The 33rd Meeting of the Scandinavian Sarcoma Group

Bergen
Radisson SAS Royal Hotel

May 8–11, 2007

Abstracts

L1 The epidemiology and prognosis of chondrosarcomas in the appendicular skeleton

F. Frihagen and A. Walløe

Dept. of Orthopedic Surgery, Ulleval University Hospital, Oslo, Norway

Introduction: This study was based on chondrosarcomas reported to the Scandinavian Sarcoma Group (SSG) Register from 1986 through 2000.

Patients and methods: The 199 patients with reported follow up of tumors located to the appendicular skeleton were selected for further analysis. Median follow up was 67 months (range 0.5–239).

Anatomical location	**Frequency, n (%)**	**Follow up available, n (%)**
Appendicular sceleton	230 (47)	199 (87)
Long bones	*207(41)*	*182 (88)*
Femur	*110 (22)*	*99 (90)*
Humerus	*55 (11)*	*47 (85)*
Tibia	*25 (5)*	*23 (92)*
Other	*19 (4)*	*13 (68)*
Foot/hand/patella	*22 (4)*	*17(77)*
Central	266 (53)	222 (83)
Not reported	4 (1)	4 (1)
Total	**500 (100%)**	**425 (85%)**

Results: There were 94 (52%) men. The mean age at diagnosis was 52 (14–93) years. 2/3 of the tumors were graded low malignant (62 (31%) grade 1 and 69 (35%) grade 2), and 1/3 were high malignant (36 (18%) grade 3 and 31 (16%) grade 4). 159 (80%) were operated with local excision and 27 (14%) with amputation. 17 patients (9 femur, 4 tibia, 4 humerus) were operated with intralesional margin and cementation. 9 had malignancy grade 1, and 8 had malignancy grade 2. There were 2 local recurrences in this group. 27 patients in total (14%) had a local recurrence (6 grade 1, 8 grade 2, and 6 of grade 3 and 4 each) after median 18 (4–113) months. 48 patients had metastatic disease, mainly to the lungs (36 (84%)). Of the total of 48 patients with metastasis 5 had malignancy grade 1, 13 had grade 2, 14 had grade 3 and 16 had grade 4. At last follow up 80 patients were dead. 112 had no evidence of disease and 7 had

recurrence/persistent disease. The deaths occurred median 26 (0–207) months after diagnosis. In 40 cases (50%) the chondrosarcoma was stated to be the cause of death, 33 of them had metastatic disease. None of the patients with malignancy grade 1 were reported as dead because of their tumor. The one year mortality from the chondrosarcoma was 8 % (16 patients) and the 5 year mortality was 18 % (36 patients).

Conclusion: It may be safe to treat chondrosarcomas of the appendicular skeleton with malignancy grade 1 with local curettage with or without cementation while maintaining an acceptable level of recurrences. Patients with multiple cartilaginous exostosis seem to have a low risk of developing chondrosarcoma before the age of 14 years.

L2 A classification system and surgical strategy for sacral tumor

W. Guo, X. Tang, Y. Yang and T. Ji

Musculoskeletal Tumor Center, People's Hospital, Peking University, Beijing, China

Objective: Retrospective study of outcome of different surgical procedures for sacral tumor based on the location and the size.

Methods: Between 1997 to July 2006, 251 (mean age 45 (8–83) years, 127 females) patients with sacral tumors were treated in People's Hospital of Peking University. These included 52 chordomas, 28 giant cell tumors, 20 neurofibromas, 2 neurofibrosarcomas, 8 neurilemmomas, 7 malignant neurilemmomas, 43 metastatic carcinomas,10 myelomas, 5 osteoblastomas, 7 aneurysmal bone cysts,6 osteosarcomas, 12 chondrosarcomas, 7 Ewing sarcomas/PNETs, 4 malignant fibrous histiocytomas,6 lymphomas, 9 teratomas, 3 liposarcomas, 3 osteochondroma and 17 other rare tumors. The disc between S2 and S3 divided sacrum in an upper (I) and a lower (II) area. A tumor involved lumber was classified as III. In area I , around the central spinal cannel, we named vertebral body as the "a" area, posterior elements as "c" area, and iliosacral joint as "b" area. According to the site of the tumor location, the tumor location was classified into 15 regions: 16 patients with tumor located at region Ia, 22 at region Iab, 28 at region Iabc, 9 at region Iabbc, 7 at region Ia II, 10 at region Iab II, 56 at region Iabc II, 45 at region Iabbc II, 1 at region Iab III, 9 at region Iabc III, 3 at region Iabbc III, 12 at region Iabc II III, 10 at region Iabbc II III and 23 at region II.

Results: Complications: 3 patients died of complications to surgery. 1 of them died of postoperative infection; 1 of hemorrhagic shock; and 1 because of MOFS. 47 patients had wound healing problems. 25 patients had temporary leakage of cerebrospinal fluid. 3 patients had rectal fistulas.

Oncological results: 5 of the 6 patients with osteosarcoma died. The 7 patients with Ewing sarcoma/PNETs recurred and none survived. Among the 12 patients with chondrosarcomas, 9 patients were followed up, 7 patients had local recurrence and 7 patients died, 2 survived without diseases. Patients with GCTs achieved intralesional excision for the complex anatomic location, but the local recurrence was still only 37 %. 2 of the patients with neurofibromas recurred. 8 of the 52 patients with chordomas died, 3 of metastatic tumor; 5 died of MOFS; 28 patients

survived without disease. the other 16 all recurred once or repeatedly. 10 patients with myelomas and 6 with lymphomas had chemotherapy before and after surgery and no local recurrence was observed.

Conclusion: Although it may give sacral nerve deficit , excision with a wide surgical marginal is the best procedure because of its minimal recurrence rate. Sometimes also in the upper area (S1–S2) a posterior-approach could be chosen for successful excision of the tumor.

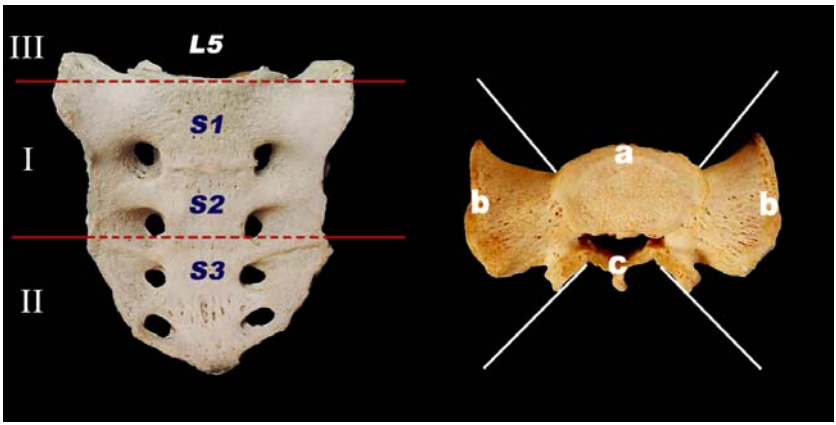


Fig. The figures shows the classification system for sacral tumor.

L3 Reconstruction with modular hemipelvic prostheses for periacetabular tumor

W. Guo, D. Li, X. Tang, Y. Yang and T. Ji

Musculoskeletal Tumor Center, People's Hospital, Peking University, Beijing, China

Introduction: Periacetabular resections for primary bone sarcoma and metastatic disease require reconstruction to restore weightbearing along anatomic axes. We designed a modular hemipelvic prosthetic system to reconstruct the pelvis and assessed earlu clinical outcome

Patints and methods: We retrospectively reviewed 28 patients who had pelvic tumor resections and reconstructions using the new hemipelvic prostheses between 2001 and 2005. 16 patients had Types II and III (periacetabular and pubis) pelvic resection, 7 had Types I and II (periacetabular and ilium) pelvic resection, and 5 had Type II (periacetabular) pelvic resection. 6 patients with osteosarcoma had chemotherapy. None received radiation therapy.

Results: Patient survival, function, and complications were evaluated at a mean follow up of 30 (10–59) months. 15 patients were free of disease, 8 patients died of disease, and 5 patients were alive with disease. The overall survival rate was 67.% at 3 years. 7 patients had local recurrence and 6 had metastasis. The mean Musculoskeletal Tumor Society score was 60. Deep infection occurred in 4 patients; dislocation occurred in 1 patient.

Conclusion: The results are encouraging because of the acceptable complication rate and satisfying functional outcome.

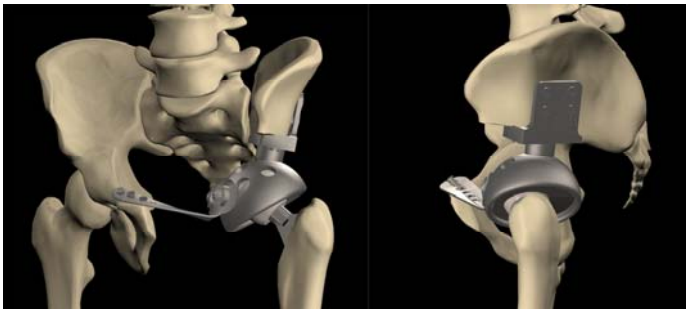


Fig 1. Front and side views of a three-dimensional model of the modular hemipelvic prosthetic design are shown.

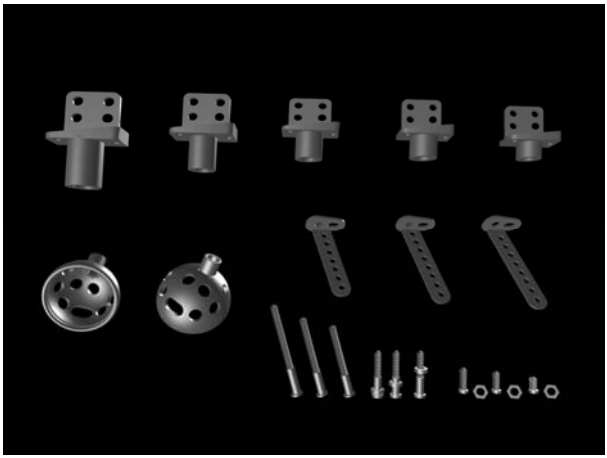


Fig 2. Components of a typical prosthesis. The set typically consists of 3 components: iliac fixation components with variable length bush, acetabular component, and pubic connection plate. All of the components are made of titanium.

L4 Type-B-IIIa rotationplasty – a case report

P. Høvding, C. Trovik and M. Nottrott

Haukeland University Hospital, Dept. of Orthopedic Surgery, Bergen, Norway

Intoduction: Professor Winkelmann at the University of Münster presented in 2000, 8 patients with reconstruction of some hipjoint function by a special variant of rotationplasty.

Material: Our patient is a 9-year old girl with intermittant pain in her right thigh for about 3–4 months. Radiological examination revealed a large Ewing sarcoma involving the upper 2/3 of the femur. In addition CT scan showed 3 nodules, less than 4 mm in her lungs. Diagnosis was established by fine-needle aspitation cytology and an [11:22] translocation was confirmed by PCR-technique.

Method: The patient was treated according to ISG/SGG III. Because of tumors extent and location a type-B-IIIa rotationplasty was preferred after interinstitutional, web based discussion among Scandinavian sarcoma surgeons. This procedure offers the possibility to reconstruct the hip joint without implant of foreign material.

Results: This is the third patient reconstructed with this type of rotationplasty in Scandinavia. It seems to be a good alternative to amputation or expandible tumor prosthesis in this patient category. Except a minor soft tissue necrosis there were no complications to the surgery, and function after 6 months seems excellent. Video of early gait control will be presented.

L5 Reconstruction for periacetabular bone metastasis. A prospective study from The Scandinavian Sarcoma Group Metastasis Registry.

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

[1]Dept. of Orthopedic Surgery, University Hospital, Aarhus, Denmark, [2]Dept. of Orthopedic Surgery, University Hospital, Tampere, Finland, [3]Dept. of Orthopedic Surgery, Sahlgren University Hospital, Gothenburg, Sweden,[4]Dept. of Orthopedic Surgery, Norwegian Rikshospitalet-Radiumhospitalet, Montebello, Oslo, Norway, [5]Dept. of Orthopedic Surgery, Haukeland University Hospital, Bergen, Norway, [6]Dept. of Orthopedic Surgery, Lund University Hospital, Lund, Sweden, [7]Dept. of Orthopedic Surgery, Ulleval Hospital, Oslo, Norway, [8]Dept. of Orthopedic Surgery, University Hospital, Linköping Sweden, [9]Dept. of Orthopedic Surgery, Karolinska University Hospital, Stockholm, Sweden.

Introduction: Treatment of periacetabular metastasis is complex. Proper patient selection and surgical planning is necessary to reduce the rate of complications and reconstructive failures.

Patients and Methods: We analyzed survival, function, pain, and complications in 41 women and 31 men (mean age 64 yr) treated with acetabular reconstruction combined with total hip replacement. Acetabular shell and Harrington methods were used for reconstruction. Carcinoma of the breast, prostate, kidney, and myeloma were the dominating primary tumors.

Results: The 1-year survival rate was 0.3. 6 patients died within the first 6 weeks and 25 patients lived more than 2 years after operation. Preoperative half o the patients were walking with or without crutches compared to two thirds of the surviving patients at 6 weeks and three forths at 6 months after operation. Preoperative two thirds had severe pain from the metastasis compared to 5 % and 6 % at 6 weeks and 6 months after operation. Preoperatively half of the patients used opioids compared to one fifth at 6 weeks an 3 % at 6 months. One fifth had complications, mainly dislocations. 6 % were reoperated because of failure.

Discussion: Surgical acetabular reconstruction for bone metastasis in carefully selected patients can improve quality of life by reducing pain and improving mobility. Major reconstructions should be chosen in patients with suspected long time survival.

L6 Status of Euramos-1; a pan-European/American Osteosarcoma Study

S. Smeland[1], O. Steen Nielsen[2], M. Eriksson[3], M. Tarkannen[4] and T. Böhling[5]

[1] Norwegian Rikshospitalet-Radiumhospitalet, Montebello, Oslo, Norway, [2]Aarhus University Hosptial, Aarhus, Denmark, [3]Lund University Hospital, Lund, Sweden, [4]Helsinki University Central Hospital, Helsinki, Finland, [5]University of Helsinki and HUSLAB, Helsinki Hospital, Finland

Background: The outcome for osteosarcoma patients have reached a plateau following the introduction of multi-agent chemotherapy. 4 multinational groups (COG, COSS, EOI, SSG) representing 14 countries in Europe and Northern America collaborate in EURAMOS to optimize treatment of osteosarcoma. Following a number of regulatory hurdles the Euramos-1 study opened to accrual in April 2005.

Methods: Eligibility criteria included patients with resectable osteosarcoma and age $\leq$40 years. Standard therapy includes 29 weeks of cisplatin, doxorubicin and high-dose methotrexate (MAP). Post-operative therapy is dependent on histological response. Good histological responders (<10 % viable cells) are randomized to continuing MAP or MAP + pegylated interferon. Poor histological responders are randomly assigned to MAP or MAP plus ifosfamide and etoposide.

Results: As of February 2007 468 patients have been enrolled (209 COG, 134 COSS, 100 EOI, 25 SSG). 12 (48 %) of the SSG patients have non-classical osteosarcoma (primary metastatic and/or axial localization). 236 patients have been randomized including 131 good responders (67 MAP) and 105 poor responders (54 MAP). In Scandinavia 12 patients have been randomized; 5 good and 7 poor responders.

Conclusions: The inclusion rate is on target and demonstrates the rapid accrual of patients made possible with Euramos. Although the implementation has been difficult and time consuming, the effort with extensive international collaboration is worthwhile for patients with rare malignancies like osteosarcoma.

L7 Euroboss; A prospective European study on high-grade sarcoma of bone

S. Smeland[1], M. Eriksson[2], O. Monge[3], K. Sundby Hall[1], H. Bauer[4]

[1] Norwegian Rikshospitalet-Radiumhospitalet, Montebello, Oslo, Norway, [2]Lund University Hospital, Lund, Sweden, [3]Haukeland University Hospital, Bergen, Norway, [4]Karolinska University Hospital, Stockholm, Sweden

Background: Bone sarcoma in patients above 40 years of age is very rare. Three European sarcoma study groups; Scandinavian Sarcoma Group, Italian Sarcoma Group and Cooperative Osteosarcoma Study Group joined to launch Euroboss, the first international prospective study in this group of patients.

Methods: Eligible to Euroboss are patients aged 41–65 years with osteosarcoma and other spindle cell sarcomas of bone. Patients with chondrosarcoma and small round cell tumours are ineligible. Patients receive neo-adjuvant or adjuvant chemotherapy with a combination of doxorubicin, cisplatinum and ifosfamide. Poor responders are salvaged with additional methotrexate ($8g/m^2$). Poor histologic response is defined as Huvos grade I, percentage necrosis $\leq$50 % or Salzer-Kuntschik grade 5 or 6.

Results: Euroboss was opened Dec 2002. By Dec 2006 121 patients including 19 with metastases at diagnosis are recruited. Three main groups of patients are identified; osteosarcoma (n=62), dedifferentiated chondrosarcoma (n=17) and others (n=42). 50 % of the patients have experienced delay in chemotherapy administration and 18 % a dose reduction. No toxic deaths are recorded. 65% of assessable patients have obtained a good histologic response to chemotherapy. 29 SSG patients are recruited from five centers in Sweden and Norway. Six patients are in CR 1 12 months or more from diagnosis and twelve patients are dead of disease.

Conclusion: The planned intensive chemotherapy is feasible and no toxic deaths are reported. The planned recruitment is accomplished but to better analyze specific aspects and characteristics on histologic subtypes and subgroups the study should continue for a three-year period to end 2009.

L8 Treatment of Ewing tumors: Future collaboration for SSG

S. Smeland

Norwegian Rikshospitalet-Radiumhospitalet, Montebello, Oslo, Norway

Background: Standard management of Ewing Tumors (ET) includes poly-agent chemotherapy in combination with surgery and/or radiotherapy. However, the optimal combination of the drugs and the place of high-dose chemotherapy need to be explored. In the current European Intergroup protocols (ISGSSG III/IV and Euro Ewing 99) these questions are addressed. In 1999 SSG together with the Italian sarcoma group (ISG) opened the ISG III and IV protocols for localised and metastatic ET. The Swedish pediatric society later decided to join the randomized (EE99). The current protocols are all planned to be closed this year and new studies are to be launced in 2008.

Results of ongoing studies: The results of the ISGSSG III protocol will be reported at the upcoming ASCO meeting. Briefly, in a non-randomized trial including close to 300 patients the overall results are promising and especially the strategy to boost poor responders with high-dose chemotherapy is a success resulting in similar outcome for good and poor responders. For the 56 SSG patients the 3-year event-free survival is 87 % ± 12 %. For EE99 no results from the randomised arms are available. The percentage of good responders has been higher than expected resulting in an unbalanced recruitment to the R1 and R2 arms. Thus, the R2 arm testing in a randomised design HDCT to poor responders and patients with primary lung-metastatic disease will continue for several years. For patients with disseminated disease included in the R3 arm, subgroups of patients (small tumors and <5 bone mets) responding to induction therapy seem to benefit from HDCT

Design of future protocols: Major improvement in survival of ET patients is unlikely without introduction of novel drugs and/or treatment principles. A targeted drug for ET is not in pipeline and will not be incorporated in the next protocols. The next ISG(SSG) protocol is based on the results of the ongoing trials and consider HDCT standard for poor responding patients. Approximately 50 % of the patients in ISGSSG III achieved good response to induction therapy. In an attempt to increase the number of good responders and by that reduce patients exposed to HDCT, patients are randomized up-front to receive either standard or intensified induction therapy. The primary endpoint will be percentage of good responders. In the EE08 study maintenance therapy is introduced for R1 patients and a

randomized element in the R3 arm. The rationale for maintenance therapy is that even in the low risk R1 arm 30 % experience relapse and 80 % of these occur within 2y from diagnosis. R1 patients are randomized to receive maintenance treatment during 6 months with bisphosphonates and/or fenretinide. Before including fenretinide to the trial a phase II has to be conducted, starting fall 2007. Randomized allocation of fenretinde will be opened as soon as the trial is completed (expected 2009). Patients with disseminated disease will be randomized to standard treatment or HDCT with treosulfan to replace busulfan. The main advantage of treosulfan is that in contrast to busulfan radiotherapy to axial sited tumors is compatible. The EE 2008 is expected to recruit patients for up to 7.5 years (2015).

Discussion: SSG has to decide strategy for the next ET studies. The experience with the ongoing collaboration with ISG is good including excellent treatment results and major scientific contributions to the sarcoma community. The planned study is straight-forward and feasible with an up-front randomized design and known drugs, but lacks innovative elements. The EE08 includes randomized questions for all groups of patients. The obvious weaknesses are both the rationale and the limited clinical data supporting bisphosphonates and fenretinide as maintenance therapy. It is possible for SSG to continue with a split-strategy, but there are obvious advantages to collaborate with one part; standard pathology assessment and chemotherapy administration and one administrative work-up required to get the study launched and running.

L9 Severe toxicity in a Ewing patient treated according to ISG/SSG III protocol, inclusive of HD-BuM with PBSCS and radiotherapy

K.S. Hall[1], Ø.S. Bruland[1], H. Holte[1], O. Norum[4], B. Bjerkehagen[2], I. Taksdal[3] and J.P. Poulsen[1]

Cancer Clinic[1], Dept. of Pathology[2], Dept. of Radiology[3], Dept. of Orthopedic Surgery[4], Norwegian Rikshospitalet-Radiumhospitalet, Montebello, Oslo, Norway

A 25-year-old man was admitted to our hospital in May 05 with a large retroperitoneal soft tissue tumor (12 x 12 x 11 cm) in the left ileopsoas region. Core biopsy showed Ewing sarcoma, confirmed by the presence of EWS-FL11/EWS-ERG fusion transcript. The patient was eligible for the ISG/SSG III protocol.

Chemotherapy: The total 8 chemotherapy cycles consisted of: vincristin 12 mg/m^2, doxorubicin 320 mg/m^2, cyclophosfamide 8800 mg/m^2, ifosfamide 27 g/m^2 and etoposide 1500 mg/m^2. In spite of parenteral nutrition (TPN) during most of the treatment period, the patient lost 10 kg due to nausea, vomiting and diarrhoea.

Surgery: The tumor was resected after 4 cycles.with a marginal surgical margin. The histopathological response was “poor” (Picci grade I).

HD-BuM: He was further treated with 4 scheduled chemotherapy cycles and HD-BuM with PBSCS. The post-transplant course was complicated with diarrhoea. Clostridium difficile toxin test was positive on day +8, requiring metronidazole treatment.

Hyperfractionated radiotherapy: 1,5 Gy x 2/day x 15 = 45 Gy, 5 fields technique towards the tumor bed, was started about 6 weeks after HD-BuM. Slight nausea and abdominal pain occurred during radiotherapy.

Post treatment: During the following months he developed abdominal pain, diarrhoea, vomiting and serious electrolyte disturbances and lost 20 kg of weight 6 months after radiotherapy upper endoscopy revealed gastric and duodenal ulcers. Rapid clinical deterioration with a large bowl perforation, lead to emergency total colectomy follwed by septicemia. Histopathology revealed ulcerations and necrotic areas in the mucosa. He was treated with antibiotics, TPN, H2-blockers and enteral nutrition through a permanent gastric tube. During the next 3 months the general condition improved slowly, gastroscopy showed normalization of the

mucosa, and he almost regained body weight. Hypothyroidism have in addition now been diagnosed

Conclusion: In this patient severe toxicity probably occurred due to the very intensive multimodal treatment. Patients undergoing radiotherapy to an abdominal field after HD-BuM may have a high risk of developing serious gastrointestinal toxicity.

L10 Intensity modulated radiotherapy (IMRT) in bone and soft tissue sarcoma – early experience

O. Monge[1], E. Wasbø[2], H. Valen[2], N. Jebsen[1], D. Goplen[1], H. Oulie[1], H. Haugland[1] and C. Trovik[1]

[1]Centre for Bone and Soft Tissue Tumors, [2]Section of Medical Physics, Dept. of Oncology and Medical Physics, Haukeland University Hospital, Bergen, Norway

Introduction: During recent years we have used intensity modulated radiotherapy (IMRT) in some tumor sites. Based on this experience and a dedicated quality assurance program, we have used IMRT in selected patients with bone and soft tissue sarcoma in which an improvement in radiation dose distribution was achieved with a specific treatment plan for IMRT as compared to conformal treatment without intensity modulation.

Patients and methods: We report early clinical experience of IMRT in 5 patients with bone and soft tissue sarcoma: A 15-year old boy with sinonasal alveolar rhabdomyosarcoma with bilateral regional lymph node metastases of the neck was treated according to the EpSSG RMS protocol. A 37-year old man with locally advanced recurrent high grade chondrosarcoma of the sacrum and iliac bone was given trimodality treatment with IMRT, chemotherapy and regional hyperthermia. A 15-year old boy with extracompartmental synovial sarcoma of soft tissue of the neck treated according to the EpSSG NRSTS protocol was given postoperative IMRT. A 25-year old man with a second solitary metastasis of Ewing sarcoma in the the 5th thoracic vertebra, 10 years after primary treatment, was given IMRT after decompressive surgery and 3rd line chemotherapy. A 25-year old man with locally advanced Ewing sarcoma of the sacrum and a solitary skip lesion of the contralateral iliac bone was given IMRT as part of treatment according to the ISG/SSG IV protocol.

Results: IMRT was feasible in all patients. The treatment plans for IMRT were superior to conformal plans in all cases. The observed acute toxicity was likely to be less than what might be expected with conformal treatment. Hopefully this will translate into reduced late toxicity. All patients were responders to the multidisciplinary treatment offered and are currently NED without late toxicity with a median observation time of 6 months.

Conclusion: IMRT may have an advantage compared to conformal radiotherapy particularly in treatment volumes partially circumscribing critical structures which motivates further studies.

L11 Chemotherapy may induce dental decay in sarcoma patients

S. Afnan[1], O. Monge[2], L. Thorsen[3], K. Størksen[3] and S. Løes[1, 4]

[1]Faculty of Dentistry, University of Bergen, [2]Dept. of Oncology, [3]Dental Clinic, [4]Dept. of Oral and Maxillofacial Surgery, Haukeland University Hospital, Bergen, Norway

Introduction: The influence of intensive chemotherapy on oral health is sparsely studied. Based on clinical observations in younger sarcoma patients we coined a hypothesis that chemotherapy induced oral mucositis might lead to increased dental decay. We performed a small follow up study in sarcoma patients in order to test this hypothesis.

Materials and methods: Patients with a history of neoadjuvant and/or adjuvant chemotherapy for high grade bone or soft tissue sarcoma were invited to have a dental examination as a part of a ordinary follow up visit for their sarcoma. The inclusion criteriae were age less than 40 years at diagnosis of sarcoma, and follow up of more than 1 year after completion of chemotherapy. We examined 12 patients. With the patients consent, information on their previous oral health was collected. During the examination information on the patients current caries and periodontal status were collected. Based on the collected data of previous oral health compared to the current dental status a score of dental decay was calculated.

Results: The mean age was 34 years. There was no influence of age on the dental decay parameter. The mean decay score was 11 (SD 8.9) in patients given high dose methotrexate. In patients not given high dose methotrexate it was 6.2 (SD 4.9). The difference between the 2 groups was not significant.

Conclusion: The calculation of dental decay based on the comparison on current dental status with previously recorded data was feasible. We observed a tendency for accelerated dental decay particularly in patients treated with high dose methotrexate. The influence of chemotherapy on oral health in younger patients with high grade sarcoma might be studied as part of prospective protocols, by which also the influence of intervention might be studied.

L12 Validity and reliability of margin assessment after surgery for extremity soft tissue sarcoma. The SSG experience.

C. Trovik[1], S. Skjeldal[2], H. Bauer[3], A. Rydholm[4] and N. Jebsen[5]

[1] Musculo-skeletal Tumor Center, Haukeland University hospital
[2] Dept. of Orthopedic Surgery, Norwegian Radium Hospital
[3] Tumor service, Dept. of Orthopedic Surgery, Karolinska hospital
[4] Dept. of Orthopedic Surgery, University hospital Lund
[5] Musculo-skeletal Tumor Center, Haukeland University hospital

In Scandinavia, a wide surgical margin without radiotherapy has been considered adequate in localized soft tissue sarcoma (STS) treatment and radiotherapy was reserved for patients after intralesional/marginal surgery.

In 1998 adjuvant radiotherapy was recommended by Scandinavian Sarcoma Group for all deep extramuscular, high-grade sarcomas regardless of margin or size. To be able to evaluate the efficacy of this change of policy regarding rate of local recurrence, the validity of the original assessment of surgical margin was evaluated. 1553 adult patients was surgically treated for STS of the extremities or trunk wall as primary procedures at sarcoma centres in Scandinavia and reported to the SSG-register 1986 to 2005.

After exclusion of liposarcoma grade I, 470 patients were treated at four large institutions 1998–2003. 25 % of these patients were randomly selected for blinded reassement of margins by four sarcoma surgeons. Reports from the operation and the pathology evaluation were available. Original margin assessment in Scandinavia requires a collaboration, most often in person, between surgeon and pathologist.

In 67 % of cases there were universal agreement with the original assessment. In 10 % one reviewer disagreed, in 10 % two reviewers disagreed and in 3 % there were universal disagreement with the margin reported to the register. The disagreement was most frequently found when reassessing marginal/wide margins.

Considered the element of judgement, inherent in margin assement we find this validity and reliability acceptable for using the register for further studies of the importance of radiotherapy for local control.

L13 Regional hyperthermia combined with systemic chemotherapy in the management of locally advanced, high grade soft tissue sarcomas of the extremities, the body wall and the abdomen: Summary report of the phase III randomized prospective trial (EORTC-ESHO Intergroup Trial)

R.D. Issels

Dept. of Internal Medicine III, University Hospital Grosshadern, Ludwig-Maximilians-University and Clinical Cooperation Group Hyperthermia, GSF-National Research Center for Environment and Health, Munich, Germany

For high-risk soft tissue sarcomas (HR-STS) of adults, new treatment strategies are needed to improve outcome with regard to local control and overall survival. Systemic chemotherapy has been integrated either after (adjuvant) or before (neoadjuvant) optimal local treatment by surgery and radiotherapy in HR-STS. The presentation summarizes the results of the combination with regional hyperthermia (RHT) as a treatment strategy to open a new therapeutic window.

Under the auspices of the European Organization for Research and Treatment of Cancer (EORTC) and the European Society of Hyperthermic Oncology (ESHO) we recently completed a randomized Intergroup phase III trial (EORTC 62961/ESHO RHT-95) of multimodal treatment in patients with primary (S1 group) and recurrent (S2 group) disease or after inadequate surgery (S3 group: resections with positive margins or macroscopic residual tumor) in high-risk STS (tumor size $\geq$5 cm + histologic grade of 2 or 3 + deep location + extracompartmental extension). In this trial, all patients with HR-STS received neoadjuvant systemic chemotherapy (four cycles of the EIA regimen) and were randomized in two arms: chemotherapy alone or combined with RHT, followed by definitive surgery and radiotherapy. Thereafter, in addition, four cycles of the EIA regimen were administered with or without RHT according to the initial randomization. The results in terms of overall outcome for extremity and non-extremity STS will be presented.

L14 Trimodality neoadjuvant treatment with chemotherapy, radiotherapy and regional hyperthermia in high risk soft tissue sarcoma – a new protocol

O. Monge, B. Schem[1], N. Jebsen, H. Haugland, H. Oulie and C. Trovik

Centre for Bone and Soft Tissue Tumors, [1]Dept. of Oncology and Medical Physics, Haukeland University Hospital, Bergen, Norway

Introduction: The EORTC-ESHO intergroup phase III trial of neoadjuvant etoposid, ifosfamide and doxorubicin (EIA) versus EIA plus regional hyperthermia in high risk extracompartmental soft tissue sarcoma was closed in December 2006. While waiting for the results of that study there is a need for an interim protocol for these patients. For this reason we have initiated a new pilot protocol for this patient cohort with the aim of improving the treatment principles in the previous phase III protocol. The protocol was approved by the regional ethics committee.

Patients and methods: The inclusion criteriae were: Locally advanced, extracompartmental, high grade soft tissue sarcoma of extremities, pelvis, trunk wall or retroperitoneum with a high risk of intralesional margin or patient mutilation with primary resection. Performance status 0–2. Age $\geq$18 and $\leq$70 years. No organ failure. Written informed consent. Exclusion criteriae: Compartmental sarcoma and small round cell histology. The treatment program involves 3 neoadjuvant treatments of thermo-chemotherapy using ifosfamide and doxorubicin concurrent with regional hyperthermia with a BSD Sigma applicator. The treatments are given on day 1 and 4 of week 1, 4 and 7. The dose of doxorubicin is 35 mg/m^2 and of ifosfamide 3 g/m^2 both days. After response assessment trimodality treatment is started on week 10 with daily fractionated radiotherapy, 3D conformal or intensity modulated according to what is found optimal. The dose spectrum of radiotherapy is from 45 Gy in 25 fractions in operable cases to 68 Gy in inresectable cases. On a weekly basis regional hyperthermia is given concurrent with ifosfamide 2 g/m^2. Resection is planned 4–6 weeks after the neoadjuvant treatment, when feasible. The primary study endpoint is acute toxicity according to CTCAE. The secondary endpoints are tumor resectability rate, amount of tumor necrosis in resection specimens, local progression free survival, overall survival and late toxicity. The number of planned inclusions are up to 14 patients.

Results: 3 patients are included so far, 2 have completed the preoperative treatment without grade 3 or 4 toxicity.

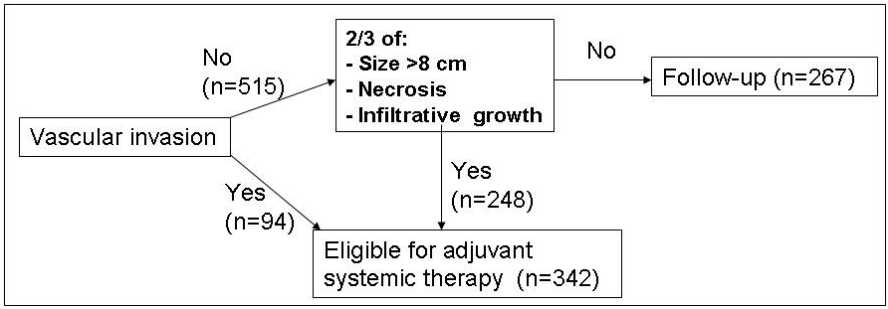
Conclusion: The new pilot protocol was based on our previous experience with the EORTC-ESHO phase III protocol. The treatment program seems feasible. The protocol is open for Scandinavian patients.

L15 Identification of low-risk tumors in histological high-grade STS of the extremities and trunk wall.

J. Engellau[1], V. Samuelsson[2], H. Anderson[3], B. Bjerkehagen[4], P. Rissler[5], K. Sundby Hall[6] and A.Rydholm[7]

[1]Depts. of Oncology, [2]Oncological Center, [3]Cancer Epidemiology, [5]Pathology and [7]Orthopedic Surgery, Lund University Hospital, Sweden, [4]Depts. of Pathology and [6]Oncology Norwegian Rikshospitalet-Radiumhospitalet, Montebello, Oslo, Norway

More than one third of patients with histopatological high-grade malignant soft tissue sarcoma will develop metastasis despite local control of the primary tumor. Hence, adjuvant chemotherapy is increasingly used for this relatively chemoresistent tumor which requires improved prognostication to exclude low-risk (despite having histologic high grade tumors) patients from overtreatment. We assessed the value of step-wise prognostication in a series of 434 histological high-grade STS of the extremity and trunk wall. The presence of intratumoral vascular invasion was used as the first discriminator whereafter the risk factors tumor necrosis, size (>8cm), and infiltrating growth pattern were used to discriminate high- and low-risk tumors. Hereby we identified a high-risk group with a cumulative incidence of metastasis >0.4, and low-risk group, comprising half of the tumors, with a cumulative incidence of metastasis <0.15 at 5 years. We validated this model in an independent series of 175 histological high-grade STS. Compared with other prognostic systems this model improved prognostication in STS which may be of value for identifying patients who probably should not receive adjuvant chemotherapy.



Example of a treatment algorithm for histological high-grade STS of the extremities and trunk wall based on vascular invasion, tumor necrosis, tumor size >8 cm and an infiltrative growth pattern. The figures are based on all 609 tumors in this study.

L16 SSG XX- A Scandinavian Sarcoma Group (SSG) treatment protocol for adult patients with non-metastatic high-risk soft tissue sarcoma (STS) of the extremities and trunk wall

K. Sundby Hall[1] and M. Eriksson[2] – for the SSG working group.

[1] Cancer Clinic, Norwegian Rikshospitalet-Radiumhospitalet, Montebello, Oslo, Norway
[2] Dept of Oncology, Lund University hospital, Lund, Sweden

SSG XX, the third adjuvant STS protocol by SSG, is a phase II non-randomized trial in patients with high risk to develop metastases. It will soon, probably in September 2007, replace the on-going protocol, SSG XIII. SSG XX is based on SSG XIII regarding use of prognostic markers to identify high-risk tumors and include very similar chemo- and radiotherapy treatment schedules compared to SSG XIII, but the new protocol also includes a treatment arm with preoperative chemo- and radiotherapy for patients with an obvious risk for intralesional surgery initially.

Patients: This new adjuvant SSG protocol for histologic high-grade malignant STS adopts an inclusion decision algorithm based on the following criteria: 1.vascular invasion or 2. presence of at least two of the risk factors: tumor size $\geq$8 cm, necrosis or infiltrative growth. The system was developed retrospectively by evaluation of 434 primary histologically high grade (III–IV) STS from the SSG registry, and was later validated in a series of 175 patients in which patients with a high risk for metastases (>40 %) and low risk (<15 %) were separated (Engellau et al. publication submitted). Inclusion criteria: age $\geq$18 y and $\leq$75 y. Primary end point is metastasis-free survival. Local recurrence and toxicity will also be studied.

Treatment: 6 cycles of doxorubicin 60 mg/m^2 and ifosfamide 6 g/m^2 will be given adjuvantly (to patients $\geq$70 y: 50 mg/m^2 and 5 g/m^2). Dependent on surgical resection margins, 36 Gy or 45 Gy (1,8 Gy per fraction, two fractions daily) will be given interpolated with chemotherapy.

Conclusion: SSG XX will evaluate chemo-and radiotherapy given adjuvantly to patients with STS and high risk for metastases. In a specified group of patients also preoperatively given therapy will be studied.

L17 ILP of soft tissue sarcoma: The Gothenburg experiences.

J. Mattsson[1], B. Gunterberg[2], P. Bergh[2] ,Ö. Berlin[2] and L. Larsson[1].

[1]Depts. of Surgery and [2]Orthopedic Surgery, Sahlgrenska University Hospital, Gothenburg, Sweden

Introduction: Isolated Limb Perfusion (ILP) with TNF-alpha and Melphalan has been shown to make limbsparing surgery possible, with good local control, in advanced soft tissue sarcoma (STS) of the limbs. We report our experience of ILP STS.

Patients and methods: At Sahlgrenska University Hospital 50 patients have been treated with TNF-alpha and Melphalan containing ILP, with mild hyperthermia, since 2000. One group of patients (27) were operated with limbsparing surgery, mean 11 weeks after the ILP. The other group (23) were not resected, due to patient risk factors, tumor extension or patient refusal.

Results: After an observation time of median 33 (4–69) months, 4 of the 27 patients with limb sparing surgery have experienced a local recurrence and 2 have been amputated, 1 due to the recurrence and 1 due to postop complications. 6 of the 23 patients not operated on after the ILP have been amputated after median 10 months, due to tumor progression. 13 of the 23 experienced good palliation with preserved limb function during the observation time.

Conclusions: ILP with TNF-alpha and Melphalan makes limbsparing surgery possible and gives good palliation in a high proportion of patients with advanced STS.

L18 High-Dose Methotrexate for the 21st Century

M. Perisoglou, D. Globe, B. Seddon and J. Whelan

Dept. of Oncology, University College Hospital, London, UK

High-dose methotrexate (HD-MTX) at a dose of 12 g/m^2, in combination with vigorous hydration and urinary alkalinisation along with a pharmacokinetically guided folinic acid “rescue” schedule, is an essential component of osteosarcoma treatment.

Despite current supportive measures, MTX-induced nephrotoxicity still occurs and may markedly enhance the other non-renal toxicities associated with MTX, leading to increased morbidity and mortality. Dialysis-based methods have limited effectiveness in removing MTX compared with the rapid reductions of >98 % in plasma MTX concentrations achieved with glucarpidase.

Glucarpidase is an enzyme that cleaves the terminal glutamate from MTX and results in the production of the inactive metabolite 4-deoxy-4-amino-N10-methylpteroic acid (DAMPA). It is a high molecular weight protein, does not gain intracellular access and would not counteract the anti-tumor effect of MTX trapped intracellularly in the form of polyglutamates. It has been used effectively to treat patients with MTX-induced renal dysfunction and has resulted in the reduction of serum MTX levels to the non-toxic range within minutes, without causing toxicity.

Early use of glucarpidase (50 units/kg, intravenously) should be considered if: **a)** plasma methotrexate concentration is $\geq$100 µmol/L at 24 hours or $\geq$10 µmol/L at 48 hours after MTX administration and **b)** there is rise in creatinine of $\geq$100 % within 24 hours of MTX administration. Further investigation of a wider role for glucarpidase is warranted.

L19 Lack of toxicological side-effects in silver-coated megaprostheses in humans

G. Gosheger, J. Hardes, H.Ahrens and W. Winkelmann

Dept. of Orthopedic Surgery, University of Muenster, Muenster, Germany

Deep infection of megaprostheses remains a serious complication. Furthermore, reinfection is a problem after revision surgery in patients suffering from infections associated with primary endoprosthetic replacement of the knee and hip joint. Many of these patients need repeated revision surgeries and in some cases even amputation.

Silver-coated medical devices have proved their effectiveness in reducing infections, but toxic side-effects concerning some silver applications have been described as well. We analyzed blood silver levels in patients with a silver-coated megaprosthesis for the first time. The silver-levels in the blood did not exceed 56 parts per billion (ppb) and can be considered as non-toxic. Additionally we could exclude significant changes in liver and kidney function as measured by laboratory values. Histopathologic examination of the periprosthetic environment in 2 patients showed no signs of foreign body granulomas or chronic inflammation, despite distant effective silver concentrations up to 1626 ppb directly related to the prosthetic surface. In conclusion the silver-coated megaprosthesis allowed a release of silver without any local or systemic side-effects.

L20 Selective antitumor activity of BAY 43-9006 (Sorafenib/Nexavar®) in musculo-skeletal sarcomas

W. Maruwge[1], A. Folin[1,2,] S. Brijn,[1] A. Davis[1], M. Lynch[3], F. Erlandsson[3], P. Darcy[1] J. Bergh[1] and B. Brodin[1]

[1]Depts. of Oncology and Pathology, Karolinska Institutet, and [2]Oncology Clinic, Karolinska University Hospital, Sweden; [3]Bayer Pharmaceutical Corporation, West Haven, Connecticut, USA

BAY 43-9006 /Sofarenib,/Nexavar® is a bi-aryl small molecule that it inhibits the activity of B-RAF (both wild type and its V600E mutant), and of receptor tyrosine kinases (RTKs) involved in tumor progression like cKIT, FLT-3, RET and neovascularization like PDGFR and VEGFR-2 and 3.

In preclinical studies it has shown to have broad anti-tumor activity as a single agent in different tumor types including melanoma ,colon, breast and small cell lung carcinoma, however in clinical trials, its efficacy has been most favorable for renal cell carcinoma.

We have evaluated the effect of Nexavar in 14 sarcoma cell lines of different histological subtypes. We found that Nexavar selectively inhibited the growth of synovial sarcomas and rhabdomyosarcomas and Ewing sarcomas (IC_{50} between 2–5 μM), but not osteosarcomas.

In responsive cells, Sorafenib inhibited the RAF/MEK/ERK pathway and induced G1 arrest and apoptosis. High expression levels of PDGFR and IGF1R in responder cells correlated with response to Nexavar. In non responsive cell lines, Nexavar did inhibit ERK phosphorylation, however no cytotoxic effect or apoptosis was observed during the time course of the experiment, suggesting that other signaling pathways are activated in these group of tumors. Nexavar in combination vincristin and doxorubicin did not show additive cytostatic effect in Nexavar responders. Interestingly, vincristin and to less extent, doxorubicin sensitized non responder osteosarcomas to Nexavar optimization of this combination and other drugs used in osteosarcoma treatment should be analyzed. The antitumor activity of Nexavar has been tested in an animal model of synovial sarcoma. Per-oral daily administration during 9 days (20, 40 and 80 mg/Kg) significantly inhibited tumor cell growth. The cytostatic effect was maintained 9 days after treatment withdrawal. Our results provide guidelines for the initiation of phase II clinical studies using Nexavar as monotherapy for synovial sarcoma and rhabdomyosarcoma patients.

L21 Thesis: Genetic Profiling in Soft Tissue Sarcoma

P. Francis

Dept. of Oncology, Institute of Clinical Sciences, Lund University

I have applied microarray-based gene expression and copy-number profiling to soft tissue sarcomas (STS) to provide clues to the genetic mechanisms involved in STS development and assess diagnostic and prognostic utility of array-based expression and copy-number profiling.

The first study showed that tumor heterogeneity in leiomyosarcoma and malignant fibrous histiocytoma/myxofibrosarcoma may have an impact on gene expression profiling, particularly within small tumor series, but conclude that a single tumor sample provides a reliable result provided adequate sample size.

The second study established expression patterns related to the *SS18-SSX* fusion variants and metastatic potential in synovial sarcomas and herein identified developmental genes, groups of histones and metallothioneins overexpressed in the *SS18-SSX1* variant. Cell cycle progression genes and proliferation markers including survivin and *TOP2A* were upregulated in the metastasizing tumors.

In the third study 177 STS of mixed histopathological types were profiled using cDNA microarrays. Distinct profiles were identified in subtypes with specific translocations or mutations, e.g. synovial sarcoma, myxoid/round-cell liposarcoma and GIST. Herein, frequent upregulation of developmental genes from e.g. the Wnt, Hedgehog and RAR signaling pathways were demonstrated. The more pleomorphic STS showed overexpression of genes involved in proliferation, adhesion, motility, and protein degradation. Moreover, a prognostic signature partly characterized by hypoxia-related genes that could independently predict the risk of metastasis was identified within the pleomorphic STS.

Study four applied array-based comparative genomic hybridization in malignant fibrous histiocytomas and leiomyosarcomas. Despite the complex genomic profiles, multiple recurrent gains and losses and novel amplifications and homozygous deletions were found. Gains in chromosomal regions 1p32 and 18q11 provided prognostic information independent of previously established risk factors.

L22 Thesis: Soft Tissue Sarcoma Patterns, multiplicity, heterogeneity, and growth characteristics

J. Fernebro

Dept. of Oncology, Lund University Hospital, Lund, Sweden

This thesis has studied various aspects – pathological, genetical, and clinical – of soft tissue sarcoma (STS).

In study I, 20 % of the patients in a population-based series of 818 STS developed second primary malignancies, and a particularly high risk of a second STS (SMR 18; 95% CI=8.–34) was identified.

In study II array-based comparative genomic hybridization was applied to 13 patients with multiple STS. Our results suggested that 8 cases represented second primary STS, whereas 5 cases likely represented metastases.

In study III cDNA microarray was applied to 26 synovial sarcomas and differentially expressed genes in relation to gene fusion type were identified.

In study IV we assessed the impact of targeting peripheral *versus* central tumor areas staining for Ki-67 in leiomyosarcomas, and demonstrated that the Ki-67 expression was higher in the tumor periphery in 18/25 tumors.

In study V, we demonstrated that tumors showing infiltration on preoperative MRI in 2/3 of the cases also showed microscopical infiltration, and that diffusely infiltrative growth on MRI correlated with a worse prognosis.

In summary, we have demonstrated that patients with STS are at increased risk of developing second primary tumors, including STS, with genetic profiles supporting independent tumor origin. We have also shown that the underlying gene fusion type in synovial sarcoma influence the gene expression profile. Finally, our studies suggest that evaluation of Ki-67 staining should be standardized, and that MRI-based classification of the peripheral tumor growth pattern may provide prognostic information.