Limb salvaging resection prior to the development of chemotherapy, CT and MRI imaging, sophisticated immunohistochemistry, and advances in both biologic and prosthetic reconstructive surgery was rarely done and carried a local recurrence rate of 40-60% and a 5-year survival rate of 10-20%. At its inception, concerns were voiced as to the survival rate, incidence of local recurrence, surgical complications, functional outcomes, and psychosocial benefits compared to the traditional surgical management of amputation. Now, 30 years later, by data provided by the International Society of Limb Salvage (ISOLS) through their biannual meetings, answers to these concerns are emerging. From the initial meeting in 1981 through the most recent meeting in 2001, the number of cases analyzed has risen from 505 to more than 10,000! – a 20-fold increase. 85% of stage I and II primary sarcomas of bone and soft tissue are currently considered to be low-risk candidates for limb salvage. Outcome data shows that survival rates at 5 years are the same for limb salvage (67%) and amputation (69%). Local recurrence rates for limb salvage at 5 years (8%), 10 years (11%), and 15 years (18%) are somewhat higher than those for amputation (3%). Significant predictive factors for local recurrence are adequate surgical margins and a satisfactory response to preoperative chemotherapy or radiation therapy. Complications compromising the outcome are more frequent following limb salvage (25%) than amputation (5%). As measured by the Musculoskeletal Tumor Society Functional Evaluation System, a satisfactory functional outcome is more common after limb salvage (66%) than after amputation (30%). Psychosocial benefits, however, appear to be the same for both procedures. Thus, although the risks for oncologic control are the same for both procedures, the choice between limb salvage and amputation must be individualized to each patient taking into consideration the patient’s age, lifestyle, occupation, education, rehabilitation potential, and access to medical care.
L2 Resection of the spine for tumors

B. Gunterberg

Gothenburg Musculo-Skeletal Tumor Center, Sahlgren University Hospital, Gothenburg, Sweden

The same surgical principles are valid for spinal tumors and limb tumors. However, it is more difficult to apply these principles in the spine because of its intricate anatomy. Also reconstruction of the spine tends to be demanding. Thus, individualized surgical plans are more important than in limb-surgery. Two different staging and classification systems for spinal tumors were introduced in 1997 to facilitate planning and understanding. Neither seems to have been widely accepted.

The best surgical margins that can be achieved in the spine are either wide or marginal. In major resections the condition to achieve such a margin is that at least one third or more of the circumference of the spinal canal is unaffected by tumor which allows an approach to the dura without entering the tumor. Most spinal resections fall into one of the categories: total spondylectomy, corporectomy, sagittal resection or posterior resection. The purpose of my presentation is to illustrate different strategies for resection and reconstruction in the cervical, thoracic and lumbar spine. Long-term results are available demonstrating that total spondylectomy with skeletal reconstruction is compatible with a long, physically active life.
L3 Pelvic reconstruction
R. Capanna, P. De Biase, P. Caldora, D.A. Campanacci

Center of Surgical Oncology and Reconstructive Surgery, AOC, CTO Florence, Italy

No reconstruction or minor and optional (a bone graft to reconstruct pelvic ring continuity, an artificial mesh to reinforce the abdominal wall) are required after resection of anterior arch or iliac wing. In periacetabular resections a wide variety of reconstructions may be used. Some (ilio-femoral or ischio-femoral coaptation or arthrodesis) are technically not demanding, fast to perform, does not require major implant or graft but leaves a residual shortening and fair functional status; these reconstructions are recommended in elderly, after extensive soft tissue removal and when there is a risk for vascular or infective complications. Others (ilio-femoral arthrodesis with intercalary allografts, saddle prosthesis) are relatively simple to perform, avoid limb-shortening, allow an acceptable function with some restrictions but require a foreign implant or graft. The remaining options (a proximal femur transposition with femoral mega prosthesis, a massive pelvic allograft, a custom made or modular pelvic prosthesis) are all technically demanding and require extensive use of foreign body material and although these allow an immediate high functional performance they are prone to failure in the long run: these reconstructions should be reserved for young, motivated patients without extensive muscle sacrifice or in case of total removal of the hemipelvis.
L4 Function after surgery for sacral tumors
P. Bergh, B. Gunterberg

Gothenburg Musculo-Skeletal Tumor Center, Sahlgren University Hospital, Gothenburg, Sweden
peter.bergh@medfak.gu.se

Introduction Major resection of the sacrum is an uncommon procedure. The indication is most often low-grade tumors. Loss of sacral nerves will inevitably lead to more or less disability for the patient. The aim of this study was to assess the functional outcome after such surgery.

Patients and methods We reviewed 38 patients (19 women) with sacral amputations or total sacrectomy and analyzed the mechanical, motor and bowel/bladder function. The mean age was 56 years. 35 tumors were chordoma, 1 chondrosarcoma, 1 localized malignant fibrous tumor and 1 sclerosing epithelioid fibrosarcoma. 27 patients had amputations proximal to the S2 vertebra.

Results 6 patients developed fatigue fractures in the remaining part of sacrum, 4 of theses healed spontaneously. 4 patients lost the L5 and all sacral nerves. They developed paralytic feet. 10 patients lost the S1 nerves. Surprisingly all these patients could stand tip toe. The rectum was preserved in 26 patients. Loss of all sacral nerves or the S2-S5 nerves bilateral caused major bowel and urinary problems. Preservation of at least 1 S3 nerve was compatible with almost normal bowel and bladder function.

Conclusions High sacral amputation is a disabling procedure with large impact on anorectal and urogenital function. However most patients learn to cope with their problems and have an acceptable quality of life,
L5 Surgical treatment for tumors of the cervical spine

1 Istituti Ortopedici Rizzoli, 2 Ospedale Maggiore, 3 Policlinico S. Orsola-Malpighi, Bologna, 4 Istituto Regina Elena, Rome, Italy

Introduction From 1912 to 2002, 356 tumors or pseudotumoral spine lesions were observed. 70 were excluded (incomplete data), 286 are presented.

Patients and methods 47% were primary, 7% from systemic lesions (plasmacytoma 85% and lymphoma 15%), 46% from secondary lesions (96% metastasis from carcinoma and 4% from sarcoma). 75% of primary lesions were benign or pseudotumoral, 25% malignant. Osteoid osteoma was the most common benign lesion (31%), followed by aneurysmal bone cyst (26%), osteoblastoma (14%) and giant cell tumor (13%) which account for 84%, the remaining 16% was subdivided in 12 histotypes. Chordoma (30%) was the most common malignant lesion, followed by chondrosarcoma (18%) and osteosarcoma (15%) representing 63% of lesions, the remaining 37% was subdivided in 6 histotypes. Pain was the main symptom in patients affected by primary lesions, lasting from a few weeks to 2-3 years. All patients were operated (biopsy, curettage or resection) and diagnosed. Only peripheral chondrosarcoma (PChs) had wide resection, the other histotypes had intralesional surgery or curettage. Postoperatively all patients used external devices (collars or minerva cast) from 1 month to several years. Over 80% of patients were followed at the Rizzoli, the remaining patients are still undergoing follow up.

Conclusions The important data that appears from this analysis is that it is difficult to perform a wide resection for high grade malignant tumors (except maybe for PChs) of the cervical vertebral body as opposed to what occurs in dorsal, lumbar and sacral spine segments.
L6 TNFα-based isolated limb perfusion for locally advanced soft tissue sarcoma: 12 years of antivascular therapy in the clinic and new developments in the laboratory

A. Eggermont

Rotterdam
L7 The Rizzoli experience in megaprostheses: function and long-term results

M. Mercuri, P. Ruggieri, N. Fabbri, A. Ferraro, M. De Paolis, N. Salducca, M. Macchiagodena, C. Errani, E. Pasini, M. Gigli

Clinica ortopedica, Istituto Ortopedico Rizzoli- Università di Bologna, Italy
mario.mercuri@ior.it

Limb salvage has become an accepted treatment for bone tumors. The reconstruction of the residual defect after wide resection in the lower limb can be restored by using an allograft, an endoprosthesis or APC (allograft-prosthesis composite). We evaluated the long-term clinical results of the modular prosthesis in 639 cases with a minimum follow-up of 3 years. Sites of reconstruction included 94 proximal femur, 389 distal femur, 120 proximal tibia, 14 total femur, 6 of both distal femur and proximal tibia. All of these cases were reviewed by clinical charts, questionnaires and X-ray in our Institute. The overall results have been quite satisfactory, evaluated according to the MSTS score. Major problems included infections (1% in the proximal femur, 7% in the distal femur and 11% in the proximal tibia) and the mechanical complications as stem loosening (6%), stem breakage, wear of polyethylene components.

From December 1996 to December 2000, 54 HMRS rotating hinge knee were implanted at our Department, with the aim of further reducing the incidence of polyethylene wear and stem loosening. The functional results were good or excellent in most patients, although follow-up is still short and the results have to be regarded as preliminary.

The reconstruction with the APC in the proximal femur and in the proximal tibia offers the advantage of better functional results due to the better musculo-tendinous reattachment. In the proximal femur (54 cases) the APC reconstruction showed (44 patients evaluated) a rate of 91% of satisfactory functional results and only 3 infections. In the proximal tibia (63 cases) the APC reconstructions showed a very high incidence of infection (14/63=22%) comparated with the infections rate of the modular prosthetic reconstructions (12/120=11%). All of the infected proximal tibia APCs were in patients who received chemotherapy.

The modular prostheses are a good reconstructive option for the treatment of high-grade bone sarcomas localized at the proximal and distal femur or in the proximal tibia. In the proximal femur a reconstruction with APC is preferable if the abductor muscle can be spared. In the patients with a high grade malignant tumors of the proximal tibia, treated with chemotherapy, the prosthetic reconstruction is preferably indicated because of the high incidence of infection in the APC reconstruction in the proximal tibia. The APC reconstruction in the proximal tibia can be used in the benign tumors (stage 3) or low grade malignant tumors.

A series of 255 cases of resection for bone tumors and reconstruction of the humerus performed at the Istituto Rizzoli was reviewed. These included 221 cases of reconstruction of the proximal humerus, 7 of the distal humerus, 2 of the entire humerus. Two types of modular prostheses were used (IOR-MRS Bioimplanti and Stryker-Howmedica). Several complications were observed, including some minor complications not requiring surgery and major complications, such as infections and mechanical complications. These latter included 5 cases of aseptic loosening of the prosthetic stem, 10 cases of disanchorage,
26 cases of subluxation of the prosthetic head (5 dislocations requiring surgical revision and 21 minor subluxations).

There were 23 infections (21 deep infections and 2 superficial), that required surgery. In 10 cases surgical debridement and irrigations led to healing, while in 13 cases the prosthesis was removed.

Functional results were assessed according to the MSTS System as reported by Enneking at al. in 1993 (Clin. Orthop. Rel. Res., 286). 35 cases were not evaluable, in the remaining evaluated cases, results were good in 56 patients (function between 51% and 75%) and excellent in 163 patients (function between 76% and 100%).
L8 Resection - arthrodesis of the shoulder. Long-term results and function
B. Gunterberg

Gothenburg Musculo-Skeletal Tumor Center, Sahlgren University Hospital, Gothenburg, Sweden

In 1982 Bertil Stener introduced a method of resection - arthrodesis of the humero-scapular joint after removal of the proximal humerus for tumor. The results in those 8 patients with the longest follow-up are assessed.

Methods After resection of the proximal humerus for tumor, the defect (8-15 cm) was reconstructed with an autologous fibular graft (6 avascular, 2 vascular) and an iliac graft. The shaft of the fibular graft was inserted into the medullary canal of the humerus and the articular cartilage of the fibula and scapula was removed. The fibular graft was fixed to the scapula with a steel wire or an AO-plate. The iliac graft was interlocked between the humeral shaft and the coracoid process. 8 consecutive patients with a mean follow-up of 11(4-21) years were reviewed and function according to the MSTS-system was recorded.

Results The mean age at diagnosis was 21 years. There were 3 chondrosarcomas, 2 osteosarcomas, 2 giant cell tumors and 1 aneurysmal bone cyst. At follow-up all patients were continuously diseasefree. 4 patients fractured their grafts. 2 healed without problems, 1 had a painfree useful pseudarthrosis and 1 a disabling osteonecrosis-pseudarthrosis (the only irradiated patient). This patient had a MSTS-score of 17/30. The other 7 patients had MSTS-scores ranging from 25/30 to 28/30.

Conclusion Excellent long-term results can be achieved with humero-scapular resection-arthrodesis. Patients that require radiotherapy should be excluded as radionecrosis may jeopardize the result. A strong, stable arthrodesis can be expected to function better than a prosthetic replacement.
Reconstructions after limb-salvage surgery in young children offer several possibilities. Our preference, whenever suitable, are biologic reconstructions using autologous vascularized fibula grafts. We report on 3 children in whom the joint function was preserved in the knee, hip and shoulder joints. Preoperative chemotherapy (ISG-SSG I) rendered clinically good response.

A 9-year-old girl had a resection of an osteosarcoma of the right distal femur. Two parallel fibulagrafts with the proximal epiphysis towards the knee-joint, joined with 2 cerclage wires, formed the reconstruction. The lateral collateral ligaments were sutured to the cruciate ligaments. Being a stage IIA lesion soft tissue resection could be kept to a minimum adding to the stability. After 33 months the patient is ambulatory and leg-length discrepancy is 4.5 cm. MSTS functional score was 18/30.

A 9-year-old girl with a resected stage IIB Ewing sarcoma of the right proximal femur was reconstructed with 2 fibulagrafts; one proximal fibula epiphysis replaced the femoral head, and the other graft served as support. The hip-joint capsule was sutured like a pouch around the fibula head. After 47 months the patient is ambulatory without brace. MSTS score; 23/30.

A 6-year-old girl with a resected stage IIB telangiectatic osteosarcoma of the left proximal humerus was reconstructed with a single fibulagraft. The origin of the long biceps tendon was sutured to the lateral collateral ligament, and the rotator cuff was reconstructed as a pouch around the fibula head. At follow-up (43 months) the MSTS score was 28/30.

The follow-up results appear encouraging and the functional score has consistently improved over time. The described surgery must still be regarded as "developmental".
L10 Preoperative radio- and chemotherapy in soft tissue sarcomas: rationale and feasibility study preliminary to the Italian Sarcoma Group neo-adjuvant protocol

S. Frustaci¹, F. Gherlinzoni², A. De Paoli³

For the Italian Sarcoma Group
sfrustaci@cro.it

Introduction Adjuvant chemotherapy in soft tissue sarcomas has proven to be effective according to the meta-analysis performed on the 13 “first generation trials” in terms of disease free survival (p<0.001) and overall survival in the subgroup of extremity tumors (p=0.03). Furthermore, the first adjuvant study of the Italian Sarcoma Group, recently updated, confirmed a 5 years overall survival advantage of the treatment arm in comparison with the control arm (p=0.04). It is important to remind that the study included high risk patients only and used a modern chemotherapy supported by hematopoietic growth factors. However, the great majority of relapsing patients developed metastatic spread and therefore died of uncontrolled disease. Therefore, taking into account the delay from diagnosis to start of chemotherapy that we observed in the Italian adjuvant study median 92 (17-288) days which could have allowed the spread and diffusion of micrometastatic disease already present at time of diagnosis and the relevant role of pre-operative radiation therapy in the local control of primary tumors, we decided to start a pilot study on the feasibility of a concomitant administration of chemo-radiation therapy. 24 patients have been entered in this feasibility, prospective study. Characteristics, toxicity, dose intensity and general compliance will be presented. The positive results of this trial further supported the start of the second Italian Sarcoma Group Study which adopted the concomitant pre-operative chemo-radiation therapy approach.
Advances in surgical techniques and adjuvant treatments have led to an era of limb-salvage surgery in advanced extremity sarcoma. The latest contribution in this field is preoperative isolated limb perfusion using TNF α, which may further decrease the amputation rate in soft tissue sarcoma. The question is whether the enthusiasm for limb-salvage has gone too far, resulting in less local control and poor quality of salvaged limbs, or not. Local control is very important in sarcoma surgery regardless of its questionable impact on survival. Amputation appears to render local control more frequently than limb-salvage surgery and adjuvant treatment. There is a positive correlation between amputation rate and local control when the results of the Scandinavian Sarcoma Group centers are compared. The ultimate amputation rate, including secondary unplanned amputations, in “limb-salvage centers” equals the amputation rate in centres where surgical treatment alone was the mainstay in treatment. Complications are much more frequent and severe after limb-salvage surgery than after amputation. Function and quality of life do not differ significantly between amputees and limb-salvage patients. Adequate surgical procedures preceded by well planned biopsies or cytologic aspirations will locally control 90% or more of extremity sarcomas. Approximately 10 - 15% of these patients are candidates for an amputation. They are not better off, some probably worse off, with limb-sparing surgery and the adjuvant treatments available today. Recent developments in amputation technique and rehabilitation modalities serve to improve function in the amputated group.
Bone anchored amputation prostheses – a new possibility

R. Brånemark, P. Bergh, B. Gunterberg

Dept of Orthopedics, Sahlgren University Hospital, Gothenburg, Sweden

Transfemoral amputations due to trauma or tumor surgery often result in a high amputation with or without soft tissue problems. These patients are frequently difficult to rehabilitate optimally with socket prostheses. Bone anchored amputation prostheses might be a solution for these patients.

Directly bone anchored prostheses according to the osseointegration concept were originally developed by Professor P-I Brånemark in Gothenburg. Osseointegration was initially used to treat edentulism and for reconstructive surgery in the craniomaxillofacial region. In a multidisciplinary approach osseointegration has been used for direct skeletal anchorage of amputation prostheses on a limited number of patients since 1990. The rehabilitation team consists of orthopedic surgeons, physiotherapists and orthopedic technicians. The results of the first transfemoral amputees treated will be summarized and considerations on patient selection, surgical technique and fitting of the prosthesis will be presented.

The patients experienced increased function and improved comfort, especially when sitting and due to easy attachment and detachment of the prosthesis. An increased sensory capability was noted (osseoperception), which might improve function and physiological acceptance. Superficial infections were frequent, but could easily be treated successfully. Deep infections were initially a major problem, but with improvements in patient selection, surgical technique and postoperative rehabilitation this problem is decreasing.
L13 Rehabilitation and function in patients with a bone-anchored transfemoral amputation prosthesis

K. Hagberg

Dept of Prosthetics and Orthotics, Sahlgren University Hospital, Gothenburg, Sweden
kerstin.hagberg@vgregion.se

Comfort and function in non-vascular patients who have severe stump-socket problems after thigh amputation can be improved by a bone-anchored prosthetic limb using the method of osseointegration. The rehabilitation, 12-18-months, includes 4 phases:

1. Preoperative assessment and information
2. Rehabilitation between surgery stage 1 (titanium fixture) and 2 (abutment and skinpenetration area)
3. Initial loading on a short training prosthesis
4. Prosthetic gait training

A prospective study is ongoing to assess prosthetic use, function, problems and health-related quality of life among 50 individuals fitted with a bone-anchored transfemoral amputation prosthesis. Case reports will illustrate details in the rehabilitation program and some preliminary results.
A case-control study has been conducted in Southern Sweden on risk factors for soft tissue sarcoma. From 1990-2003 591 cases and 3771 controls has been recruited. The postal questionnaire included information on occupational titles and exposures such as to herbicides and insecticides, family history of cancer, hormonal risk factors (exposure to HRT, oral contraceptives, pregnancies), radiation exposure and smoking and alcohol habits. Age matched controls were both recruited from the same parish and the same county as the patient. Results will be presented on various risk factors analyzed both by univariate and multivariate methods.
**L15 Local recurrence in soft tissue sarcoma**

*S. Eriksson, B. Gunterberg, P. Bergh*

Gothenburg Musculoskeletal Tumor Center, Gothenburg, Sweden

**Introduction** Local recurrence may not play a major role in the overall survival in soft tissue sarcomas, but could cause great morbidity for the individual patient. In order to reduce the local recurrence rate, there are proposals that all deep-seated high-grade or marginally excised soft tissue sarcomas should have adjuvant radiotherapy, (i.e. approximately 60% of all sarcomas). The aim of this study was to evaluate the local recurrence rate in patients treated at our center.

**Patients and results** We reviewed 190 consecutive soft tissue sarcoma patients with a minimum 5 years follow-up. There were 103 men and 87 women with a mean age of 62 years (9-100 yrs). Tumor size ranged from 1- 35 cm. 64% of the tumors were deep seated and 80% were high-grade sarcomas (III-IV). The primary operation was performed in our center in 73% and 10% of the patients were amputated. Adjuvant radiotherapy was given in 23%. The overall local recurrence rate was 8% and for deep seated tumors 7%.

**Conclusion** The treatment at our center of patients with soft tissue sarcomas with 90% limb salvage procedures and with 23% adjuvant radiotherapy rendered a reasonably low local recurrence rate of 8%.
L16 Function after resection of the sciatic nerve for sarcomas

Ö. Berlin, R. Tranberg, R. Zügner, B. Gunterberg

Dept of Orthopedics and Lundberg Laboratory for Orthopedic Research, Sahlgren University Hospital, Gothenburg, Sweden
berbiz@algonet.se

Introduction High-grade sarcomas in or adjacent to the major nerves of the lower extremity has previously been regarded as an indication for extensive amputations. We have performed functional evaluations of our patients who had limb-salvage surgery and lost their sciatic nerve.

Patients and methods 5 eligible patients were examined with gait analysis. One patient was incapacitated from a contralateral stroke, hence her results were excluded from the calculations. Despite this she was able to walk with a stroller. Functional evaluation (Enneking/AmMSTS) by a non-biased observer (RZ) was performed. 18 retro-reflective spherical markers were attached to the skin over well-known bony landmarks. 6 infrared cameras sampling at 240 Hz were used for the recording of kinematic data. 2 force plates were used to record ground reaction forces during walking.

Results All 4 patients are walking independently; 3 walk without any support, the fourth is using a cane and an ankle-foot orthosis. They walk with a slightly slower speed, 0.92 m/sec (SD: 0.12), than normal (0.96 – 1.68) and with a cadence in the lower normal range, 95 steps/min (SD: 2.54), compared with normal (82-126). The stance on the ipsilateral side showed a moderate decrease, 57% (SD 3.69) (normal: 58-62%). The contralateral side had a marked increase of the stance; 67% (SD 4.2). Walking ability varied from 400 meters up to 2.5 km. The average MSTS score was 23/30 (range: 18-27).

Conclusion Our study indicates that wide excisions including the sciatic nerve for sarcomas of the lower extremity seems, whenever feasible, to be a better functional solution than an amputation.
Purpose To explore prognostic factors in surgically treated extra-abdominal aggressive fibromatosis.

Patients and methods 203 consecutive patients treated with surgery at a single center were retrospectively reviewed. 75 patients had a recurrent tumor, while 128 had a primary. All patients underwent macroscopically complete resection. Margins were negative in 146 patients (97/128 primary, 49/75 recurrences). Median follow-up was 135 months.

Results Patients with primary disease had a better disease-free survival (76% versus 59% at 10 years). Recurrence was the strongest predictor of local failure. In primary disease, size and site had a prognostic impact, while microscopically positive margins had not; in recurrent disease there was a trend towards a better prognosis if margins were negative.

Conclusion In primary presentations of extraabdominal desmoid tumors, microscopical disease would not seem to necessarily impact the disease-free survival. Function-sparing surgery may thus be performed whenever feasible without leaving macroscopical residual disease. In recurrences, positive margins impact prognosis more clearly. In selected cases, it could be reasonable to consider adjuvant radiation.
L18 Clinical and imaging studies of desmoid tumors left without treatment

M. Dalén, P. Bergh, B. Gunterberg

Dept of Orthopedic Surgery, Sahlgren University Hospital, Gothenburg, Sweden
mikael.dalen@orthop.gu.se

Introduction Desmoid tumors are rare benign, locally aggressive tumors originating in musculoaponeurotic tissue. Surgery is considered to be the treatment of choice. Spontaneous tumor regression has been reported. The aim of our study was to assess the clinical and radiological outcome of patients with desmoid tumors left without treatment.

Patients and methods We reviewed 8 patients (5 women) with desmoid tumors. Mean age was 35 years. Mean follow-up time was 47 months. Largest mean tumor diameter was 6 cm. 5 tumors were located in the abdominal wall, 1 in the triceps brachii muscle, 1 in the back and 1 in the pectoralis major muscle. The patients were followed with clinical examination and imaging techniques. Tumor volume was calculated and plotted as a function over time.

Results No patients had any symptoms but a palpable mass. There was a complete remission in 1 patient, a partial remission in 4 patients, stable tumor in 2 patients and increasing tumor growth in 1 patient.

Conclusion Spontaneous tumor regression is possible in patients with desmoid tumors. Repeated clinical and imaging observations without treatment may be considered in selected cases.
Extremity soft tissue sarcomas have an expected incidence of .5-1 cases per 100000 inhabitants per year in western countries, with approximately 600 new cases every year in Italy. Adequate local control is essential for cure, but the final outcome is mainly affected by metastatic spread of the disease. Size, depth and grade of the primary tumor are well known prognostic factors. Approximately 50% of patients with high grade soft tissue sarcoma die because of distant metastases. The role of chemotherapy is controversial. Overall survival of today is not so different from that reported 20 years ago. What has really changed is the amputation rate. Thanks to multidisciplinary surgery and sophisticated techniques, conservative resections can be offered to 95% of the patients at presentation and still to 90% of the patients, who present at a referral center with local recurrence. However, we have paid this conservative approach with a higher rate of marginal operations which translates in a higher rate of local recurrence. What is the significance of local recurrence in terms of disease free survival and disease specific survival is still a matter of debate. The impact of positive surgical margins on disease specific survival has not been clearly defined.

From 1980 through year 2000, 712 adult patients with primary extremity soft tissue sarcoma were operated at our center. 33 (5%) patients were primarily amputated because of local extension of the disease. The remaining 679 patients were treated by limb-salvage, with a 10 year local control rate of approximately 85%. 96 patients (14%) had positive surgical margins, while 616 (86%) had negative surgical margins. Local failure at 10 years was 34% for the former group and 14% for the latter.

More critical has been the outcome of 348 patients, who presented in the same period at our center with a local recurrence. 26 (7%) patients were amputated, while the remaining 322 patients had limb-salvage with a 10-year local control rate of 72%.

102 (29%) patients had positive surgical margins, while 246 (71%) had negative surgical margins. Local failure at 10 years was 36% in the former group and 26% in the latter.

Metastasis free survival was between 70% and 80% at 10 years in all the subgroups. Therefore in our experience positive margins seem to negatively affect local control but not survival, confirming the feeling that local recurrence in soft tissue sarcoma is a marker of biological aggressiveness, but not a clear cause of metastasis.

Limb-salvage for extremity soft tissue sarcoma should be carried out by experienced teams, able to obtain the highest rate of negative margins resections with the best functional outcome.
L20 Gastrointestinal stromal tumour – diagnosis, epidemiology and prognosis

L-G. Kindblom¹, J.M. Meis-Kindblom¹, P. Bümming², B. Nilsson²

Depts of Pathology¹ and Surgery², Lundberg Laboratory for Cancer Research, The Sahlgrenska Academy at Gothenburg University, Gothenburg, Sweden
lars-gunnar.kindblom@llcr.med.gu.se

Background For a long time gastrointestinal stromal tumours (GIST) have caused problems with regard to diagnostic criteria, prediction of clinical behaviour and treatment. Recent breakthroughs in our conceptual understanding of GIST and its pathogenesis have led to re-defining diagnostic criteria and the development of molecularly targeted drug therapy. New treatment options mandate accurate information regarding the incidence, prevalence, clinical behavior and prognostic factors of GIST - hence the need for a large population-based study with extended and detailed follow-up information.

Methods All cases (approximately 1,500) of potential GIST diagnosed from 1983 to 2000 in southwestern Sweden (population 1.2–1.5 million) were reviewed. Among these, 288 primary GIST were identified. Incidence and prevalence were determined and predictive prognostic factors, including current risk group stratifications, statistically analysed.

Results 72% of GIST were clinically detected due to symptoms; the remainder of cases were incidental findings at surgery (19%) or autopsy (9%). 43% of clinically detected GIST were either “high risk” (29%) or overtly malignant (14%) at diagnosis, with tumour-related deaths in 90% (median survivals 30 and 18 months, respectively). The overall survival of patients in the very low, low, and intermediate risk groups did not differ from the normal population. The annual incidence of GIST was 14.5 per million and the prevalence of high risk and overtly malignant GIST was 30 per million.

Conclusion Based on this first large population-based study, we conclude that GIST has been underrecognised; moreover, its incidence, prevalence and clinical aggressiveness have been underestimated. Current risk group stratification systems based on tumour size and mitotic rate (alternatively proliferative index) are useful to delineate GIST patient groups that have a poor outcome when treated solely with surgery.
Imatinib mesylate has become standard therapy for advanced GISTs, following the case report about the first Finnish patient treated with Imatinib as from March 2000, and two Phase I-II studies, rapidly carried out in US and in Europe soon after. Observed progression-free and overall survival compare favourably with any historical control, with roughly 80-90% of patients being sensitive to Imatinib. Two large randomized trials were then launched, for obvious reasons without any no-Imatinib control arm. The results of these two trials are awaited, in regard to both the optimal starting dose (400 vs 800 mg) and the medium/long-term outcome in terms of progression-free and overall survival. Major concerns currently focus on the possible occurrence of acquired resistance. At the moment, it is not known how many GIST patients will be affected. However, this prompted to resort widely to surgery of residual disease, as well as to anticipate the use of Imatinib in the adjuvant setting. Adjuvant trials have been launched in US, and are about to start in Europe, focusing on the “high-risk” patients. In the meantime, biomolecular studies are ongoing, to elucidate mechanisms of resistance to Imatinib, and to help find out salvage molecular-targeted new agents for resistant patients.
L22 Metastasectomy in soft tissue tumors – the present status

U. Pastorino

Istituto Nazionale Tumori, Milan, Italy
ugo.pastorino@istitutotumori.mi.it

In the last 20 years, pulmonary metastasectomy has been extensively applied to soft tissue sarcoma patients as a potentially curative treatment. The meta-analysis of the International Registry of Lung Metastases (IRLM), by pooling 1065 cases from unselected series and extensive follow-up of major thoracic oncology centres worldwide, has contributed to define the long-term survival after pulmonary metastasectomy and predict the outcome based on relevant prognostic factors. Overall survival of 938 patients with initial complete resection was 30% at 5 years and 22% at 10 years (peri-operative mortality 1%).

A new system of classification has been validated, combining anatomical (number of lesions, completeness of resection) and biological (disease free interval - DFI) features. The curve illustrates the 10 year survival figures for the four prognostic groups: 1 = resectable, no risk factors (DFI ≥ 36 months and single metastasis), 2 = only one risk factor (DFI < 36 months or multiple metastases), 3 = two risk factors, 4 = unresectable. Median and 5-years survival were respectively 43 months and 40% for group 1, 35/37 for 2, 23/21 for 3, and 12/13 for 4. In patients with more than one lesion, survival was 31% for accurate CT staging and 23% for radiologically occult disease. Overall, 5-year survival was 36% for monolateral surgical approach and 30% for bilateral approach. 37% of completely resected patients had a pulmonary relapse, and 81% of them underwent re-do metastasectomy. Survival was 30% in 208 cases that received 2 metastasectomies, and 58% in 73 cases that received 3 or more metastasectomies.

Beyond the Registry data, recent experiences suggest the important role of PET in the selection of surgical candidates to lung metastasectomy. Preoperative PET can improve detection of extra-thoracic disease or primary site relapse, identify nodal metastases and increase the diagnostic accuracy of solitary lung lesions in patients with prior soft tissue sarcoma.
STS metastasectomy:
the IRLM staging system
L23 Neoadjuvant chemotherapy with high-dose ifosfamide added to methotrexate, cisplatin, and doxorubicin for patients with localized osteosarcoma of the extremity. A joint study by the Italian (ISG) and Scandinavian (SSG) sarcoma groups

S. Smeland¹, T.A. Alvegård¹, T. Wiebe¹, O. Brosjö¹, G. Sæter¹, G. Bacci², S. Ferrari², P. Picci², F. Bertoni², M. Mercuri²

For the ¹Scandinavian and ²Italian Sarcoma Groups

sigbjorn.smeland@klinmed.uio.no

The ISG/SSG I study was undertaken to explore the effect of adding high dose ifosfamide (HDIFO) in first line treatment for localized osteosarcoma in patients ≤ 40 years. Primary treatment consisted of two blocks of HDIFO (15 g/m²), HDMTX (methotrexate 12 g/m²), CDP/ADM (cisplatin 120 mg/m²; doxorubicin 75 mg/m²). Postoperatively, patients were given two cycles of ADM (90 mg/m²), three cycles of HDIFO (15 g/m²), MTX (12 g/m²) and CDP (120-150 mg/m²). Patients with total necrosis received only two cycles of each drug. G-CSF support was mandatory after cycles with HDIFO and CDP/ADM.

From March 1997 to Sept 2000 181 patients were entered. 156 (91%) patients underwent limb-salvage surgery, 11 (6%) were amputated and 4 (2%) underwent rotation plasty. 93% of the patients had wide or radical margins. 60% of the patients obtained > 90% tumor necrosis and 10% had complete necrosis. There were 3 treatment related deaths (sepsis + electrolyte imbalance). 59% of courses (methotrexate excluded) were followed by grade IV neutropenia and 33% by febrile neutropenia. Grade IV trombocytopenia was reported after 35% of courses. 15 patients experienced transient nephrotoxicity; 7 following high-dose HDMTX, 5 following HDIFO and 3 following CDP. Compared to protocol schedule, the median delay to surgery was 2 weeks and the whole treatment period was prolonged by a median of 7 weeks. With a median follow-up of 40 months the projected 3-year event-free and overall survival rates are 0.68 +/- 0.04 and 0.86 +/- 0.03 respectively. The 3-year projected risk of local recurrence is 0.047 +/- 0.015. In conclusion, the addition of high-dose ifosfamide to MTX, CDP, and ADM neither improve histologic response nor outcome in localized osteosarcoma compared to four drug regimens in which standard dose ifosfamide was used.
L24 Preliminary results of the Italian-Scandinavian ISG/SSG II protocol for the treatment of high-risk osteosarcoma

A. Brach del Prever, S. Smeland, A. Tienghi, M. Aglietta, O. Brosjö, G. Bernini, F. Fagioli, K. Sundby Hall, S. Ferrari, T. Wiklund, M. Berta, T.A. Alvegård

For the Italian and Scandinavian Sarcoma Groups
adalberto.brachdelprever@unito.it

Introduction
Significant progress has been registered over the last 25 years in the management of localized osteosarcoma of the extremities with the combined use of surgery and chemotherapy. In contrast, prognosis remains poor for patients with metastatic disease at presentation and for those with pelvic or axial primary tumors. In the attempt to improve cure rates in pelvic and metastatic osteosarcoma, the Italian and Scandinavian Sarcoma Groups activated the protocol ISG-SSG II with high dose chemotherapy (HDCT) and peripheral blood stem cell (PBSC) support in addition to intensive multiagent chemotherapy.

Patients and methods
From May 1996, 49 (28 male) patients with a median age of 17 (2-38) years entered the study. 39 patients presented with metastatic disease at diagnosis (primary site: 19 femur, 9 humerus, 5 tibia, 4 pelvis and 2 vertebra) and 10 with pelvic localization. All 39 metastatic patients had lung metastases (more than 2 nodules in 28 patients), 3 had also lymphonodal and 1 bone metastases.

Preoperative chemotherapy consisted of Methotrexate 12 g/m² on days 0 and 42, Cisplatin 120 mg/m² in 48 hour i.v. continuous infusion followed by Adriamycin (ADM) 75 mg/m² in 24 hour i.v. continuous infusion from days 7 and 49, Ifosfamide (IFO) 15 g/m² in 5 day continuous infusion from days 28 and 70. After surgery, two cycles of ADM 90 mg/m² were administered, intercalated by 1 cycle of Cyclophosphamide 4000 mg/m² + Etoposide 600 mg/m², and followed by 2 consecutive cycles of HDCT containing Etoposide 1800 mg/m² + Carboplatin 1500 mg/m² over 4 days with PBSC rescue.

Results
Resection of the primary tumor was performed in 31/49 patients, amputation in 6/49 and rotationplasty in 2/49. 22 patients underwent lung metastasectomy. Surgical margins and histological response are at present evaluable respectively in 36/39 and 35/39 cases, respectively; 5 patients had radical margins, 25 wide, 5 marginal and 1 intralesional; 1 patient had total necrosis (TN), 13 almost total necrosis (ATN), in 21 there was viable tumor (PN) in the resected specimens.

Data regarding HDCT are evaluable in 45 patients: a median of 7.6 (1.7-19) x 10⁶ CD34+/kg were collected with a median of 2 (1-7) aphereses; 2 patients needed additional bone marrow harvest. 23 patients received 2 cycles of HDCT and 9 patients 1 cycle for a total of 55 evaluable cycles.

1 patient developed renal failure after IFO and 1 veno-occlusive disease after Cyclophosphamide + Etoposide (toxicity resolved but disease progressed before HDCT). Conditioning regimen was well tolerated with a median time of 10 days to recovery of neutrophils to > 0.5x10⁹/l and platelets to > 25x10⁹/l. Except for expected hematological toxicity and mucositis, no grade III or IV were reported after HDCT. No treatment related deaths were observed.
After a median follow-up of 37 (4-82) months 20/49 patients are alive: 13 patients are in first complete remission (CR 1), 5 in second or more complete remission (CR>1) and 2 are alive with disease (AWD); 29 have died after median 19 (4-42) months from diagnosis. 33 patients achieved surgical complete remission: 13 are still in CR 1, 5 in CR>1, 15 have died after relapse. 16 patients presented progression of disease during the treatment: 14 have died and 2 are AWD (7 and 12 months from diagnosis).

The projected overall (OS) and event free survival (EFS) at 36 months from diagnosis are 35% and 21%, respectively. 3-year OS and EFS rates for the group of 39 patients with metastatic disease are 31% and 19%, for the group of 10 patients with pelvic localization 49% and 35%, respectively. In the group of 33 cases who achieved complete remission these percentages are 50% and 32%. We observed a different prognosis between the group of 14 patients with TN or ATN and the group of 21 patients with PN (3-year OS 46% vs 26%, p=0.01; 3-year EFS 41% vs 10%, p=0.001).

**Conclusion** These preliminary data show that the treatment is feasible with most patients receiving intended therapy. At present, the analysis seems to suggest that intensive preoperative chemotherapy coupled with aggressive surgical resection of primary and secondary lesions may improve the prognosis in poor risk osteosarcoma patients. The role of HDCT and its impact on survival must be better clarified.
L25 ISG/SSG III. An Italian-Scandinavian treatment protocol for nonmetastatic Ewing’s family tumors

G. Bacci¹, S. Ferrari¹, M. Mercuri¹, F. Bertoni¹, P. Picci¹, F. Fossati Bellani¹, P. Casali¹, A. Brach del Prever¹, A. Tienghi¹, S. Smeland², T. Wiebe², T. Böhling², O. Brosjö², T. A. Alvegård²

For the ¹Italian and ²Scandinavian Sarcoma Groups

gaetano.bacci@ior.it

From June 1999 to March 2003, 147 (ISG 124, SSG 23) patients with non metastatic Ewing’s sarcoma entered the study. Median age was 15 (3-9), 92 (63%) patients were male. Tumor had an extremity location in 80 (55%) patients, pelvic location in 25 (17%), and other central location in 41 (28%) patients (missing data in 1). Data on local treatment were available for 119 patients: 74 (62%) underwent surgery, 22 (19%) surgery and radiotherapy, 23 (19%) had only radiotherapy. Data on histological response were available for 87 patients: it was poor (grade I) in 39 patients, and grade II-III (good) in 21 and 27 patients, respectively. Overall a good radiological or histological response was observed in 62 (52%) of the 120 patients who completed the induction chemotherapy. So far data on high dose treatment are available for 40 patients. No chemotherapy related deaths were recorded, 1 patient died of pneumonia 10 months after chemotherapy completion, a severe radionecrosis did not allow the high dose treatment in a poor responder patient. With a median follow up of 15 (1-40) months the 2-year progression-free survival (PFS) was 82%. Patient with good or poor response to induction treatment showed similar probability of PFS (2-year PFS:GR 84%. PR 79%) as well as patients with different tumor location (2-year PFS: extremity 82%, pelvis 82%, central 81%). The results are encouraging especially for poor responders/non extremity patients. The study is ongoing.
Ad interim report of the Italian-Scandinavian Sarcoma Group (ISG-SSG) IV protocol for high risk Ewing’s sarcoma. The Italian experience.

From June 1999, 37 patients were enrolled in the Protocol in Italy. There were 22 males and 15 females; median age was 15 years (range 5-34). Primary site of tumor was: pelvis-12, ribs-8, femur-5, soft tissue only-5, vertebra-2, fibula-2, scapula-2, tibia-1. Metastatic sites were: lung-29, pleural effusion-6, single bone met.-2. Chemotherapy induced a manageable grade III-IV hematological toxicity in almost 100% of cycles. Local treatment (32 pts evaluable) consisted of surgery (13/32), RT (14/32), or surgery+RT (5/32); no local treatment was done in 1 patient. Grade II-III necrosis was recorded in 53% of the cases. Resection of lung metastases was performed in only 5 patients, while RT on the lungs was given in 66% of cases. The median n° of harvested CD34+ cells was 10x10^6/kg (range 5-36). After megatherapy, neither toxic deaths nor severe VOD were encountered; take of PMNs and platelets was at a median of 10 and 12 days, respectively. So far, 7 pts are on treatment, 6 pts did not complete the program for progression of disease before megatherapy, and 24 completed the treatment program. As to December 2002, 26 pts (70%) are relapse-free, while 11 (30%) had progression/relapse and 7 of them died of disease. The treatment is feasible and the toxicities are manageable; the median follow-up, 15 months, too early to draw any definitive conclusion.
L27 Pharmacokinetics of cytostatics in patients treated according to the ISG/SSG I protocol

T. Skärby\textsuperscript{1}, T.A. Alvegård\textsuperscript{1}, G. Bacci\textsuperscript{2}, O. Björk\textsuperscript{1}, S. Eksborg\textsuperscript{1}, S. Ferrari\textsuperscript{2}, A. Johnsson\textsuperscript{1}, P. Picci\textsuperscript{2}, G. Saeter\textsuperscript{1}, K. Sundby Hall\textsuperscript{1}, T. Wiebe\textsuperscript{1}, P. Höglund\textsuperscript{2}

For the \textsuperscript{1}Scandinavian and \textsuperscript{2}Italian Sarcoma Groups
tor.skarby@pharmacia.com

Introduction Several studies indicate a correlation between the pharmacokinetics of cytostatics, toxicity and survival during cancer treatment. By use of population pharmacokinetics the number of blood samples may be reduced to a number that is clinically feasible to obtain. The present study was performed to assess the pharmacokinetics of cytostatics used during treatment of osteosarcoma according to the ISG/SSG I.

Material and methods Blood sampling was performed from 1997 to 2000 at 5 institutions in Sweden, Italy and Norway. The population pharmacokinetics was evaluated for Methotrexate (19 patients; 45 treatment courses), Ifosfamide (23 patients; 51 courses), Doxorubicin (24 patients; 46 courses) and Cisplatin (26 patients; 52 courses).

Results In a first preliminary evaluation NONMEM (Nonlinear Mixed Effects Model) has been used to evaluate clearance for each cytostaticum in each patient. An one compartment model was used for Doxorubicin, free Cisplatinum and 4-OH-Ifosfamide whereas a two compartment model gave a better fit for the Methotrexate data. AUC (Area Under the Curve) was calculated from dose and clearance. The results (table) indicate a pronounced variability in AUC.

<table>
<thead>
<tr>
<th>AUC</th>
<th>Methotrexate (μmol/L*h)</th>
<th>Doxorubicin (μg/L*h)</th>
<th>Free Cisplatin (μg/L*h)</th>
<th>4-OH Ifosfamide (μmol/L*h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>7054</td>
<td>2526</td>
<td>10469</td>
<td>235</td>
</tr>
<tr>
<td>Range</td>
<td>5164-10123</td>
<td>596-3998</td>
<td>5442-18362</td>
<td>156-426</td>
</tr>
<tr>
<td>Mean</td>
<td>7045</td>
<td>2381</td>
<td>10864</td>
<td>240</td>
</tr>
<tr>
<td>SD</td>
<td>1227</td>
<td>753</td>
<td>3163</td>
<td>43</td>
</tr>
</tbody>
</table>

Further evaluations will be presented at the SSG meeting in Gothenburg, June 2003.
**L28 Analysis of P-glycoprotein expression in high-grade osteosarcoma patients treated according to the ISG/SSG I protocol**

*M. Serra*¹, *M. Pasello*¹, *K. Scotlandi*¹, *M.C. Manara*¹, *G. Bacci*¹, *S. Ferrari*¹, *F. Bertoni*¹, *S. Smeland*², *T.A. Alvegård*², *P. Picci*¹

For the ¹Italian and ²Scandinavian Sarcoma Groups

massimo.serra@ior.it

*Introduction* We evaluated the prognostic value of P-glycoprotein in high-grade osteosarcoma (OS) patients, treated according to the ISG/SSG-I protocol.

*Patients and methods* The ISG/SSG-I treatment protocol included 144 patients with primary, non-metastatic, high-grade OS. By using immunohistochemistry, P-glycoprotein was assessed in 83/180 cases (46%). Immunohistochemistry results were analyzed in relation to other clinico-pathological features and clinical outcome.

*Results* P-glycoprotein-positivity was found in 47/83 cases and was significantly associated with a higher incidence of relapse and a worse outcome, with survival rates of 47% and 78% in P-glycoprotein-positive and –negative patients, respectively. No significant association was found between P-glycoprotein-positivity and clinico-pathological features.

*Conclusions* Overexpression of P-glycoprotein at clinical onset is the most important adverse prognostic factor for high-grade OS patients, treated with ISG/SSG-I protocol. Increased P-glycoprotein levels should be taken into consideration to identify, at time of diagnosis, high-risk subgroups of OS patients.
L29 Presentation of the nephrotoxicity data in the ISG/SSG I protocol
L. Hjorth¹, S Ferrari²

¹Dept of Pediatrics, Lund University Hospital, Lund, Sweden, ²Dept of Chemotherapy, Istituto Ortopedico Rizzoli, Bologna, Italy
lars.hjorth@skane.se

Objectives To further analyze the extent of nephrotoxicity in the ISG/SSG I protocol for the treatment of high-grade osteosarcoma of the extremities involving a combination of nephrototoxic drugs, i.e. ifosfamide, cisplatinum and methotrexate.

Patients Collected from the Rizzoli Institute in Bologna, Italy, as well as from participating Nordic centres within the SSG from 1st of March 1997 to February 2003 at the longest.

Results In September 2000 we presented the 3-year nephrotoxicity data at the first joint meeting of the ISG and SSG in Capri, Italy. We showed that the glomerular filtration rate decreased and the serum-creatinine increased when baseline values were compared to values at longest possible follow-up. The ratios of u-albumin (glomerular marker) and u-alpha-1-microglobulin (tubular marker) to u-creatinine were higher than normal at follow-up indicating a necessity for continued surveillance. The latest nephrotoxicity results of the ISG/SSG I protocol will be presented at the second joint meeting of the Italian/Scandinavian Sarcoma groups in Gothenburg, June 2003.
Imatinib mesylate (Glivec®) is the first effective systemic therapy for gastrointestinal stromal tumor (GIST). About 60% of patients with overtly metastatic GIST achieve a durable response with imatinib, and the therapy is usually relatively well tolerated at doses of about 400 to 600 mg o.d. However, about 10 to 15% of GISTs are primarily resistant to imatinib, and most GISTs acquire resistance with prolonged treatment. Several studies are currently ongoing or being planned in the adjuvant or neoadjuvant setting. In these trials 1 or 2-year adjuvant imatinib therapy is used, although the optimal duration of adjuvant therapy is not known. Patients with a high risk of disease recurrence can be reasonably well identified using the primary tumor size and some measure of the cell proliferation rate, such as the mitotic count. Patients with a large primary tumor (>10 cm in diameter), a high mitotic count (>10 mitoses/50 HPFs), or a combination of the two (a diameter >5 cm and the mitotic count >5/50 HPFs) have greater than 50% risk for recurrence within 5 years of the diagnosis, and form a high risk group well-suited for research on adjuvant therapy. Patients rendered free from metastatic disease by surgery have close to 100% risk for recurrence. Such high risk patients should be preferably treated in prospective, multicenter study protocols. These need to evaluate imatinib efficacy and toxicity in placebo controlled studies, and investigate treatment duration, optimal dosage and possibly in the future combination therapies.
L31 Preoperative chemo-radiation therapy and intraoperative or postoperative boost in retroperitoneal soft tissue sarcomas. The Italian Sarcoma Group protocol

A. De Paoli¹, A. Gronchi²

¹Radiation Oncology Dept CRO-INT, Aviano, ²Surgical Oncology Dept INT, Milan, Italy adepaoli@cro.it

Local recurrence is common after surgery for retroperitoneal sarcomas. Post-op radiation therapy (RT) has not been successful because of dose-tolerance of the surrounding normal structures which prevents adequate dose of radiation.

Pre-op RT offers some potential advantage in the treatment planning and adequate radiation dose may be more safely delivered. In addition, large part of tumor cells may be inactivated minimizing the risk of tumor implantation during surgery and the possible reduction in tumor size with the thickening of the pseudo-capsula may facilitate surgical resection. The combination of pre-op RT with intraoperative (IORT) or post-op RT boost, could allow to escalate the dose to the tumor bed, specifically targeting areas at highest risk of recurrences. A pilot study of ISG Institutions demonstrated the feasibility of this approach and encouraging results have been reported.

To further improve disease control, combined chemotherapy and preoperative RT has been considered. The expected additive activity of this combination may be useful in maximizing the local effect in low-grade tumors and a systemic benefit may also be expected in high-grade tumors to reduce the metastatic potential. Continuous infusion high-dose Ifosfamide (14 g/sqm) for 14 days has demonstrated effect in sarcomas and its potential radio-enhancing effect has been reported in laboratory and preliminary clinical studies.

From these considerations, a pilot study has been planned by ISG to explore the feasibility, activity and effectiveness of concurrent Ifosfamide and preoperative radiation therapy with intraoperative or postoperative boost in primary and recurrent retroperitoneal adult soft tissue sarcomas.
L32 ISG/OS1. Prospective randomized study for the treatment of nonmetastatic osteosarcoma of the extremity

G. Bacci

Dipartimento di Oncologia Muscoloscheletrica, Istituto Ortopedico Rizzoli, Bologna, Italy
gaetano.bacci@ior.it

Aims To evaluate clinical outcome and toxicity of two chemotherapy regimens based on methotrexate (MTX), cisplatin (CDP), adriamycin (ADM) and ifosfamide (IFO) delivered at the same cumulative dose.

Study design Randomized study. Patients are randomized to receive treatment with MTX, CDP, ADM, IFO, or with MTX, CDP, ADM, with IFO only in the postoperative phase in patients poor responders to the other 3 drugs.

Number of patients Patients will be recruited over a 5-year period. Number of patients: 246 power: 80%; p 0.05, evaluable difference 15%.

Inclusion criteria Histologically proven diagnosis of high grade extremity osteosarcoma, age ≤ 40 years, no metastases evident on CT and bone scan. No contraindications to the use of drugs in the protocol. Informed consent.

Exclusion criteria Presence of metastases, osteosarcoma subtypes, previous malignant neoplasms, contraindications to the use of drugs in the protocol, no informed consent.

Date of activation April 2001.

Recruitment April 2003, 103 patients.
Aims To evaluate clinical outcome (EFS, PFS, DFS, MFS, OS) and chemotherapy-related toxicity in patients 41-65 years old with high grade bone sarcoma treated with a three drug (ADM-CDP-IFO) chemotherapy regimen, and MTX in poor responder patients (PR).

Study design Non controlled clinical trial. Depending on clinical features, and feasibility of adequate surgical removal of the tumor, eligible patients may receive a primary chemotherapy treatment followed by post operative chemotherapy or only adjuvant chemotherapy treatment. In case of adjuvant treatment patients will be treated with the 3-drug regimen (CDP-ADM-IFO). In patients who will receive primary chemotherapy, the histologic response will be evaluated, and graded according to Salzer-Kuntschik, % of necrosis, Huvos). In patients with a poor histologic response (S-K 5-6, <50% tumor necrosis, Huvos I), MTX will be added (in case of adequate glomerular function) in the postoperative phase. Patients will be enrolled for a 3 year period for an estimated number of patients/year of 45.

L34 European-American osteosarcoma study (EURAMOS)
S. Smeland

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

A randomized trial of the European and American Osteosarcoma Study Group
Principal Investigators: Dr Neyssa Marina (COG), Dr Stefan Bielack (COSS), Dr Jeremy Whelan (EOI), Dr Sigbjørn Smeland (SSG)

Background and rationale EURAMOS 1 is a joint protocol of four of the world’s leading multi-institutional osteosarcoma groups (COG, COSS, EOI, SSG). The main aim of the study is to optimize the treatment of patients suffering from resectable osteosarcoma based on histological response to pre-operative chemotherapy.

Patient selection and study design The EURAMOS 1 trial is open for all patients with resectable high-grade osteosarcoma of the limbs or axial skeleton, be the tumor localized or primary metastatic, who are considered suitable for neo-adjuvant chemotherapy. All patients registered will receive a standard three-drug induction regimen consisting of 2 cycles of cisplatin and doxorubicin along with 4 cycles of methotrexate (MAP). Post-operative therapy is determined by the histological response of the tumor. Good responders (< 10% viable tumor) will be randomized to continue with MAP, or receive interferon-α as maintenance therapy after MAP (MAPifn). Poor responders (≥ 10% viable tumor) will be randomized to continue with MAP or to receive the same regimen with the addition of ifosfamide and etoposide (MAPIE).

Statistical considerations Event-free and survival is the primary endpoint whilst overall survival, toxicity and quality of life are secondary end-points. Randomization of 1260 patients is required (1400 registered patients). The planned recruitment rate is 400 patients per year and the estimated accrual time 3.5 years.

The protocol is planned to be activated by the end of this year.
L35 European relapse osteosarcoma register (EURELOS)
S. Smeland

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

A joint European protocol for prospective registration of relapsed osteosarcoma.
Principal Investigators: Dr Stefan Bielack (COSS), Dr Stefano Ferrari (ISG), Dr Sigbjørn Smeland (SSG)

Background and rationale Relapsed osteosarcoma harbors a very poor prognosis and there is no standard therapy. Important issues such as the role of second line chemotherapy remains to be determined. The purpose of this study is to prospectively collect data from patients with relapsed osteosarcoma as a basis for future studies.

Data collection Patient, initial tumor and relapse data will be recorded prospectively and sent to a common study database in Münster. Data will be sent every 6 months and the planned study duration is 3 years.

The protocol is planned to be activated by the end of this year.
L36 Methodological problems for clinical trials in rare tumors

P. Bruzzi

National Cancer Research Institute, Genova, Italy
paolo.bruzzi@istge.it

The methodology of cancer clinical trials is increasingly affected by the progress in the understanding of cancer biology and genetics, and by the availability of drugs with specific biochemical or molecular targets. Incidence data by histology and stage provide a grossly inadequate picture of the number and complexity of clinical situations encountered in any cancer. Even in common cancers, the need to modulate treatments based on an increasing number of patient’ and tumor’ characteristics creates a number of subgroups of patients, each relatively uncommon, and often frankly rare. Many new promising treatments proposed for clinical trials are best suitable for one or few of these subgroups, while they may represent the most promising option in cancers affecting different sites and/or with different histology. Accordingly, the problems in the design and conduct of clinical trials that once were typical of less frequent cancers are rapidly pervading all clinical research in cancer therapy.

Until recently, cancer research strategies were based on the uncritical assumption that phase III trials had to be randomized and could be conducted only if an adequate number of patients was available. Conversely, the uncontrolled phase II trial was considered a flexible tool that could be adapted to meet the needs of researchers who wanted (or had to) to run small trials, and was considered the only solution in rare cancers.

As a consequence, the available therapeutic evidence in many rare tumors is represented by a series, of ‘phase II trials’ and ‘case series’. Treatment choices are often based on ambiguous and/or questionable, criteria, and there is a striking heterogeneity in treatment strategies among clinical centers, even within the same country.

It must be acknowledged that the traditional methodology of clinical trials is not applicable to rare cancers. Its foundations and principles need to be critically revisited to provide clinical researchers with flexible and efficient tools that will make it possible to accumulate sufficient ‘valid’ evidence to enable rational clinical decisions in rare cancer conditions.

Several of these tools have been proposed in the last 10-15 years and include phase III trials with historical controls, RCT’s with surrogate endpoints, underpowered RCT’s, and Bayesian approaches to clinical trials. Among these, a Bayesian approach represents the most promising solution with a sound statistical rationale for the design and analysis of clinical trials in rare tumors and conditions.
L37 Core needle biopsy performed by the cytopathologist: a technique to complement fine needle aspiration of musculoskeletal tumors

H. A. Domanski1, B. Carlén1, J. Engellau2, P. Gustafsson3, K. Jonsson4, F. Mertens5, A. Rydholm3, M. Åkerman1

Depts of 1Pathology & Cytology, 2Oncology, 3Orthopedics, 4Radiology, 5Clinical Genetics, Lund University Hospital, Lund, Sweden
henryk.domanski@pat.lu.se

Introduction Fine needle aspiration biopsy (FNAB) has been used as the primary diagnostic modality in evaluating patients referred to the Musculoskeletal Tumor Center at Lund University Hospital for over 30 years. In most patients the diagnosis can be rendered from aspiration smears alone. The main limitation of FNAB is lack of tissue architecture and that the specimen is not always adequate for ancillary studies.

Patients and methods A consecutive series of 130 patients with soft tissue and bone tumors was examined by core needle biopsy (CNB) performed by the cytopathologist in conjunction with FNAB. These findings were compared to histologic diagnoses made on resected specimens (80 cases) and to clinical findings and other examinations which confirmed the benign diagnoses in 50 patients not operated on.

Results: FNAB combined with CNB could correctly identify all malignant (n=79) and 50 of 51 benign lesions. The tumor subtype was determined correctly in 40 and the grade in 48 of 50 patients with primary sarcoma. The tumor type was diagnosed in all patients with primary malignant tumors other than sarcoma.

Conclusions FNA evaluation of orthopedic lesions complemented by CNB, combines cytology with histology and increases the chance of obtaining a specimen adequate for adjunctive diagnostic methods. In this study, obtaining both FNA and CNB at the same session by the cytopathologist speeded diagnosis, increased the number of correct diagnoses and subtyping / malignancy grading of sarcomas.
Bone sarcomas may appear in any site of the children skeleton but usually affect the long bones of the limbs. Surgical options are conditioned by patient’s age, skeletal location and soft tissue extension.

The presented algorithm addresses the surgical treatment of bone sarcomas of the limbs in children (2-14 year/old ) and it is based on the experience achieved on more than 300 cases from 1990 to 2002.

Preoperative imaging studies define the choice of the main surgical parameters. Limb amputation is still the first choice, as in adult population, if a wide margin cannot be achieved by limb-salvage surgery or in distal tibia tumors. In the lower limb, modified amputation techniques as rotationplasties, still play a great role in young children, particularly for knee reconstructions.

Skeletal locations are stratified as follows:
- arm (shoulder/intercalary humerus/elbow)
- forearm (elbow/intercalary radius or ulna/wrist)
- thigh (hip/intercalary femur/knee)
- leg (knee/intercalary tibia, ankle)

The patients are stratified for age in three groups: age <6; age 6-9, age 10-15. In limb salvage surgery, skeletal reconstruction often includes the major joints but progress in tumor imaging and preoperative treatment has increased the possibilities of joint preservation. In selected cases it is possible to preserve the articular portion of the epiphysis, or the whole epiphysis including the growth plate. In these cases, intercalary bone allografts often supplemented by vascularized bone autografts are considered the best reconstructive option.

If otherwise the joint has to be reconstructed, different options are taken in account:
- modular prostheses with stems adapted for children (shoulder, knee)
- lengthening prostheses (knee)
- customized methylmetacrylate implants (shoulder)
- osteoarticular allografts (shoulder, elbow, knee, wrist)
- composite allograft/prostheses (shoulder, hip, knee)
- osteoarticular vascularized autografts (shoulder, wrist, hip)
L39 Surgical and reconstructive procedures in children with osteosarcoma. The Scandinavian Sarcoma Group experience

O. Brosjö, H. Bauer

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

We retrospectively analyzed the choice of surgical procedure and preferred reconstruction in children with high-grade osteosarcoma (OS).

Patients and methods Since 1986 the surgical treatment of 152 children under the age of 16 at diagnosis of OS, have been reported to the Central Registry of the Scandinavian Sarcoma Group (SSG). OS of the axial skeleton was excluded. All children received neoadjuvant chemotherapy according to the specific SSG-protocol running at the time of diagnosis.

Results An amputation was performed on 56 children. However, the majority (52) was performed during 1986-96. Only 4 children have been amputated since 1997. Local excision was performed in 96 children. The most common reconstructive procedure in 49 distal femur OS was megaprostheses (26) followed by rotationplasty in 14 children. A few osteochondral allograft reconstructions (6) have been performed in the distal femur, but only 1 since 1995. Reconstruction of the proximal tibia was mainly performed with megaprostheses or a massive allograft whereas the most common reconstruction of proximal humerus was megaprostheses or vascularized fibulagraft.

Conclusions This retrospective, multicenter study shows that a child with OS of the extremity nowadays has a very low risk of needing an amputation. Megaprosthetic replacement is the most common reconstructive procedure after local excision for OS in distal femur and proximal tibia/humerus. Rotationplasty seems to be rather popular for children with OS in distal femur.
Introduction The aim of surgical treatment of skeletal metastases is to achieve immediate restoration of function while alleviating pain. In 1999 the Skeletal Metastasis Registry developed under SSG as a regional, multicentric, prospective study to provide a scientific basis for treatment recommendations and to provide participating departments a tool for quality assessment.

Patients and methods From Sept 1999 to Feb 2003, 227 female and 195 male patients with an average age of 63 years underwent 456 operations for non-spinal skeletal metastases in 9 Scandinavian Sarcoma Centers. 34/422 (8%) patients had more than one operation.

Results Main indication for surgery was fracture (72%), followed by impending fracture (8%) and pain (7%). Operations concerned mainly femur (61%), humerus (19%) and pelvis (12%). 45% of the patients were treated by prosthetic procedures. 44% had internal fixation. Carcinoma of the breast, prostate, kidney and lung were the most common primary tumors. 90 patients had only 1 metastasis, while 200 patients had more than 4 known metastases at time of operation. 107 patients had preoperative radiation (25%). 39/422 (9%) had complications, mainly wound infection and prosthetic dislocation. 6% had reoperation related to the first surgically treated metastasis.

273 patients died; 85% due to cancer. Overall 1-year survival was 36%. 76/422 (18%) patients died within 6 weeks after operation. 40% died within 6 month. 21% of the patients were confined to bed or a wheelchair before operation, decreasing to 14% at 6-weeks- and 12% at 6-month follow-up.
L41 Giant Cell Tumor (GCT) in the thoracic wall with pulmonary metastases, a case report and literature study

J.P. Poulsen¹, L.H. Jørgensen², B. Stenwig³, I. Taksdal⁴, K. Sundby Hall¹

Depts ¹ Oncology, ²Surgery, ³Pathology, ⁴Diagnostic Radiology, The Norwegian Radium Hospital, Oslo, Norway
j.p.poulsen@klinmed.uio.no

Introduction
GCT of bone is exceptionally rare in the scapula, ribs, sternum, clavicle and skull. It rarely (3-5% ?) gives pulmonary metastases.

Patient
31-year-old woman was admitted to us June 01 with a 7 cm tumor located in the 2nd right costal region. Open biopsy showed a GCT with some components of aneurysmal bone cyst. The tumor was considered benign, and, the patient was not operated until August. The tumor measured 12 x 9 cm at the time of operation, and on CT, one lesion suspicious of metastases, had appeared in each lung. She was operated on with resection of the thoracic wall and reconstruction with gore-tex graft and wedge resection in both lower pulmonary lobes. The histological examination showed the same GCT, without any findings indicating malignant transformation, marginally excised as well as 3 lung metastases. Due to the marginal excision we gave her postoperative radiotherapy. In January 2002 a CT scan showed 8 lesions (< 9mm) in her left lung and 2 lesions (< 7 mm) in her right lung. She got 2 courses of chemotherapy (one with Cisplatin 90mg/m² & Adriamycin 75mg/m², and one with Ifosfamide 2,4g/m² x 5 days). On evaluation in March 02 she had progressed, and chemotherapy was stopped. In May she was operated with a left posterolateral thoracotomi, enucleating the lung tumors with laser. The histological examination again showed GCT. No further treatment was given. She has since been regularly controlled with CT scans, and shortly after last surgery 3 more lesions were found in the left lung and 1 in the right. We decided not to treat her any further. At the last control in March 03, she is doing well, no new lesions have appeared, 2 lesions have disappeared and the sizes of the other known metastases are unchanged.

Literature
Even if this is a rare condition, several cases have been reported in the literature in the last few years. The literature will be reviewed and the different treatment options will be discussed.
Radiotherapy in soft tissue sarcoma: indications based on results from the SSG Register

H.C.F. Bauer

Oncology Service, Dept of Orthopedics, Karolinska Hospital, Stockholm, Sweden
henrik.bauer@ks.se

Based on results from early Scandinavian series of soft tissue sarcoma (STS) patients, postoperative radiotherapy has mainly been indicated after an intralesional or marginal margin. Furthermore, myectomy, i.e., removal of the whole muscle from origin to insertion has been considered to provide a similar low local recurrence rate as after a compartmental margin.

In an analysis based on the SSG Register of 943 primary STS patients operated at a sarcoma center in Finland, Sweden, or Norway 1986-93, the overall 5-year local control rate was 0.80. The rate was 0.87 for subcutaneous tumors, 0.89 for deep and low grade tumors, and 0.74 for deep and high grade tumors. In this latter group only 31% had adjuvant radiotherapy, overall 22% had radiotherapy. A myectomy was not associated with better local control than other wide margins.

Based on these findings adjuvant radiotherapy appears indicated after all surgical margins for high grade and deep STS. For low grade tumors radiotherapy is only indicated after a marginal excision and for subcutaneous tumors in anatomical locations where it is difficult to assure a 5 cm margin, e.g., distal to elbow or knee.

In an analysis of 1243 patients from the SSG Register operated 1994-2001 shows that radiotherapy was increasingly applied, overall 32%. This leads to better local control, overall 0.86 at 5 years. Only 42% of patients with high grade and deep STS had adjuvant radiotherapy. Hence, there are still many patients who do not receive adjuvant radiotherapy and who remain at an undue risk of local recurrence.
L43 SSG XIII: A treatment protocol to high-risk non-metastatic soft tissue sarcoma of extremities and trunk wall


For the Scandinavian Sarcoma Group
sigbjorn.smeland@klinmed.uio.no

SSG XIII: Adjuvant treatment for adult high-risk soft tissues sarcoma in extremities and trunk wall.

Introduction Non-metastatic high-grade soft tissue sarcoma of adults is associated with a relatively poor prognosis. The SSG XIII study was undertaken to determine whether adjuvant chemotherapy improves outcome in a high-risk subgroup.

Patients and methods A high-risk subgroup has been identified from the SSG database and all patients fulfill at least two out of three adverse risk criteria: tumor size > 8 cm, presence of tumor necrosis and vascular invasion. Patients are intended to receive 6 adjuvant courses of ifosfamide (5g/m²) and doxorubicin (50 mg/m²). Accelerated radiotherapy is given interposed between chemotherapy courses to a total dose of 36 Gy or 45 Gy.

Results From June 1998, 61 patients are recruited. One fourth of the patients had all three risk factors at inclusion. Median age is 55(21-70) years and median tumor size 10 cm. Nine tenth of the tumors are histologically assessed as malignancy grade IV. All but 1 patient have received the intended 6 courses of chemotherapy and 35 patients have been given additional radiotherapy according to protocol. The 3-year overall and metastases-free survival rates are 69 +/- 9% and 65 +/- 9% respectively. 6 patients have experienced a local relapse at a median time of 10(7-18) months from surgery.

Conclusion The treatment is feasible and well tolerated. The preliminary results compare favorably to non-chemotherapy treated historical controls (40% five-year metastases-free survival). Recruitment is less than expected and effort will be undertaken to improve this.
L44 Recommendations for treatment of metastatic soft-tissue sarcomas: a proposal of the SSG

K. Sundby Hall¹, P. Lindholm², J.O. Fernberg³, M. Eriksson⁴

Depts of Oncology, ¹The Norwegian Radium Hospital, Oslo, Norway, ²University Hospital of Turku, Finland, ³Radiumhemmet, Karolinska Hospital, Stockholm, ⁴Lund University Hospital, Lund, Sweden
k.s.hall@klinmed.uio.no

Treatment strategies for patients with metastatic soft-tissue sarcomas were discussed in SSG’s chemotherapy group at a meeting in Stockholm 27 January 2003.

Adult patients presenting with soft tissue sarcomas (STS) are at a significant risk of metastatic disease. Of patients with localized, high-grade STS 10% will have metastases at presentation and about 50% will develop metastases despite local control of the tumor. With metastatic disease median survival is 12 months. Accordingly patients with metastatic disease constitute a rather large group of all patients with STS. Their poor prognosis and special problems needs to be addressed.

In 70% of all cases metastatic disease only involves the lungs. In selected patients metastatectomy seems to be of value whereas the role of chemotherapy is unclear. A 5 years survival of about 40% can be obtained with surgery alone. EORTC/SSG initiated in 1996 a randomized study to explore the value of adding chemotherapy to surgery. Unfortunately, the study was closed in 2000 due to low inclusion rate.

Adult patients with inoperable metastatic STS are generally considered as incurable. However, long-term survivors are observed in all prognostic subgroups of patients, in particular those achieving a CR to first-line chemotherapy. In the case of treatment failure after first-line chemotherapy good palliative care should be focused. In many cases radiotherapy is the treatment of choice.

The opinion from the participants on the meeting was that SSG needs principles for treatment of metastatic soft tissue sarcoma. A working group was settled and the first draft of the recommendations will be presented at the SSG meeting.
L45 Thermochemotherapy in high risk sarcoma patients

Bergen Sarcoma Group and Bergen Hyperthermia Oncology Group, Dept of 1 Oncology, 2 Radiophysics, 3 Orthopedics, 4 Radiology, 5 Pathology, 6 Surgery, Haukeland University Hospital, Bergen, Norway
odd.monge@helse-bergen.no

Introduction We report pilot experience in 4 patients with locally advanced high risk sarcoma given thermochemotherapy as preoperative treatment, i.e., chemotherapy with etoposide, ifosfamide and doxorubicin (EIA) concomitantly with regional hyperthermia. There is a rationale for the use of heat treatment to overcome chemo resistance in malignant tumors.

Patients and methods The first patient was an 18-year-old boy with a 24 cm synovial sarcoma of the 12th left rib. The second patient was a 56-year-old woman with a 9 cm high grade pararectal MFH. The third patient was a 34-year-old female with NF1 and an 8 cm recurrent high grade MPNST of the left sciatic nerve. The fourth patient was a 36-year-old man with NF1 and a 12 cm high grade MPNST of the right lumbar plexus. All tumors had extracompartmental extension. The heat treatment was given using a BSD Sigma 60 applicator suited for heating tumors in the thighs, pelvis and trunk. Invasive thermometry was used to monitor tumor and normal tissue temperatures during heating. During each heat treatment we aimed for a minimum temperature of at least 42°C in the tumor for 60 min. The patients were given 3-6 courses of chemotherapy, 3 weeks interval, and 3-6 sessions of heating. All patients were given adjuvant radiotherapy after resection.

Results The toxicity of the thermochemotherapy was as expected for chemotherapy alone. All tumors responded to thermochemotherapy and were subjected to marginal or wide resections. In patient 3 there was no sign of viable tumor in the resection specimen. Patient 1 and 3 are alive NED after 8 and 5 years, respectively.

Conclusion The 2 patients with long time survival showed remarkable response to preoperative thermochemotherapy, i.e., major down staging of a very advanced synovial sarcoma that became resectable, and a complete pathological response in a large MPNST. The latter is probably very rarely seen after chemotherapy alone. The pilot experience indicated that the treatment schedule was feasible in our hands. A basis was provided for continued investigation of the position of thermochemotherapy as participants in a international multi centre phase III-study (EORTC 62961/ESHO RHT-95) comparing a similar thermochemotherapy schedule with the same chemotherapy alone as neo-adjuvant treatment in high risk extracompartmental sarcoma.