), fibula (22), hand/foot (17) and other parts (4). 256 patients were referred to the tumor centre virgin or after FNA, 20 after coarse needle or open biopsy, 12 after intralesional and 2 after marginal or wide surgery. 5 had recurrent tumor. All had surgery for their tumor, in 22 cases outside the tumor center. Patients having the first surgery for primary tumor in tumor center had 1.04 surgeries, those outside had 1.36 surgeries. The margin obtained was intralesional in 182, marginal in 61, and wide or better in 51. The reconstruction used was in 22 patients prosthesis, in 17 cases allograft, in 149 cementation, in 45 bone graft, and miscellaneous in 4. 40 patients had no reconstruction, 4 of those had a primary amputation.

Results After mean 62 (2–182) observation time 48 patients (16%) had 1, 9 had 2 and 3 had 3 local recurrences. 42 had a new resection, 2 were amputated. 25 patients had surgery for breakdown of the reconstruction, 25 once, 8 twice and 3 thrice. Risk factors for local recurrence were intralesional margin, first surgery outside center, and patient referred not virgin. 4 patients had metastasis at diagnosis, 5 developed metastasis during observation. A total of 396 surgeries related to the tumor are recorded. 215 patients needed only one operation. The remaining 81 patients had 181 surgeries, 2,2 per patient. Risk-factors for repeated surgery were non-virgin tumor and bone graft reconstruction,

Conclusion The recurrence rate is in line with other investigators. It is still a challenge to reduce the number of surgeries needed to treat this benign, but aggressive tumor.

L23 The SSG Skeletal Metastasis Registry. Survival after surgery for bone metastases in the pelvis and extremities

B. H. Hansen[1], R. Wedin[2], J. Keller[1], M. Laitinen[3], P. Berg[4], S. Skjeldal[5], C. Trovik[6], J. Nilsson[7], A. Walløe[8], A. Kalén[9]

Depts of Orthopedic Surgery, [1]University Hospital, Aarhus, Denmark, [2]Karolinska Hospital, Stockholm, Sweden, [3]University Hospital, Tampere, Finland, [4]Sahlgren University Hospital, Gothenburg, Sweden, [5]The Norwegian Radium Hospital, Oslo, Norway, [6]Haukeland University Hospital, Bergen, Norway, [7]Lund University Hospital, Lund, Sweden, [8]Ullevål Hospital, Oslo, Norway, [9]University Hospital, Linköping, Sweden
email: bhhan@akh.aaa.dk

Introduction The assessment of the prognosis for the individual patient is important for the choice of surgical treatment of skeletal metastases. In 1999 the Scandinavian Sarcoma Group (SSG) initiated the Skeletal Metastasis Registry as a multi-centric, prospective study to provide a scientific basis for treatment recommendations. To improve prognostication we analyzed the survival of patients with skeletal metastases surgically treated at 9 SSG centres.

Patients and methods 460 patients with an average age of 64 years underwent 501 operations for non-spinal skeletal metastases. 7 % were operated for more than one metastasis. Carcinoma of the breast, prostate, kidney and lung were the dominating primary tumors.

Results The survival rate was 0.4 at 1 year, 0.3 at 2 years and 0.2 at 3 years. Univariate analysis showed that survival was related to bone localization, skeletal metastatic load, presence of visceral metastases, Karnofsky performance score, primary tumor type, presence of a complete pathological fracture and preoperative hemoglobin content. Multivariate regression analysis showed that pathological fracture, visceral metastases, hemoglobin content < 7 mmol/L and lung cancer were negative prognostic factors for survival. Myeloma was the sole positive prognostic factor for survival.

L24 Should all trochanteric metastases undergo a total hip replacement

A. Kalén, O. Wahlström

Dept of Orthopedic Surgery, University Hospital, Linköping, Sweden
email: anders.kalen@lio.se

It is well known that the risk of failure after conventional osteosynthesis of pathological fractures is high (R. Wedin, Acta Orthop Scand Suppl 302; 2001). Recommendations for treatment given by the Tumor centers in the SSG emphasize that many pathological fractures require bone cement enforcement or endoprosthesis to reduce the failure risk. Hip replacement should always be considered for a proximal femur metastasis. However, these recommendations are not always followed:

Case 1 A 45-year-old woman had been operated because of breast carcinoma 2 years before intramedullary fixation of a pathologic trochanteric fracture. 14 months later, the nail had fractured and a THR was performed.

Case 2 A 47-year-old woman who had been operated 7 years earlier for breast carcinoma underwent plate and screw fixation of a pathological trochanteric fracture. 13 months later the osteosynthesis failed with "cutting out" of the screw and a THR was performed.

Conclusions These cases illustrate that the recommendations given by the Tumor centers of SSG are motivated but not always followed. When seeing a pathological fracture of the proximal femur, the surgeon should ask himself: Why should this patient not undergo a THR?

L25 Identifying patients at high risk for toxicity by monitoring serum methotrexate at 18 hours

K.S. Hall[1], J.P. Poulsen[1], A.K. Thøgersen[2], A. Andersen[2], H. Olsen[2], G. Saeter[1]

[1]Dept of Oncology, [2]Section of Clinical Pharmacology, Central Laboratory, The Norwegian Radium Hospital, Oslo, Norway
email: k.s.hall@klinmed.uio.no

Persisting high se-MTX resulting in severe toxicity secondary to acute renal dysfunction can give life-threatening myelosuppression and GI-toxicity in patients treated with high-dose methotrexate (HDMTX).

A young male osteosarcoma patient treated after SSG XIV with MTX 12g/m^2 had 24h after infusion start se-MTX 250 mmol/L and se-creatinine 185 mmol/L. Neutropenia, mucositis and vomiting was serious for several days. After vigorous hydration, urinary alkalinization and increased doses of leucovorin given intravenously for nearly 14 days, he completely recovered.

This event forced us to evaluate our HDMTX treatment procedures and the intervals for se-MTX monitoring. Bacci et al. (2003) reported that se-MTX >100 mmol/L at 18h predicts a decreased elimination. In this situation they start leucovorin rescue at 18h. We retrospectively calculated se-MTX at 18h for 280 HDMTX-cycles given to 64 osteosarcoma patients treated at NRH from 1994 to 2002. Se-MTX levels were monitored after 4, 12, 24, 48 and 72h.

Results Of 280 cycles, 8 had se-MTX above toxic levels at 24h, 48h, and 72h and only these had se-MTX at 18h >100 mmol/L. In none of the cycles (221) with normal elimination (below the toxic level at 24, 48 and 72h) se-MTX >100 mmol/L at 18h. In 32 cycles se-MTX was >20mmol/L at 24h alone. In none of the cycles se-MTX first appeared above the toxic level at 48h if se-MTX at 24h had been below.

Conclusions Se-MTX concentration at 18h is a useful parameter to identify delayed MTX clearance and has now being added to our se-MTX monitoring. If se-MTX >100 mmol/L at 18h, leucovorin rescue and increased hydration with sodium bicarbonate is started considering early high creatinine values when doses and fluid volume are determined.

Reference Bacci G, Ferrari S, Longhi A, et al. Delayed methotrexate clearance in osteosarcoma patients treated with multiagent regimens of neoadjuvant chemotherapy. Oncology reports 2003; 10: 851-857

L26 Interferon alone and in combination with doxorubicin in osteosarcoma xenografts –a microarray study

C. Müller[1,2], H.M. Namløs[2], G. Saeter[1], S. Smeland[1], O. Myklebost[2]

Depts of [1]Medical Oncology and Radiotherapy, [2]Tumourbiology, The Norwegian Radium Hospital, Oslo, Norway
email: christoph.muller@klinmed.uio.no

Strander et al. have shown that interferon-a has activity as single adjuvant in the treatment of primary osteosarcoma. Modern combination chemotherapy does not utilize this drug and little data exist on how to optimally integrate interferon into modern treatment protocols.

We have started to screen a panel of osteosarcoma xenografts established at the Norwegian Radiumhopital for response to treatment with pegylated interferon-α. Of the 5 xenografts tested to date, all responded at the molecular level, i.e. induction of specific genes as measured by cDNA arrays, but only one responded with considerable growth delay. The transcriptional response was specific for interferon and reproducible in all 5 cell-lines. The one xenograft responding with growth delay has also been treated with a combination of interferon and doxorubicin. Preliminary results suggest that the combination at high doses inhibits growth. Microarray studies of gene expression are in process, as are studies of cell-cycle parameters, markers of apoptosis and pharmacokinetics of pegylated interferon-α in nude mice.

We postulate that an optimal combination of pegylated interferon-a and conventional aggressive chemotherapy may further improve osteosarcoma survival.

L27 Management of bone sarcomas over a 20-year period at The Norwegian Radium Hospital (NRH

L.H. Aksnes[1], K.S.Hall[1], G. Follerås[2], A.E. Stenwig[3], B.Bjerkehagen[3], I. Taksdal[4], M. Winderen[5], G.Saeter[1]

Depts of [1]Oncology, [2]Surgery, [3]Pathology, [4]Radiology, [5]Nuclear Medicine, The Norwegian Radium Hospital, Montebello, Oslo, Norway
email: livak@klinmed.uio.no

*Introduction T*his study is a retrospective analysis of all bone sarcoma patients treated at the NRH from 1980 to 1999.

Patients and methods 449 patients with bone sarcomas were treated. In this retrospective analysis, patients were allocated to consecutive 5-year periods by their first admission to NRH.

Results Patient accrual to the sarcoma group at NRH has been relatively stable over the study period, at all time constituting 60-70% of all Norwegian bone sarcoma patients. Patient and tumor characteristics have remained relatively stable, but there has been a little tendency towards decreasing dominance of male patients, higher median age, more axial tumors and slightly lower malignancy grade.

The percentage of all patients receiving chemotherapy has been stable around 45–50%, but chemotherapy intensity has increased over time. The use of radiotherapy has decreased (from 33% to 18%), as has the amputation rate (from 78% to 14%). Sarcoma specific survival at 5 years for all patients has increased significantly from 43% in the first treatment period to 71% in the last.

In multivariate analysis, independent prognostic factors for improved survival were non-metastatic disease at diagnosis, low-grade malignancy, age under 40, extremity tumors, tumor size < 8 cm and treatment after 1989.

Conclusion As no major improvements in treatment options have emerged over these 20 years the results indicate significant improvements in the quality of established care, based on continuous improvements in the organization and performance of the NHR multidisciplinary sarcoma group.

L28 Evaluation of tumor response with isolated limb perfusion (ILP) in patients with limb-threatening soft tissue sarcoma

W. Reed[1], A.M. Wiedswang[2], B. Bjerkehagen[1], S. Stoldt[3]

Depts of Pathology[1], Radiology[2], Surgery[3], The Norwegian Radium Hospital, Oslo, Norway
email: wenche.reed@labmed.uio.no

Introduction ILP is an approved treatment for extremity soft tissue sarcomas otherwise requiring amputation.

Patients From 2000 to 2003, 6 patients underwent ILP with TNFa and Melphalan followed by surgery. All tumors were primary, locally advanced high grade sarcomas without metastasis. MRI was done 6 to 10 weeks after ILP. Radiological partial response (PR) was defined as $\geq$30% regression of tumor size or > 90% necrosis, histological PR as necrosis $\geq$50% of the tumour.

Results The mean interval time from ILP to surgery was 11 (9–14) weeks. 5 patients were treated with limb salvage, 3 had partial loss of function. Amputation was performed in 1 case because of tumor-infiltration into the tibia. Radiologically, none of the tumours showed $\geq$30% size reduction, though 5 (83%) showed $\geq$50% necrosis. Histologically, PR was seen in 4 patients. There were no complete responses (Table).

Patients	Radiological response Size, Necrosis%, Overall R[1]	Histological response	Final result	Histological margins
1 FS[2]	PD[4], 50, PD	NC	limb salvage	wide[7]
2 MFH[3]	NC[5], 40, NC	NC	limb salvage	intralesional
3 MFH	PD, 90, PR[6]	PR	limb salvage	marginal[8]
4 MFH	NC, 70, NC	PR	amputation	wide
5 MFH	NC, 80, NC	PR	limb salvage	wide
6 MFH	NC, 90, PR	PR	limb salvage	marginal

[1]R response, [2]FS fibrosarcoma, [3]MFH malignant fibrous histiocytoma, [4]PD progression of disease, [5]NC no change, [6]PR partial response, [7]wide ≥ 3 cm, [8]marginal < 3 cm.

Conclusions Contrast enhanced MRI can be used to evaluate tumour necrosis after ILP. Together with changes in tumour size, overall radiological response can be determined. We found a good concordance between radiologically detected tumor necrosis and histological evaluation of tumor response. The optimal time of surgery after ILP is not yet determined. Since radiological response was seen as early as 6 weeks, this could suggest that limb-sparing surgery could effectively be performed as early as 6 to 10 weeks after ILP. These results should be evaluated in further studies.

Reference Eggermont AM, de Wilt JH, ten Hagen TL. Lancet Oncol. 2003; 4: 429-37.

L29 Quality assessment of adjuvant radiotherapy for extremity and trunk wall sarcoma. 2006 patients from the Scandinavian Sarcoma Group Register

N. Jebsen, C. Trovik, O. Monge

Centre for Bone and Soft Tissue Tumours, Haukeland University Hospital, Bergen, Norway
email: njeb@haukeland.no

Introduction In Scandinavia a wide surgical margin without radiotherapy was traditionally considered adequate in soft tissue sarcoma (STS) treatment. There are several reports on equal local control rates after less extensive surgery combined with radiotherapy. Consequently the use of radiotherapy has increased in recent years. In 1998 adjuvant radiotherapy was recommended (SSG XIII) for inadequate margins regardless of tumor depth, and for deep extramuscular, high-grade sarcoma regardless of margin or size. We have evaluated the implementation of these treatment recommendations and their impact on local control.

Patients and methods 2006 patients with extremity STS reported to the SSG Register in the period 1986–2001 and a minimum follow up of 2 years, were stratified in three groups: diagnosis in 1986–91, 1992–97, and 1998–2001. The use of adjuvant radiotherapy relative to surgical margin, average time between surgery and radiotherapy and local recurrence rates were analyzed. Median follow-up was 3.3 years in the 1998–2001 group.

Results Use of adjuvant radiotherapy increased from 23% to 35%. Median time from last surgery to start of radiotherapy was 44 days and did not change. Observed local recurrence rate rates significantly improved from 20% to 7%, without improvement of surgical margins.

Conclusion There has been better compliance with SSG radiotherapy guidelines in recent years. This may be an important reason for better local control rates. However, several parameters concerning the quality of radiotherapy are not reported to the SSG Register, i.e. methods of fixation, conformal vs. non-conformal techniques, principles for definition of clinical target volume, field margins and quality control routines during treatment. Further studies on the impact of these parameters on treatment results and side effects are needed.

L30 Neoadjuvant regional hyperthermia, chemotherapy and radiotherapy for high risk soft tissue sarcoma

N. Jebsen[1], B.C. Schem[2], C. Trovik[1], H.E. Oulie[1], J. Eide[1], O. Monge[1]

[1]Centre for Bone and Soft Tissue Tumours, [2]Bergen Hyperthermia Oncology Group, Haukeland University Hospital, Bergen, Norway
email: njeb@haukeland.no

Introduction We report experience with regional hyperthermia to enhance the effect of chemotherapy and radiotherapy in 16 patients with high risk sarcoma.

Patients and methods Chemotherapy with etoposide, ifosfamide and doxorubicin (EIA) was given concomitantly with regional hyperthermia in 3 groups of patients with high risk extracompartmental sarcoma of the extremities, pelvis, retroperitoneum and trunk wall: 4 patients were treated according to a pilot protocol. 7 of 14 patients were randomized to receive regional hyperthermia in addition to chemotherapy in a phase III study. 5 patients with locally advanced tumors, recurrences or a solitary or dominating metastasis, were also treated, 2 of these received thermoradiotherapy. Hyperthermia was given with BSD Sigma applicators using invasive thermometry, aiming at > 42ºC in the tumor for 60 min. Mean age was 48 (18–67) years. The mean tumor size was 15 (5–29) cm.

Results 12 of the 16 patients were resected. Total or subtotal necrosis was found in 10 of the specimens. Local recurrence was seen in 1 patient. Median observation time was 15 (2–109) months. 1 patient had heat induced soft tissue necrosis with minor functional deficit. 2 patients had mild neuropathy after heat treatment. All patients had symptom relief. We did not observe enhanced toxicity of neither the chemotherapy nor the radiotherapy.

Conclusion The combination of chemotherapy and radiotherapy with regional hyperthermia was feasible in patients with locally advanced high risk sarcoma. There is a group of patients with high risk sarcoma of the proximal thigh, pelvis and trunk wall that is not suited for the current protocols with neoadjuvant isolated limb perfusion or (thermo) chemotherapy. There is a potential for a phase II protocol for neoadjuvant “trimodality treatment” (chemotherapy, radiotherapy and regional hyperthermia) in this subgroup of patients with poorly resectable primary or recurrent (very) high risk tumours.

L31 Quality of life and long-term morbidity in bone sarcoma patients – current status. A SSG project

L.H. Aksnes[1], N.L. Jebsen[2], H.C.F. Bauer[3], S.D. Fosså[4], K. Sundby Hall[1]

Depts of Oncology, [1]The Norwegian Radium Hospital, Oslo, [2]Haukeland University Hospital, Bergen, Norway, [3]Dept of Orthopedics, The Karolinska Hospital, Stockholm, Sweden, [4]Dept of Clinical Cancer Research, The Norwegian Radium Hospital, Oslo, Norway
email: livak@klinmed.uio.no

Introduction The aim of this study is to evaluate functional outcome, long-time morbidity and quality of life (QoL) in 120 Swedish and Norwegian patients treated for extremity localized Ewing's sarcoma or osteosarcoma.

Methods The function is evaluated according to Enneking's system and Toronto Extremity Salvage Score (TESS). Long-term morbidity is investigated by objective means and questionnaires. QoL is measured by SF-36, HADS, IES and fatigue questionnaire in addition to demographic data. SF-36 and HADS responses are compared to age and gender adjusted data from The Survey of Level of Living in Norway 1998 and the Health Study of Nord-Trøndelag county, Norway (HUNT-2).

Results 51 (28 men) of 68 invited Norwegian patients agreed to participate and 43 have been examined. The median age at follow-up was 31 years and median time since diagnosis was 13 years. Limb sparing surgery was done in 29. Median Enneking score was 75% (20–100) and median TESS was 90% (43–100) with no significant difference between amputation and limb sparing.

3 patients had developed heart failure and 1 renal failure. Other comorbidities were hypertension, pericarditis, diabetes, reflux, and hyperthyroidism. Audiogram showed bilateral hearing loss (> 20dB at 4000Hz) in 15 patients.
26 were living with a partner. 15 patients have become parents. 26 had completed a college- or university degree. 28 were working full time. All had a lower score in the Physical health components of SF-36 compared to the normal group. The mental health components and mean level of anxiety and depression were not different from the normal group. Even so, one third of the women and one fifth of the men had increased anxiety score and increased depression score were seen in 1 woman and in 31 men. 2 men were receiving psychiatric treatment.

Final analysis will be performed when investigation of all patients has been completed.

L32 Italian Sarcoma Group (ISG

P. Picci

Rizzoli Orthopedic Institute, Bologna, Italy
email: piero.picci@ior.it

The Italian Sarcoma group, activated in 1997, was constituted 2002 and now includes 172 members, representing 53 centers. ISG includes specialist panels and multispecialist committees and collaborates with major national study groups and international societies (CTOS, EMSOS, MSTS, APMSTS). The main aim is to improve sarcoma treatment by working groups which compile Diagnostic, Therapeutic, and Research Protocols. From 1997 to 2003 annual meetings were held, two of them together with the Scandinavian Sarcoma Group.

The major activity is based on clinical protocols: For Osteosarcoma, the protocols ISG/SSG I (localized) and ISG/SSG II (metastatic) are already closed with satisfaction. The current ISG/OS I (opened in April 2001) already includes 122 patients. The EUROBOSS (over 40 years of age) - in collaboration with SSG, COSS and EOI - was activated in December 2002, as well as a protocol for Italian relapsed patients.

For Ewing's sarcoma, the protocols ISG/SSG III (standard risk) and IV (high risk), both activated in June 1999, already include more than 180 and 50 patients, respectively. In December 2002 the very high risk patient and the relapsed patient protocols were activated on a national base.

For adult soft tissue sarcoma several protocols are ongoing, including the neoadjuvant one for high risk localized patients (in collaboration with the Spanish Sarcoma Group), and others, specific for advanced diseases or for specific entities. ISG is involved in Imatinib studies.

L33 Cooperative sarcoma study group activities: COSS

S.S. Bielack

Dept of Pediatric Hematology and Oncology, University Children's Hospital Muenster, Muenster, Germany
email: coss@uni-muenster.de

History COSS has run prospective osteosarcoma trials since 1977.
Organization: COSS registers patients with osteosarcomas or related bone cancers. The group assists with individual therapeutic decisions.

Studies Randomized studies were performed for patients with localized extremity osteosarcomas. Examples of findings: Response to preoperative chemotherapy is important (COSS-80); negative prognostic implications of poor response persist after aggressive post-operative salvage (COSS-82); intraarterial is not superior to intravenous cisplatin (COSS-86); continuous infusions of doxorubicin and cisplatin reduce toxicity without loss of efficacy (COSS-91/-86C); chemotherapy should not be abbreviated even in prognostically favorable situations (COSS-96). The recruitment of a wide variety of bone sarcomas, almost population based recruitment and long-term follow-up allows COSS to address questions about osteosarcoma in general and about rare subgroups. Examples of publications include analyses of prognostic factors for high-grade, for primary metastatic, for axial, and for secondary osteosarcoma, and for outcome after relapse.

Plans Together with SSG and others, COSS is developing a European-American Osteosarcoma Study (EURAMOS). Another projects with SSG and the Italian Sarcoma Group target older patients (EURO-B.O.S.S.) or relapsed osteosarcomas (EURELOS). Like others, COSS has to deal with ever increasing regulatory demands, which complicate the implementation of investigator initiated clinical trials.

L34 The EORTC Soft Tissue and Bone Sarcoma Group (STBSG)

O.S. Nielsen[1], J.Y. Blay, P. Hogendoorn, P. Hohenberger, A.T. van Oosterom, M. van Glabbeke, I.R. Judson

[1]Dept of Oncology, Aarhus University Hospital, Aarhus, Denmark
email: osnie@akh.aaa.dk

Historic background The EORTC STBSG was founded in 1976. The founding members came from Italy, France, Germany, Belgium, Switzerland, UK and the Netherlands.

Organization The objectives were to develop, stimulate and co-ordinate studies on all aspects of the treatment of soft tissue sarcomas (STS) as well as to organize congresses, symposia and conferences to promote these studies. The Group has developed strict quality control procedures and played a major role in the development of the RECIST criteria. The quality assurance program involves a strict membership policy, central review of responses, central review of pathology, use of a systemic therapy checklist and on site monitoring visits. Today the STBSG has members from 40 institutions from 13 countries.

Types of studies The activities have primarily been within the areas of standards for local and systemic treatment strategies especially in advanced STS. So far, more than 45 clinical trials have been conducted and more than 200 pts per year have been included. A unique database with over 2500 patients has been developed and based on this a number of important studies have been published on prognostic factors, long term survivors and new response criteria. Several new drugs have been tested in STS but doxorubicin and ifosfamide are still the most effective agents. Other drugs with some first line activity are dacarbazine, caelyx and possibly ET743. Imatinib is very effective in GIST where it is now the treatment of choice – a development in which the group has played an important role. Several phase 3 trials have also been performed on both single agent and combination chemotherapy. The group has also participated in an osteosarcoma intergroup study. Recently a phase 3 study on adjuvant doxorubicin and ifosfamide in STS has been closed and awaits further analysis. Presently the group is performing studies on caelyx + ifosfamide, high dose ifosfamide + doxorubicin, hyperthermia, exatecan, brostallicin, and gefitinib (Iressa). The group also participates in the EE99 study of Ewing's/PNET. Finally studies on translational research have been initiated, including a study of the molecular biology of GISTs.

Intergroup co-operations An increasing number of studies have recently been performed in collaboration with other groups such as SWOG, ECOG, NCIC, AGITG, FSG, ISG and SSG.

L35 Cooperative sarcoma study group activities: The Spanish experience

A. Patiño[1], M. San Julián[2], F. Lecanda[3], N. Ibargoyen[1], L. Sierrasesúmaga[1]

Depts of [1]Pediatrics, [2]Orthopedics, [3]Center of Applied Medical Research, University of Navarra, Pamplona, Spain
email: msjulian@unav.es

Organization There are currently 3 cooperative groups: GEIS (Grupo de Estudio de Sarcomas, composed by adults oncologists), GRETAL (Grupo de Estudio de los Tumores del Aparato Locomotor, composed by orthopedic surgeons) and SEOP (Sociedad Española de Ocología Pediátrica, composed by Pediatric Oncologists)

The groups have worked on surgical and non-surgical protocols, both randomized and non-randomized studies, prospective and retrospective studies, with european and american colleagues. In the field of molecular biology there have been also very interesting co-operative studies, such as that relating type of transcript and prognosis in Ewing sarcoma. (University of Navarra and Memorial Sloan-Kettering, NYC). Spanish Groups have also a special relationship with South American groups, and thus the possibilities of cooperative studies with such countries are developed.

Some ongoing studies are: risk factors, comparison of several chemotherapic regimens in STS, genetic instability induced by the antitumoral regimens; carcinogenesis of pediatric osteosarcoma and Ewing sarcoma; gene by gene approach; development of a metastasis model and a tissue-array for osteosarcoma.

The need for intergroup cooperations is clear, since the incidence of these diseases is extremely low. Some of these current projects will be exposed. Partners are very welcome.

L36 The French Sarcoma Group

J.Y. Blay

Dept of Oncology, Lyon, France
email: blay@lyon.fnclcc.fr

The French Sarcoma Group is an independent Group of french speaking physicians and researchers involved in Sarcoma research including 37 centers and more than 120 members as of January 2004. The FSG includes members from University Hospitals and anti Cancer Centers in France and Switzerland. Its goals are to improve the clinical management of sarcoma in French speaking countries, and to develop clinical research.

The data center for clinical studies is hosted by the French Federation of Cancer Centers, although some clinical and research studies are sponsored by hospitals on behalf of the FSG. 7 studies are currently ongoing and 5 are scheduled to be activated within the group or through an intergroup setting with EORTC SBSG in 2004. The principal are:

(PALSAR II ou PAC II) : A randomized phase III trial of first line chemotherapy testing HDCT as consolidation treatment in advanced STS
Coordonnateur: Binh Bui, Institut Bergonié, and Jean Yves Blay , E Herriot

EuroEwing Coordonnateur principal : Odile Oberlin, Institut Gustave Roussy.

A phase II pilot study of the API AI regimen in localized osteosarcomas aged 18 or more.
Coordonnateur: Axel Le Cesne, Institut Gustave Roussy.

Continuation vs interruption of Imatinib (Glivec®) treatment in GIST patients with advanced disease: a prospective randomized phase III trial of the French Sarcoma Group.
Coordonnateur: Jean Yves Blay, E Herriot.

L37 The British Sarcoma Group

M. Robinson

Cancer Research Centre, Sheffield, U.K.
email: m.h.robinson@sheffield.ac.uk

The British Sarcoma Group as such does not yet exist – it is being formed next week! We aim to try and emulate in a very short time the achievements of the past 21 years of the SSG! Despite this lack of a central group the UK has been active in sarcoma research for many years, through the MRC and the EOI osteosarcoma studies, the UKCCSG Ewing studies and through collaboration in EORTC soft tissue sarcoma studies.

The organization of cancer research in the UK has changed and there is now a group called the National Cancer Research Institute which is funded by all of the main grant givers for cancer research (CRUK, Welcome and MRC) with the aim of increasing accrual to cancer trials and preventing repetition of studies as well as encouraging new studies and trying to incorporate translational research. There are 15 groups with sarcomas being one. Any national trial has to be approved by this group and the studies are then rolled out across the country – if they reach a rigorous standard for funding. Current studies are:

Euroewing, EORTC STS**, EORTC radiotherapy for inoperable fibromatosis study

Planned studies include: EURAMOS, SOFI – a planned follow up study, Studies for other bone sarcomas

Under the guidance of the cancer tsar there have been numerous improvements including guidance for early diagnosis, a guaranteed two week wait for anyone with suspected cancer, the establishment of cancer centres and cancer units and the centralization of care. Evidence based guidelines are being produced and a national minimum cancer dataset to complement the existing cancer Intelligence Units. The British Sarcoma Group will arrive in order to take advantage of these initiatives and hopes in one year to emulate our Nordic colleagues!!