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1. Surgical indication in lower limb bone sarcomas of infancy—20 years experience at Istituto Ortopedico Rizzoli

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In 1977–1996, 252 lower limb bone sarcomas in a patient population under age 13 (mean age 9.5), have been surgically treated at Istituto Ortopedico Rizzoli.

There were 205 osteogenic sarcomas, 42 Ewing sarcomas and 5 MFHS. 99% of the patients received perioperative chemotherapy according to the diagnosis and to the different historic protocols. A limb-salvage approach was preferred in 152 cases (60%), 139 of whom had a skeletal reconstruction. Rotationplasty was performed in 30 patients (12%) while the remaining 70 cases were amputated (28%). Enormous changes with respect to surgical indications have been characterizing the evolution of the series along the years. Classic amputations represented the 58% (53/92) of the surgical treatments during the first decade 1977–1986 while in the latter one (1987–1996) they decreased to 11% (17/160). An opposite trend was shown both for rotationplasty (from 3% to 17%) and limb-salvage surgery (from 39% to 72%). Moreover, if we analyze surgery and indications according to child age, we realize that below age 8, a limb-salvage was performed just in 42% of the cases versus 67% in the group 9–12 years old. In the 139 cases where the bone was reconstructed, the tumor was localized mainly in distal femur (53 cases) and proximal tibia (46) followed by diaphyseal (23) and proximal femur (15), diaphyseal (9) and distal tibia (2), distal fibula (1) and 1st metatarsus (1). Reconstructive techniques as well have been improving in the last 20 years: in the period 1977–1986 the most common reconstruction was represented by cement arthrodesis (62%), while in the next decade the main surgical group was that of biological reconstructions (74%). 10 patients have been treated by secondary lengthening procedure.

Local recurrence (LR) rate ranged from 3% of classic amputations (2/70) to 7% of both rotationplasties (2/30) and limb-salvage (10/152). In reconstructed patients, 50% had a

secondary surgery because of septic or mechanical complications; 13 cases (10%) underwent a secondary amputation (8 infections and 5 LRs). In this group, 117 patients with more than 1 year follow-up were available for functional evaluation according MSTS: 44% of the cases presented a satisfactory result (excellent or good), 28% fair and 28% poor.

The younger bone sarcoma patients represent a subpopulation with a high risk of primary lower limb amputation; when reconstructed, they present a high risk of secondary amputation. Nevertheless, biologic reconstructions are improving. Recently the expanded indication to intraepiphyseal resections and to osteoarticular allografts even in prepubertal age, together with the application of modular lengthening or composite prostheses have allowed us to cancel the use of temporary implants and to save joint functions.

2. Incidence of bone tumors in young children

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From 1989 through 1993, 543 patients with tumors of the locomotor system and tumorlike lesions underwent surgically procedures at the Department of Orthopedic Surgery, School of Medicine, University of Zagreb and Clinical Hospital, University of Ljubljana.

Different tumors with classical age distribution were registered in 543 treated patients and only 10 (1.8%) patients were 5 years or younger. 6 were girls and 4 were boys. Almost all bones of the skeleton were tumor-invaded. Upper extremity was affected in 6 children and lower extremity in 4. The most frequent presenting complaints of our young children with tumors and tumorlike lesions were local tenderness and reduction of function, or local swelling and pain discovered by parents mostly at the time of bathing.

The distribution of tumors and tumorlike lesions made according to the histological diagnosis varies from numerous

benign and malignant primary bone tumors. The tumorlike lesions were aneurysmatic bone cyst treated in 2 young children and osteoid-osteoma, osteosarcoma, chondroma, osteochondroma, juvenile bone cyst, eosinophilic granuloma and benign soft tissue tumor were surgically treated in 1 patient each.

The 4-year-old boy with osteosarcoma of the proximal humerus, grade 3B was treated with en bloc resection without reconstruction and with chemotherapy, but he died after 16 months with metastasis. All other young children were surgically treated successfully and are still alive WED.

The incidence of tumors and tumorlike lesions in young children surgically treated in our hospitals is rather small, especially that of malignant bone tumors. The age of patients and anxiety with the panic of the family members play important role in choosing modality of treatment.

3. Ewing's sarcoma limb primaries in patients aged under 5 years—an EICESS review of 40 cases

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Ewing's sarcoma is uncommon in children under 5 years of age. Out of a combined data set of 684 patients with limb primaries registered with GPOH/CESS or UKCCSG/MRC trials offices 47 (7%) were under 5 years old. The aim of this review is to describe treatment and outcome with specific attention to local therapy issues related to treating young children with limb primaries. Out of these 47 cases 23 were girls, 6 had metastases at diagnosis. The patients were treated between 1980 and 1997. There are 36 patients surviving (4 still on treatment) with a median follow-up of 62 (3–161) months. Overall prognosis was not different to that for older patients with limb primaries (5-year RFS 64% vs. 58%, $p=0.9$). Decisions relating to local therapy were made on an individual basis depending on site, age and other factors. In the patients with lower limb primaries 11 had resections, 10 had amputations, 7 had a combination of surgery and radiotherapy, 1 had no local therapy (PD) and there were 4 for whom local therapy data was not yet available. For those with upper limb primaries, 4 had resections, 4 had radiotherapy alone, and 1 was unspecified. The choice of which mode of local therapy to use in these patients is complex, given the potential side effects of radiotherapy to surgery to developing limbs: amputation has obvious costs. In the patients over 5 there has been an increased proportion of patients having resections (alone or in combination with radiotherapy); this accounted for 35% of limb primaries before 1986 and then 75% in the following period. There was no significant increase in resections in the patients under 5 years, the use of endoprosthetic surgery is now common for older patients, in this series 4 children under 5 had an endoprosthesis, all with femoral primaries (ages 23, 29, 47 and 48 months). 3 of the 4 patients remain alive, 1 having a lengthening operation after

3 years; the others have less than 2 years follow-up. To what extent such patients can benefit from advances in surgical techniques raises complex questions in quality of life issues which require further investigation. The long term consequences of each mode of local therapy has been reviewed and recommendations are made for future management of this difficult group of patients.

4. Physeal distraction and bone lengthening in young children with malignant bone tumors

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In this study we report additional follow-up on a series of young children with sarcomas treated with external fixation. 33 patients underwent 41 distraction procedures for osteosarcoma (19) or Ewing's sarcoma (12). Operations include primary physeal distraction (26), distraction callotaxis (DC) for limb length discrepancy (LLD) (11), tumor resection and bone transport (1) and combine DC and compression for LLD and concurrent diaphyseal nonunion (3). The average age at each procedure was 10+7. All bone grafts healed at the distal site within a mean time of 4 months. Complications include LLD (8), allograft fracture (4) and infections (2) in 12 patients. 21 patients (63%) suffered no complications. 4 patients treated with physeal distraction before excision of the tumor and 9 cases treated with other original limb salvage procedures, had latter DC. The mean length gained was 9.5 cm. At a mean follow-up of 7 (1–13) years, 27 patients remained disease free. The Mankin limb function for all patients was graded as excellent or good in almost 70% of cases.

We believe that physeal distraction prior to limb salvage is a viable means to safely preserve the patient's normal joint cartilage in young children. We have also successfully used DC for LLD following limb salvage. Complications and healing rates of DC appears to be similar to results in standard lengthening.

5. Free vascularized growth plate transplantation for tumoral upper limb reconstruction in childhood

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In limb sparing surgery for malignant bone tumors affecting patients in growing age, an important aim to achieve is to preserve the limb length discrepancy after resection. In order to obtain this result, we performed a free vascularized fibula growth plate transplantation in 12 patients affected by osteosarcoma in 10 and Ewing sarcoma in 2 of the upper limb

(3 distal radius and 9 proximal humerus). Ten grafts were supplied by the anterior tibial artery, two by the peroneal artery. All the patients were treated by pre- and post operative chemotherapy. At an average follow up of 16 (3–48) months, 8 patients were continuous disease free, 3 were alive with disease, 1 was dead of disease. All but 2 the transplantation grew, and the average growth rate of the grafts where more than 1 (0.75–1.33) cm per year. For radial reconstruction excellent functional results has been obtained when the ulna was spared by the resection, enhancing joint stability and providing a good range of motion. Functional results were satisfactory in shoulder reconstruction where the reduced abduction was well compensated by the scapulothoracic joint.

Conclusion: Growth plate transplantation represents a successful solution for reconstruction of the upper limb in children.

6. Clavicle pro humero for malignant bone tumors in the proximal humerus in children

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We describe a new surgical limb salvage procedure for malignant bone tumors in the proximal humerus. The vascularized clavicle is shifted to bridge the defect after resection of the tumor. The acromioclavicular joint takes over shoulder joint function.

Design: 14 patients with tumorous lesions in the proximal humerus were operated on following this procedure. The follow up time in 8 patients is more than 2 years. The tumors were Ewing's sarcoma, osteosarcoma and chondrosarcoma.

Preoperative planning involves radiographs, MRI and CT scans of the tumor as well as measurement films of the clavicle to estimate the possibility for reconstruction. The clavicle is shifted after wide or radical excision of the tumor. The AC joint, as well as the proximal vascular supply, is preserved. Remaining muscles are reattached to the clavicle and glenoid. Internal fixation of the clavicle to the distal humerus is carried out with an small fragment AO-plate and screws. Postoperative care involved immobilization of the arm in an Desault bandage. Passive mobilization of the new functional shoulder joint starts after wound healing. A cast was given for 3 month. Partial weight bearing was started after fusion of the osteotomy and full weight bearing was allowed after hypertrophy of the clavicle was thought to provide enough stability.

Results: In 3 of 8 children the relatively thin clavicle fractured and needed revision surgery involving refixation and iliac crest bone grafting. The functional results after hypertrophy of the clavicle were comparable to endoprosthetic or osteochondral allograft replacement.

Conclusion: After remodeling and hypertrophy of the clavicle into an new proximal humerus, the AC-joint provides the functional shoulder joint. A careful fixation and postoperative immobilization is mandatory. Once the sensi-

tive early phase has passed and hypertrophy is monitored a long lasting biologic reconstruction is achieved.

7. Update on expandible prosthesis for lower limb salvage in children with bone sarcomas

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New techniques in care of children with malignant bone sarcomas have contributed to the increased length of survival. To improve the quality of life becomes now a priority and leads us to unproven techniques of limb sparing reconstructive surgery.

Growing children, especially those younger than 10 years of age have until recently fared better with an amputation than with limb saving reconstruction because of the unavoidable limb length discrepancy. After Sneath, then Lewis, we used expandible prostheses. We review here our 12-year experience with tibial and femoral prostheses and our successive models, the 2 last grow without open surgery.

Methods: The prostheses are produced in titanium, chosen for its better mechanical properties, twice as elastic and light as stainless steel. The prosthesis is manufactured following the recommendations of the surgeon for each patient with individualized size. The size of the epiphyseal part is small enough to be inserted from age 5 years and its smooth edges limit the soft tissue damage. The increase of the prosthesis has no limits, can be more than 15 cm, even for resection of 10 cm.

Patients: From 1984–1996, we used 32 growing prostheses for children aged 4.5–17 years: 5 tibial growing prostheses, 3 superior femoral prostheses, 5 total femur replacements, 19 inferior femur prostheses. The patients had Ewing's sarcoma (8), osteosarcomas (23), or other (1).

Results: 5 patients died from the illness. 28 had increasing of the prosthesis. The mean lengthening was 6 (0.2–12) cm. The function was much improved by the lengthening. Following EMSOS criteria, functional results at last examination are rated : excellent or very good (18), fair (9), bad (5). 2 patients suffered of aseptic loosening and 4 of infection following open surgery to increase the limb, leading extraction of the prosthesis to treat the infection. 1 was subsequently amputated. 3 had a new growing prosthesis.

Conclusion: The expandible prosthesis provides an excellent alternative to amputation in young children. Nevertheless, the infection risk appended to multiple surgical procedures in generation 1 growing prostheses, leads us to develop new generations of growing prostheses which do not need open surgery for lengthening.

8. Preservation of the epiphysis in children with endoprosthetic replacements around the knee

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Limb salvage in children with tumours around the knee must take into account the expected growth of the epiphyses of the bone(s) which is removed. Extensible endoprostheses have been used for this.

Material: In 124 patients we have also used a noncemented implant passing across the epiphyseal plate to anchor one side of an endoprosthetic replacement. The smooth, circular stem of the implant crosses the growth plate and is secured in the bone by a polyethylene sleeve which is fitted into the intramedullary canal. Rotation is prevented by anti-rotation lugs on the base of the implant. This "sliding" component has been used to date in 42 cases across the distal femoral epiphysis and 82 across the proximal tibial epiphysis. Data is now available on the amount of growth taking place in these physes up to skeletal maturity in 34 cases.

Results: The amount of growth occurring in the epiphysis is unpredictable and is not related to age at insertion, percentage of growth plate damaged, type of prosthesis inserted, functional use of the limb by the patient or distance of the base plate from the growth plate. There is a very low failure rate of these uncemented implants used in conjunction with a hinged knee.

The growth of the distal femoral epiphysis is found to be 67% (33%–95%) of that on the normal side and 80% of that predicted from growth charts. For the proximal tibial epiphysis the growth is 76% (18%–136%) of that on the normal side and 80% of that predicted from growth charts. Some of the diminished growth is due to the effects of chemotherapy.

Conclusion: "Sliding" components across the epiphysis allow valuable normal growth to take place in the immature skeleton in the remaining epiphysis. Cementing these prostheses in place does not appear to be necessary.

9. Treatment of malignant bone tumors in young children—complications and revisions

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Introduction of neoadjuvant chemotherapy and the increased need for limb salvage procedures led to the application of endoprosthetic reconstruction even in children. Reconstruction of defects in growing limbs in which the eventual shortening can be predicted requires the use of extendable prostheses. Between 1981 and 1986 custom made prostheses were used in children who had a growth potential of less than 40 mm at the appropriate epiphysis, and since 1986 an extendable type of prosthesis that matched the Kotz Modular Femur Tibia Reconstruction (KNIFTR) system and its suc-

cessor, the Howmedica Modular Reconstruction (HMR) system, was used.

We report on 23 patients with a mean age of 11 (4–17) years who were treated by resection of primary bone tumors and implantation of extendable prostheses. Resection of the distal femur was performed in 15 patients, 4 patients underwent a replacement of the total femur and in 3 patients the proximal tibia was replaced. The mean length gained was 13 (4.5–19.5) cm requiring a mean of 6 (1–13) procedures. In 3 patients a new automatically extending model was used.

Complications included restriction of movement due to a solid tubular scar around the prostheses, deep infection, skin slough, avulsion of the patellar ligament and prosthetic failure. Implantation of extendable endoprostheses in children provides a reasonable alternative to rotationplasty, but limb salvage requires a higher number of operations.

10. Longtime clinical and psychoemotional outcome studies following rotationplasty for malignant above knee tumors

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The purpose of this study was to investigate patients long-term psychosocial outcome, functional feature as well as the incidence of degenerative joint affection and osteoarthritis within the rotated leg. To avoid bias, we took special effort in investigating the complete population of 23 surviving patients, who underwent surgery more than 10 years ago. Only one patient was lost for follow up, the median observation time was 15 years.

During the reviewed period only 2 patients needed revision surgery of the rotated leg. 1 required hip exarticulation for local recurrence, caused by invasion of the not resected popliteal vein, the other angulation osteotomy for malrotation. None of these patients was revised twice. Regarding the Enneking MSTS scoring system 91% rated excellent or good, activities of daily living scored unaffected or with minimal impairment in 83%. There were no major signs of osteoarthritis or ankle joint disturbances notable. Personal style of living was found to be equal to reference groups, education and state of employment superior. There was no increased incidence of depression. In contrast to previous studies, we were able to describe a statistical relevant correlation between psychosocial and clinical parameters.

11. Functional results and quality of life measurements in 39 young children with multimodal treatment of musculoskeletal tumors

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Objective and methods: With the increasing number of pa-

tients surviving disease free following the diagnosis of malignant bone tumors and the availability of different modalities of local therapy and limb salvage procedures late functional results and quality of life measurement have become essential. The functional evaluation score of Enneking for orthopedic sequelae, and quality of life measurements (EORTC QLQ-C30) are being determined in a cohort of 39 young children with musculoskeletal tumors treated in a single institution (Münster) over the last 10-year period.

Results: To date data of 39 patients from a total cohort of 390 patients are complete. The diagnosis are osteosarcoma in 15 patients, Ewing's sarcoma in 19, and other musculoskeletal tumors in 6 patients. The median age at diagnosis was 7 years, 22 patients were women. Median time since diagnosis was 56 (13–319) months. The major primary tumor site was the femur (20 patients, 51%). Most patients had undergone surgery, 20/39 in combination with chemotherapy as specified for the given diagnosis, 15/39 patients had also received locoregional radiation. The surgical procedures included rotationplasty in 17 patients, amputation in 3, tumor resection in 7, tumor resection and reconstruction with either endoprosthesis in 3, allograft 1 or autograft 6 patients. The mean functional status scored 22 of a maximum of 30. No patient required constant pain medication. The majority of patients has satisfactory quality of life measurements, global health status (mean 82.7), physical functioning (mean 85.0), role functioning (mean 80.0), emotional functioning (mean 85.5), social functioning (mean 75.5) and pain (mean 0).

Conclusion: The given questionnaire and examination profile allows differential functional assessment of different local therapy approaches and will help to provide future guidelines. The analysis allows differentiation between surgical procedures and techniques.

12. Apoptosis in osteosarcoma cells

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The CD95/APO-1/Fas receptor/ligand system plays a crucial role in growth control by mediating apoptosis. To investigate the role of CD95 mediated apoptosis in osteosarcoma we studied three human osteosarcoma cell lines (HOS/TE 85, MG 63 and Saos-2) and osteoblasts derived from bone biopsies. Expression of apoptosis related genes was analyzed by PCR, induction of apoptosis by AnnexinV-staining. Westernblot and flow cytometry analysis were used to detect receptor expression. In contrast to osteoblast-like cells all cell lines were resistant to anti-APO-1 induced apoptosis despite constitutive CD95 expression. Blocking of macromolecular synthesis by cycloheximide or actinomycin D or modulation of CD95 expression by cytokines (TNF-A and/or γ -interferon) restored sensitivity to anti-APO-1 induced

cell death. PCR analysis of the CD95 transcripts revealed the production of a truncated splice variant that codes for a soluble form of the CD95 receptor. Synthesis and secretion of soluble CD95 protein into the culture supernatant could be demonstrated. Treatment with sensitizing cytokines led to upregulation of full length CD95 transcripts and the encoded membrane bound CD95 protein but not the truncated mRNA splice variant. The biological activity of soluble CD95 secreted by osteosarcoma cells could be demonstrated by the ability of osteosarcoma supernatants to protect the sensitive T-cell-line Jurkat from anti-APO-1 mediated apoptosis.

Taken together these results suggest that the production of soluble CD95 by osteosarcoma cell-lines that may block physiological death signals and the production of membrane bound CD95 are differently regulated by cytokines via modulation of RNA splicing.

13. Pattern of gene alterations in osteosarcoma: RB1, p53, DCC, MDM2, and SAS

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Antioncogene inactivation and oncogene activation are the central events of tumorigenesis. Different patterns leading to clinically identical or different results are of principle biological interest. We addressed the frequency and pattern of osteosarcoma (OS) associated gene alterations by studying the cell cycle regulating tumor suppressor genes RB1 (13q) and p53 (17p), the putative tumor suppressor DCC (deleted in colon carcinoma) (18q), and the MDM2 and SAS (sarcoma amplified sequence) oncogenes (12q) in human OS (20-35 OS including 2 periosteal and 2 low-grade OS). MDM2 overexpression is assumed to inhibit p53 function, the SAS and DCC gene products are thought to participate in signal transduction during growth control. We performed Southern blot analysis to detect gross structural DNA alterations (RB 8/20; p53 3/20 OS) and DNA amplifications (MDM2 3/25; SAS 3/25; coamplification 2/25) P53 point mutations were identified by heteroduplex analysis of PCR products of exons 5, 6, 7, and 8 followed by direct sequencing (10/35 OS, mainly in exons 7 and 8). A reduce or loss of DCC expression was observed by RT-PCR (17/27 OS) and as far as possible also by IHC. When comparing the results we found that the majority of OS including the 4 intermediate/low grade OS showed direct or indirect evidence for (obligatory?) p53 abnormalities. Most of these tumors revealed additionally loss of DCC expression or expression became decreased during the course of the disease. This was observed also in relapse specimens of 3 intermediate/low-grade OS. In contrast, gross structural RB1 gene mutations have been detected until now exclusively in high-grade OS and always in combination with p53 (and DCC) alterations perhaps indicating an association of this genetic event with a special OS subgroup.

14. Analysis of SAS gene and CDK4, MDM2, P16 proteins in osteosarcoma

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Amplification of chromosome 12q13-15 is a common finding in many tumor types. Some genetic alterations of SAS, MDM2, CDK4 genes located in this region have been seen in human sarcomas (1). The finding that gains or amplifications of the long arm of chromosome 12 are characteristic for low grade parosteal osteosarcoma (OS) (2), prompted us to study the amplification of SAS gene and the expression of MDM2 and cdk4 protein also in low grade central OS for its histological similarity to parosteal OS. The expression of p16^{INK4} protein that was recently identified as a specific inhibitor of cdk4 and may be considered a tumor suppressor gene product (3), was also studied.

Methods: Genomic DNA was extracted from paraffin-embedded tumor specimens of 16 cases of primary low-grade central OS observed between 1986 and 1994. SAS amplification was analyzed by quantitative PCR. MDM2, cdk4 and p16^{INK4} proteins were studied by immunohistochemistry from the same paraffin-embedded samples. The expression of the p16^{INK4} protein was evaluated also in 18 cases of high grade OS.

Results: SAS amplification was found in 2/16 (12%) of the low grade OS. High nuclear expression levels of cdk4 protein was seen in 7/16 (44%) cases. The MDM2 protein was found overexpressed in 5/16 (31%) cases. In the 2 cases in which SAS amplification was detected, the cdk4 protein expression was low, while MDM2 expression was high. The p16^{INK4} protein expression was moderate to strong in 8/16 (50%) low grade OS and in 7/18 (39%) high grade OS.

Conclusion: This study indicates that SAS, MDM2 and cdk4 genes may be involved in tumorigenesis of low grade OS. Moreover, the high p16^{INK4} expression in these tumors suggests that it functions as a checkpoint, maintaining a low level of cell proliferation in low grade tumors compared to the more aggressive course in high grade OS.

References:

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15. Human osteosarcomas express the heat shock

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Heat shock proteins (hsp) are physiologically essential, highly conserved proteins, acting as chaperones, which can be recognized by T cells during various immunological pro-

cesses. Recent studies have shown that they play a role in tumor immunology. Hsp 72 expression, investigated immunohistochemically on 8 paraffin-embedded sections after antigen retrieval by microwave, using a specific monoclonal antibody, was found in the cytoplasm of osteosarcoma cells. From 3 osteosarcomas in vivo activated T lymphocytes were expanded from tissue obtained at surgery by stimulation with recombinant interleukin-2 (IL-2) for 1 week only and restimulation with autologous, irradiated peripheral blood mononuclear cells (PBMC) in combination with anti-CD3 monoclonal antibody and IL-2. When T cell lines were tested after three weeks by proliferation assays (³H thymidine incorporation) for their ability to respond to recombinant human hsp 72, all T-cell lines gave a significant proliferative response upon stimulation with recombinant human hsp 72 in combination with irradiated recipient PBMC as antigen presenting cells (up to 8.6-fold, background versus stimulation, $p < 0.05$). No T-cell proliferation was observed when T cells were co-cultured with irradiated recipient PBMC alone (background). These findings suggest a possible role of hsps as antigens in osteosarcoma. A stimulation of hsp expression in the tumor cell or a propagation of hsp specific T cells could be a possible approach to enhance tumor rejection.

16. Molecular cytogenetic and molecular genetic characterization of embryonal and alveolar rhabdomyosarcoma

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Rhabdomyosarcoma (RMS) especially if poorly differentiated may pose enormous difficulties in terms of classifying these tumors either as embryonal (eRMS) or alveolar RMS (aRMS), the two major histological subtypes. A reciprocal translocation t(2;13), rarely t(1;13), is a genetic hallmark of aRMS, whereas eRMS often carry chr. 11p 15 alterations.

Material and methods: 10 eRMS and 9 aRMS with molecular genetically proven chr.13 rearrangement were studied by means of comparative genomic hybridization (CGH). PCR-based microsatellite analysis and FISH were employed to investigate 11p15.5 region for loss of heterozygosity (LOR).

Results: CGH of eRMS primarily revealed low level gains of genetic material mostly involving the entire length of chr. 2, 8 and 11. Evidence of genomic amplification was only observed in 2/10 eRMS whereas CGH ratio profiles, of almost all aRMSs showed evidence of genomic amplification with multiple amplicons in some cases. CFXH demonstrated low level gains or no alterations of the entire chr. 11 in the majority of eRMS and in 1 aRMS, all of which were found to carry LOI-1 of 11p15.5. In another aRMS loss of chr. 11 was found both by CGH and microsatellite analysis.

FISH studies of cases with observed low level gains by CGH and allelic loss of 11p15.5 revealed chr. 11 polysomy.

Conclusion: CGH analysis support the concept that eRMS and aRMS are genotypically distinct tumor types with a characteristic pattern of low level gains in eRMS and regional high level gains indicating gene amplification in aRMS. CGH detected gains of CGH, 11 with simultaneous loss of constitutive heterozygosity of lip13.3 suggest a selective involvement of a specific parental allele indicating uniparental di- or polysomy. Since these findings are not restricted to eRMS, alterations of chromosomal region 11p15.5 may play a crucial role in the tumorigenesis of rhabdomyosarcoma.

17. Different EWS-chimeric transcripts as prognostic factors in Ewing tumor patients

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EWS/ets-oncogen fusion transcripts are detectable in about 98% of Ewing tumors (ET) by RT-PCR. So far, on DNA level at least 16 different chimeric transcripts resulting from variable chromosomal breakpoint locations have been described, however physiological consequences of this heterogeneity are not known. We have recently reported on 85 patients treated in the European Cooperative Ewing Sarcoma Studies in whom molecular results were analyzed in comparison to all clinical data available (JCO 1996; 14: 1245. Progression free survival (PFS) for the 31 patients with localized disease and EWS-FLI fusion type I was significantly longer compared to the 24 patients with localized tumors bearing other chimeric transcripts ($p=0.04$). Recently, this observation was confirmed by Alava et al. on a larger cohort of patients with localized disease ($n=77$). However, also patients with metastatic disease and fusion type 1 seem to have a better prognosis for progression-free survival than patients with other fusion types. These results indicate that EWS-FLI fusion type 1 may be prognostically relevant in ET, probably independently of tumor site and stage. A multivariate European analysis on a large cohort of patients is in preparation.

18. Mobilisation of Ewing's sarcoma cells during surgery detected by RT-PCR

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Intraoperative dissemination of tumor cells might support the development of metastases as reported in preclinical set-

ups and in humans. Relapses of localized Ewing's sarcoma are known despite of resection after good response to chemotherapy and irradiation. We designed this study to observe the mobilization of tumor cells in peripheral blood during surgery. Differences between intralesional surgery and resection and differences before and after systemic treatment should be evaluated. Therefore a close monitoring in patients with Ewing's sarcoma was performed to detect tumor cells during biopsy before treatment and during second looks and tumor resection after chemotherapy and irradiation according to the protocol of the Cooperative Ewing Sarcoma Study (EICESS) 92. At an age between 1 and 27 years 11 patients underwent 13 surgeries. Blood samples were collected from the venous blood and the operation site before, during and after surgery. The method of reverse transcriptase polymerase chain reaction (RT-PCR) was used for high sensitivity detection of tumor cells monitoring expression of tumor specific chimeric transcripts. Tumor cells were detected in the peripheral venous blood of 5 patients during intralesional surgeries ($n=9$) and of 2 patients during resection ($n=4$). The mobilization of tumor cells into the operation field took place already before osteotomy even during resection. These results suggest that systemic treatment does not completely prevent mobilization of tumor cells during surgery. The future will prove whether this sensitive detection of tumor cells is of any prognostic value.

19. Growth inhibition of Ewing tumors by suramin

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The insulin-like growth factor I receptor (IGF-IR)-mediated autocrine circuit plays a pivotal role in the pathogenesis of Ewing tumors. The inhibition of IGF-IR-mediated circuit by aIR3 murine antibody suppresses the growth and the migratory ability of Ewing tumor cells, indicating that inactivation of the IGF-IR signaling pathway can be an effective therapeutic modality. The use of murine antibodies, however, is severely limited by the rapid generation of neutralizing immune responses in patients, and the pharmacologic inhibition of the IGF-IR-mediated loop could be an attractive alternative for clinical applications. To this purpose, we analyzed the *in vitro* and *in vivo* effects of suramin, a polysulfonated naphthylurea that interferes with the binding to a number of receptors, including IGF-IR.

In vitro, suramin showed a significant dose-dependent inhibition of the growth ability of all of the 6 Ewing tumour cell lines analyzed. In particular, a 90% inhibition of cell growth was achieved at a dose of 33 mg/mL, which is well below the therapeutic window of suramin. *In vivo* studies in nude mice confirmed the ability of suramin to inhibit the growth of Ewing tumor xenografts. In fact, local treatment with 50–500 mg/injection induced a significant reduction of the growth rate of tumors obtained by s.c. inoculation. A

similar trend was obtained by i.p. injection of suramin with respect to the metastatic ability.

This study demonstrates an inhibitory effect of suramin on the *in vitro* and *in vivo* growth of Ewing tumor cells. Suramin acts via interference with IGF-1/IGF-IR interaction, a pathway that is relevant for the pathogenesis of Ewing tumors. Treatment with suramin is therefore likely to be of clinical use in association with conventional chemotherapy.

20. Metastatic Ewing's tumor cells preferably secrete tissue-type plasminogen activator—regulation by phorbol ester, TNFA and IFNY

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Plasminogen activators (PAs) are serine proteases that convert the proenzyme plasminogen into the serine protease, plasmin. The PA-plasmin system is involved in many physiological and pathological processes, such as fibrinolysis, tumor invasion and dissemination. This study evaluates the protein and activity expression of two types of PAs, i.e. tissue-type PA (t-PA) and urokinase-type PA (u-PA), and PA inhibitor-1 (PAI-1) in 12 cell lines derived from primary and metastatic Ewing's tumors (Ewing's sarcoma, PNET, Askin's tumor). Enzyme-linked immunosorbent assay (ELISA) revealed minimal t-PA levels in 3/7 primary cell lines and prominent t-PA levels in 4/5 metastatic cell lines. Detectable u-PA protein was secreted by only 2 cell lines that were derived from the same patient with high u-PA levels in the primary cell line and low u-PA levels in the metastatic one. The tumor promoter phorbol 12-myristate 13-acetate (PMA) and the cytokine tumor necrosis factor (TNF)A stimulated the production of t-PA, u-PA and PAI-1. The latter neutralized t-PA activity but not u-PA activity. Pretreatment of cells with interferon (IFN) γ , which resulted in enhanced production of PAI-1, attenuated t-PA activity and also u-PA activity. In summary, the data indicate that t-PA secretion prevails over u-PA secretion in Ewing's tumor cells and suggest that IFNY may play a role in abrogating the metastatic propensity of these tumor cells. Furthermore, PAI-1 is not an inhibitor of u-PA activity in Ewing's tumor cells.

21. Orthotopic homing of the human Ewing tumor cell line VH64 in immune-deficient NOD-SCID mice

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Ewing tumors represent the second most common bone tumor of childhood and adolescence. So far there has been a lack of a suitable *in vivo* model to study its biology and develop new treatment strategies. As neuroblastoma cells have been shown to grow in immune-deficient SCID mice in a fashion similar to that seen in patients [Cancer Res 1994; 54: 6286-93; Int J Cancer 1996; 67: 379-85] the aim of this study was to analyze homing of human Ewing tumor cells in the even more immune-deficient NOD-SCID mice. 10^5 – 10^6 VH64 cells were transplanted via tail vein injection onto sublethally irradiated (3.5 Gy) 6–12 weeks old NOD-SCID mice. Following intravenous transplantation of 1×10^6 VH64 cells, 3 out of 3 NOD-SCID mice showed successful engraftment after 39 to 67 days. Interestingly, the mice only developed bone and lung tumors and showed a diffuse infiltration of the murine marrow. No tumors were found in other organs such as spleen, liver and brain. By immunohistology, the tumor cells stained positive for the MIC2 antigen. RT-PCR showed the same EWS-FL11 transcript in the tumor and bone marrow cells as detected in the original cell line. This proves that the human VH64 Ewing tumor cells were initiating tumor formation in the transplanted mice. Even after transplantation of 1×10^5 VH64 cells, human cells could be detected in the murine marrow by PCR. These data indicate that Ewing tumor cells are able to home and grow in immune-deficient NOD-SCID mice in a fashion similar to that seen in patients. This model can now be used to characterize *in vivo* clonogenic Ewing tumor stem cells and to study the role of integrins, such as VLA-6, in metastasis of human Ewing tumor cells *in vivo*.

22. Response of the primary to upfront chemotherapy—an important prognostic indicator for osteosarcoma with synchronous pulmonary metastases

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Primary pulmonary dissemination of osteosarcoma is often believed to carry a very poor prognosis with standard treatment. Therefore, an experimental upfront window approach is advocated by some groups. In order to learn if this might be appropriate, we evaluated patient and tumor characteristics, treatment and prognosis of affected patients, with emphasis on the effect of upfront chemotherapy, on outcome.

Methods: Search of the COSS-database (1980–1996) for all patients with primary, previously untreated, high-grade central osteosarcoma plus primary metastases restricted to the lungs. Recommended treatment included polychemotherapy and surgery as for localized osteosarcoma plus surgery of pulmonary foci.

Results: 101 eligible patients were identified (51 men, 50 women; median age 14 (2–49) years; 94 extremity, 7 trunk).

At 3.9 (0.5–15) years median follow-up (at risk), actuarial 1/ 2/ 3/ 5/ 10 year survival probability was 81%/ 55%/ 45%/ 38%/ 30%. 22/56 primaries for whom data on histological response to preoperative chemotherapy were available had <10% viable tumor, which was associated with a favorable survival probability (61% vs. 23% for poor responders).

Conclusion: Aggressive therapy can cure a considerable number of patients with primary pulmonary osteosarcoma metastases. As a good response to frontline chemotherapy indicates a more favorable outcome, abandoning standard osteosarcoma regimens in favor of an experimental upfront window does not seem warranted.

23. Synchronous multifocal osteosarcoma—results in 8 patients treated with neoadjuvant chemotherapy and simultaneous resection of all the involved bones

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From 1990 through 1994, 8 patients with synchronous multifocal osteosarcoma (SMO) were treated with neoadjuvant chemotherapy (NC) and simultaneous resection of all the involved bones (SRAIB). The bones involved were two in 6 patients and 3 and 4 in the remaining 2 patients. Chemotherapy was performed according to the 5th Rizzoli's neoadjuvant protocol (HDMTX, CDP, ADM and IFO). The primary tumors were located in the femur (6), tibia (1) and humerus (1) while the eleven secondary lesions were in the rib (3), humerus (3), tibia (3) and femur (2). Surgery was a resection in 18 sites and an amputation in the remaining lesion.

The histologic response (HR) was good (90% or more tumor necrosis) in 10 sites and poor (less than 90% tumor necrosis) in 9. In the primary and secondary lesions the HR was concordant in 6 cases (good/good in 3 and poor/poor in 3) and discordant in 1 (good/poor). One patient had a good response in the primary tumor while the HRs of the 3 secondary lesions were good in 2 and poor in 1.

At a follow-up ranging between 2 and 7 years 2 patients remained continuously free of disease and 6 patients relapsed for metastases, initially located in the lung, 2 cases, and in other bones in 4. The average time to relapse was 21 (8–36) months. Of the 6 patients who relapsed, 5 died for the tumor mean 28 (15–49) months after the beginning of treatment and one is alive with uncontrolled disease at 30 months.

Conclusion: In spite of a very aggressive treatment the prognosis of patients with multicentric osteosarcoma remains poor and the correlation found between the HR in the different bone lesions of the same patient, seems to suggest that SMO is not an originally multicentric tumor but an unicentric neoplasm which metastasizes to other bones.

24. Primary osseous spread of osteosarcoma—bad news?!

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In order to learn how osteosarcoma patients with primary bony spread fare with current multimodal therapy, we evaluated their patient and tumor characteristics, treatment and prognosis for all neoadjuvant COSS-studies.

Methods: Search of the COSS-database (1980–present) for all patients with primary, previously untreated, high-grade-central osteosarcoma with more than one osseous site involved at diagnosis. Recommended treatment included polychemotherapy and surgery as for localized disease, plus local therapy for all additional foci, whenever feasible.

Results: 66 eligible patients were identified. 39/66 had skip metastases (28 skip only, 8 skip plus extraosseous metastases, 3?) and 27/66 had spread to distant bones (5 solitary, 22 multiple; 12 bone only, 14 bone plus extraosseous metastases, 1?). Five-year actuarial survival probability was 41% for skip lesions (53% if skip only) but only 7% for distant bone lesions. Only 1/27 patients with spread to distant bones achieved a complete surgical remission, this was the only of these to survive past 5 years. No patient survived past 2.1 years if bony spread was combined with extraosseous metastases.

Conclusion: Patients with isolated skip metastases of osteosarcoma have a realistic chance for long-term survival. All others with more than a single bony site involved at diagnosis had a dismal prognosis in our series. These might be candidates for more aggressive local and/or systemic treatment approaches.

25. Survival analysis of 177 primary metastatic (stage 4) Ewing tumor patients—a report from the EICESS studies

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For localized Ewing tumors, in the multicenter European Intergroup Cooperative Ewing's Sarcoma Studies combination chemotherapy was applied with surgery and/or radiotherapy. Stage 4 patients (patients) were treated in high risk protocols.

Patients and methods: From 1990 through 1995, 177 stage 4 patients were registered. 59 patients with pulmonary involvement received whole lung irradiation. Event-free survival (EFS) was estimated by Kaplan-Meier analysis. Prognostic factors were identified by log-rank statistics and logistic regression.

Results: February 1997, at a median observation time of 19 (4–75) months, 89/177 patients had died. 171 patients were evaluable for life table analysis. EFS 4 years after diagnosis was 0.27. Age or sex did not influence outcome. Metastases in one organ system (lung or bone/bone marrow) led to a somewhat better EFS (0.34 and 0.28, respectively) than metastases in multiple organ systems (0.14), $p=0.002$. Patients with pulmonary involvement benefited from whole lung irradiation (0.37 vs. 0.10, $p=0.001$).

Conclusions: Survival in primary disseminated Ewing's sarcoma is poor but not dismal with an EFS of 0.27 four years after diagnosis. Whole lung irradiation improves prognosis in patients with pulmonary involvement.

26. Surgery of lung metastasis in Ewing's sarcoma—report on 18 cases

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The authors report the results achieved in patients with Ewing's sarcoma (EW) treated with surgery for lung disease detected at presentation (3 cases) or relapsed during follow-up (15 cases), observed in the years 1972–1994. 12 patients were men and 6 women, with a median age at diagnosis of 19 (9–38) years. The primary tumor was located in the extremities in 14 cases (humerus 4, femur 3, fibula 2, tibia, calcaneus, ulna, metacarpal, and metatarsal 1) and in the axial skeleton in 4 (clavicle 2, sacrum, and spine 1). As local treatment 6 patients received radiotherapy alone, surgery alone in 8 cases (with preoperative chemotherapy in 5), and surgery plus radiotherapy in 4 cases (with preoperative chemotherapy in 3). All patients received chemotherapy according to the protocols used at the time of diagnosis.

Median disease-free interval in the 15 patients who relapsed during follow-up was 24 (8–180) months. Lung surgery consisted in 8 wedge monolateral resections, 7 wedge bilateral resections, in 1 lobectomy, in 1 lobectomy plus wedge resection, and 1 pneumonectomy.

Results: 8 patients (44%) are alive and disease-free at a median follow-up of 32 (14–136; average 58) months from the treatment of the recurrence. Of the 3 patients with metastasis at diagnosis only one is alive and free of disease 14 months after treatment. Excluding these 3 patients 7 of the 15 patients who relapsed during follow-up are free of disease (47%).

Conclusion: These data support the role of lung surgery also in the treatment of metastatic Ewing's sarcoma.

27. Treatment of metastatic Ewing's sarcomas with a strategy based on busulfan and melphalan high dose chemotherapy consolidation after conventional chemotherapy—a study of the French Society of Pediatric Oncology (SFOP)

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In the EW88 study of the SFOP, 25 patients with metastatic Ewing's sarcoma (ES) were treated with conventional chemotherapy (CT) from 1988 through 1990. The 3-year DFS and overall survivals were respectively 12% and 25% (MPO 21: 572, 1993). The efficacy of HD busulfan containing regimens in relapsing patients prompted us to design a new study for metastatic patients with busulfan and melphalan HDCT as a consolidation after conventional chemotherapy.

From 1991–1996, 54 patients entered the EW91 study. Sites of metastases were isolated lungs (28), bone (6), combined (20). Bone marrow involvement was present in 10 patients. Median age at diagnosis was 12 (1–28) years. Induction CT consisted of cyclophosphamide 150 mg/m² p.o. x 7 days followed by doxorubicin 35 mg/m² IV on day 8 for 5 courses beginning at day 1, 15, 29, 50 and 71, followed by 2 courses of ifosfamide 1.8 g/m² + VP16 100 mg/m² for 5 days. Patients who achieved a complete response (CR) or a very good partial response (VGPR) of metastases were consolidated with HDCT consisting in Busulfan (600 mg/m²) and melphalan (140 mg/m²) followed by autologous stem-cell Transplantation. Local therapy was performed either before or after HDCT.

15/54 did not achieve initial control of metastases or progressed during induction CT; 13 and 26 achieved VGPR or CR of metastases and underwent HDCT; 2 toxic deaths occurred, 14 relapsed after HDCT. 23 are alive in continuous remission with a median follow-up 38 (8–69) months from diagnosis. By May 1997, the 3-year disease-free and overall survivals of the whole group of patients are 44% and 55%, respectively. They are 56% and 76% for the selected group of 39 patients who underwent HDCT. Response to initial conventional CT was the only prognostic factor.

Despite the need of a longer follow-up, these results compare favorably with those observed after treatment with conventional CT alone.

28. EMSOS-survey—malignant fibrous histiocytoma of bone

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In order to learn more about presentation and outcome of malignant fibrous histiocytoma (MFH) of bone, the Europe-

an Musculo-Skeletal Oncology Society (EMSOS) initiated a retrospective survey among its members.

Methods: Information requested by questionnaire included patient and treatment related variables as well as outcome. Patients with a histologically proven, primary, localized osseous extremity MFH were eligible for analysis if surgical tumor removal had taken place and disease status was documented for at least one follow-up date.

Results: 125 patients from 16 institutions or multicentric groups were evaluable (74 men/51 women; median age 34 years, tumor site femur 81, tibia 26, humerus 12, other 6). Local treatment was surgery only for 110, surgery plus radiotherapy for 15. Pre- and/or postoperative chemotherapy according to a variety of regimens, mostly including high-dose methotrexate and doxorubicin, was given to 97/125 patients (78%). With a median follow-up of 4 years, 40/125 tumors had relapsed (6 locally, 1 combined, 33 systemically (mostly lung). Actuarial disease free survival (DFS) at 5 years was 59%. Younger vs. older age and use of chemotherapy vs. none were associated with a more favorable outcome in uni- and multivariate analyses, as was limb-salvage vs. ablative surgery (selection bias?). Information on tumor response to preoperative chemotherapy was available for 66 tumors, of which 23 achieved > 90% necrosis, which in turn indicated a particularly favorable prognosis (DFS 93%).

Conclusion: EMSOS was able to accumulate data on a large group of patients with osseous NWH. With similar treatment, prognostic factors and outcome for MFH were similar to those reported for osteosarcoma.

29. ISG/SSG I—an Italian-Scandinavian treatment and research protocol for high-grade osteosarcoma of the extremities

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Based on the results from 7 previous studies on neoadjuvant chemotherapy for osteosarcoma conducted by the Rizzoli/Italian Sarcoma Group and the Scandinavian Sarcoma Group, a new collaborative phase II protocol (ISG/SSG 1) was activated on March 1st 1997. Eligible are patients of age <40 years with high-grade osteosarcoma of the extremities. For patients with nonmetastatic disease at presentation, the study objectives include good histological response to preoperative chemotherapy in 70% of the patients and 80% overall survival at 5 years. The protocol aims at optional dose intensity for all chemotherapeutic agents, including individual dose modifications for methotrexate (MTX) based on serum levels, the introduction of high-dose ifosfamide (15 g/m² over 5 days) in the preoperative treatment, and dose escalations of MTX and cisplatin for poor histological re-

sponders. Reduction of long term organ toxicity is attempted by prolonged infusions of doxorubicin (24 h), cisplatin (48 h) and ifosfamide (120 h). For patients with subsequent metastatic relapse or metastases at initial presentation, a 5-year survival rate of 40–50% is aimed at by the introduction of high-dose chemotherapy with carboplatin and etoposide, followed by peripheral stem cell rescue. 82 patients have been treated in a pilot study, showing that the treatment is feasible with good protocol compliance and acceptable short term toxicity. Also, preliminary data indicate that the study aim as regards tumour response is realistic. ISG/SSG 1 also includes 4 selected research projects; a renal toxicity study monitoring short and long term effects on glomerular and tubular function, a detailed study of the pharmacokinetics of all utilized chemotherapeutic agents, a study of P-glycoprotein expression at various time points during the course of the disease, and the detection of micrometastatic disease in bone marrow and peripheral blood utilizing monoclonal antibodies and microbeads. A major aim is the identification of new strong prognostic factors to facilitate future differentiation of treatment intensity, based on a risk-adapted approach.

30. Surgical management of osteosarcoma—outcomes from a European trial

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Objective: To review the surgical outcomes of 202 patients treated at the three main contributing centres in the EOI Osteosarcoma Trial (1986).

Results: The mean age of the patients was 18 (5–44) years. The intended surgery following diagnosis was limb salvage in 84%, amputation in 15% and rotationplasty in 1%. Following chemotherapy the actual surgery performed was different in 21%. 154 patients had limb salvage, 40 had amputation and 8 rotationplasty. Half the patients originally planned to have amputations (13/27) were able to have limb salvage following chemotherapy but conversely 23 patients required amputation who had originally been planned for limb salvage. In the limb salvage group 13 had allografts, 13 had excision alone and 107 endoprostheses.

The rate of amputation varied between the centres. One centre had a 36% amputation rate but only 2.5% local recurrence (LR) whilst the other two centres had amputation rates of 16% and LR rates of 11% and 6%. The overall death rate was no different between the centres and was 44%.

The margins of resection were radical in 18 cases (all being amputations), wide in 134, marginal in 34 and intralesional in 6. Local recurrence arose in 15 patients and was closely related to margins of excision (40%, 26% and 4% for intralesional, marginal and wide respectively), effectiveness of chemotherapy (a poor response doubled the risk) and limb salvage surgery (none in patients with amputation vs. 11% for limb salvage). LR was not influenced by the type of biop-

sy (open vs. needle), the use of a tourniquet or anatomical site. The mortality following local recurrence was 60%. 11 patients had a pathological fracture prior to definitive surgery and in these cases limb salvage was possible in half, none developed local recurrence.

Chemotherapy was restarted on average 19 days following the date of operation but was higher (28 days) following allografts and rotationplasties and averaged 18 days following endoprosthetic replacement or amputation. Subsequent amputation in limb salvage cases was necessary in 8 cases for local recurrence and 6 cases for infection. Infection arose in 1 allograft, 15 endoprostheses (14%) and 1 rotationplasty. 26% of proximal tibial prostheses became infected. Major surgery (amputation or revision) was needed in 3 allografts and in 41 of the 107 endoprostheses, the most common reason being mechanical loosening in the younger patients with endoprostheses.

Functional scores have been calculated for patients still alive. These were: 87% for patients with prostheses, 68% for patients with allografts, 85% for patients with rotationplasty and 56% for patients with amputations.

Conclusion: This study shows that whilst survival is not influenced by surgery (carried out at a major treatment centre) the functional score and incidence of complications is.

31. Oncologic results after ablative or limb sparing surgery in osteosarcoma patients

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Limb sparing surgery in many studies has been shown to be associated with a higher rate of local recurrence in comparison to amputation or rotationplasty. This study analyses differences between ablative and limb-sparing surgery in osteosarcoma patients regarding local and systemic relapse under further consideration of independent prognostic factors.

130 consecutive patients (61 women, 69 men) treated for osteosarcoma of the extremities were followed for a mean of 77 (1–227) months. Mean age at the time of operation was 17 (5–21) years. All except 4 patients were treated by adjuvant or neoadjuvant chemotherapy (various COSS treatment protocols in 112, other polychemotherapy in 14) and all of them had surgery (14 amputations, 32 rotationplasties and 84 resections-reconstruction). The ratio between ablative and limb-sparing surgery was the same both in large (> 100 cm) and small tumors (< 100 cm).

The surgical margins according to Enneking were classified wide in 109 cases and radical in 10 cases. Only 2 patients had marginal resection margins, however, there was no intraleisional resections. The 5-year metastatic-free survival (MFS) was 60% for patients treated by amputation or rotationplasty, but 71% for those patients treated by limb sparing surgery. The overall local recurrence rate was 2.3%, 4.3% for ablative surgery and only 1.2% for limb-sparing surgery. The following parameters with an independent effect on overall survival were evaluated by multivariate analysis: tumor volume ($p=0.001$), response to chemotherapy

($p=0.001$) and metastases at the time of diagnosis ($p=0.0001$).

The results of this study are in contrast to those of several studies by other authors as the rate of local recurrence in the present group was not higher in the ablative group as compared to the limb-sparing group. Interestingly, there was also no selection bias of tumor volume for either limb sparing or ablative surgery. The missing difference in the rate of local recurrences can only be explained by the high rate of adequate surgical margins achieved in almost all cases. These results, however, do not indicate that limb sparing surgery should be applied in every patient, as the functional outcome—not evaluated in this study—may be inferior in patients with large tumors resected with adequate wide margins.

32. Local recurrence in high grade osteosarcoma of the extremities treated with neoadjuvant chemotherapy—the Rizzoli experience

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545 patients with high grade osteosarcoma of the extremities (HOE) were treated from 1983–1994 with 5 different protocols (PTs) of neoadjuvant chemotherapy (NC) successively activated. The rate of limb salvages (LS) was 83% and increased from a 72% of the first P (1983–1986) to a 95% of the last one (1993–1994).

With a mean follow-up of 7 (2.5–13) years, 328 patients (60%) remained free of disease, 5 died for toxicity and 212 relapsed. 32 of the relapsing patients (15%) had local recurrence (LR). The overall incidence of LR for all the 540 evaluable patients was 6%. According to surgery the rate of LR was 3.2% for the 61 amputated patients, 7.1% for the 27 patients treated with rotation plasty and 6.3% for the 452 patients treated with LS. According to the chemotherapy PTs, the lowest rate of LR was observed with the PT (the 2nd) that gave the highest rate of DFS, while the highest rate was registered in the PT (the 5th) in which the highest number of LS was performed.

The probability of LR resulted significantly related to: a) the surgical margins (SM) with 2.4% of LR for the 458 patients with adequate SM vs 25.6% for the 82 patients with inadequate (ISM), $p=0.0001$; b) the histologic response to chemotherapy with 3.9% for the 359 “good responder” (GR) patients (tumor necrosis >90%) vs 9.9% for the 181 “poor responder” (PR) patients (tumor necrosis < 90%), $p=0.005$. In patients with adequate SM the rate of LR was relatively low also in PR patients (8/148; 4.4%) while in patients with inadequate SM the rate of LR was very high also in GR patients (11/50; 22%).

Metastases developed in 31 of the 32 patients who had LR (3 earlier, 8 contemporary and 19 later LR) and, in spite of

the following treatments, only one of these patients is alive and free of disease. This postrelapse outcome is significantly worse than the one observed in the 180 patients who relapsed with metastases but without LR. In fact 45 of these 180 patients (25%) are presently alive and apparently free of disease mean 42 (6–132) months from the last treatment performed since relapse.

Conclusions: a) in HOE treated with NC it is possible to avoid amputation in most patients, however, when SM are inadequate, the risk of LR is very high; b) the prognosis of patients who relapse with LR is very poor; c) a more effective chemotherapy PT besides reducing the rate of systemic relapses may also contribute to the local control of the tumor.

33. Secondary osteosarcoma—experience of the Cooperative Osteosarcoma Study Group (COSS)

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Description of patient and tumor characteristics of osteosarcoma (OS) occurring as a second malignancy and evaluation of the outcome of affected patients when treated according to modern multidisciplinary protocols.

Methods: All patients registered at the COSS-study-center between 1/80 and 6/96 whose OS arose as a second malignant tumor were analyzed.

Results: 31 cases of secondary OS were registered. The first malignancies had been retinoblastoma in 10, rhabdomyosarcoma in 5, Ewing-tumor in 4, fibrosarcoma in 1, lymphoma in 5, gynecologic tumors in 3, gastric cancer in 1, histiocytosis X in 1 and medulloblastoma in 1. Treatment had included radiotherapy in 25, chemotherapy in 15 and surgery in 20 cases, respectively. The secondary OS occurred a median of 87 (29–216) months after diagnosis of a first cancer.

13 secondary OS were situated in the trunk or skull, 18 in an extremity. 18/31 OS were located within a former radiation field. 3/31 patients presented with primary metastases of OS (2 skip, 1 lung). Local control was achieved in 23 patients. All 31 patients received chemotherapy, only 9/31 a complete COSS-regimen. After 7.5 years median follow-up, actuarial survival was 46% for all 31 patients (64% for 23 patients with local tumor control; no patient without local control survived past 3 years).

Conclusion: The prognosis of secondary OS can be similar to that of primary OS, provided local control is achieved and chemotherapy applied.

34. Treatment and oncologic outcome of pelvic chondrosarcoma—a clinical and retrospective study of 34 patients

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The purpose of this paper is to report the treatment and oncologic results of surgically resected pelvic chondrosarcoma.

Method: Medical records and original radiographic studies or photographic slides of 34 patients with pelvic chondrosarcoma treated by the Orthopedic Oncology Division of University of Florida between January 1975 and June 1994 were reviewed. All patients were treated surgically only. The minimum follow-up for the surviving patients was 24 months (mean 69 months). Staging, and functional evaluation were determined according to the system of the Musculoskeletal Tumor Society. The type of resection was classified as per Enneking.

Results: There were 25 men and 9 women, with mean age 45 (17–74) years. 21 patients had primary chondrosarcoma. Secondary chondrosarcoma were seen in the remaining 13 patients. The location of lesions were as follows: 12 in the ilium, 18 in the periacetabular area, and 4 in the ischiopubic region. 25 patients had low grade lesions and 9 had high grade. There were 4 IA, 21 IB, and 9 IIB. There were 11 type I, 15 type II, and 3 type III resections. 5 patients required primary classic hemipelvectomies. 3 intralesional, 10 marginal, 14 wide, 7 contaminated surgical margins were achieved. 65 complications were seen in 26 patients. 15 patients suffered major complications including 5 patients with oncologic complications. Low-grade lesions were managed with a relatively low major complication, high-grade tumors had a high risk of major complications. 18 patients had only surgery related complications requiring 26 reoperations. Patients with no or minor complications had an improved survival curve compared to those with major complications ($p=0.002$). The complication rate was higher for patients that underwent complex reconstruction versus simple reconstruction ($p=0.021$) with infection being the most common complication. Patients with no complication had a mean functional score of 21.8, while those with minor and major complications had scores 16.6 and 16.3 respectively.

Conclusion: Surgical complications are at least as important as the oncologic complications when considering survival. Complex reconstructions using plates, prostheses, and/or allografts were often complicated by infection, dislocation, fracture, and/or resorption. Simple reconstruction with subsequent pseudarthrosis seems to be appropriate treatment due to its lower complication rate even though arthrodesis provides a more reliable functional result.

35. Diagnosis, treatment and prognosis in synovial sarcoma—a Scandinavian Sarcoma Group Register project

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127 patients with synovial sarcoma were reported to the SSG Register 1986–1994. In 104 cases, the diagnosis was confirmed by the SSG pathology board, in 13 the diagnosis was not accepted, and 10 await further review. Patient charts have been reviewed and the follow-up has been continuously updated. No patient has been lost to follow-up, and the median follow-up time for survivors was 6 years.

The median age was 38 (7–87) years and there was an even sex distribution. 11% of the tumors were localized to the trunk, 21% to the upper extremity and 68% to the lower. 8% were subcutaneous, 17% intramuscular, and 75% extra-muscular. The median tumor size was 5 cm. 7% of the patients had lung metastasis at the time of diagnosis.

48% of the patients were referred before surgery. 12% were referred after open biopsy, 35% after an intralesional or marginal excision, and 5% after local recurrence. Surgery with an adequate margin, *i. e.*, wide, myectomy, compartmental, was achieved in 60% and an inadequate margin in 40%. The amputation rate was 29%. Postoperative radiotherapy was given in 25% and only 8% had adjuvant chemotherapy.

The 5-year local recurrence rate was 0.14 and the metastasis-free survival rate 0.68. All 11 local recurrence and 27 of 29 metastases appeared before 5 years. Univariate analysis showed that large tumor size, Grade IV, tumor necrosis, vascular invasion, and mitotic rate were risk factors for metastases. Cox regression analysis showed, however, that only Grade IV and tumor size >5 cm were independent risk factors.

The study shows a better than expected survival in synovial sarcoma. Based on the prognostic analysis, adjuvant chemotherapy appears only indicated in patients with large and high grade lesions.

36. Local and systemic control after unplanned inadequate primary excision in soft-tissue sarcomas

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Under assumption of a benign disease unplanned resection often is performed initially in patients suffering from soft-tissue sarcomas. The aim of the study was to evaluate overall survival rates in patients who underwent initial unplanned resection followed by a planned resection as compared to patients who underwent primary planned biopsy and resection.

Between 1970 and 1995, 232 patients suffering from soft-tissue sarcoma of the upper extremity (23%), lower extremity (64%), pelvis (11%), neck and trunk wall (2%) located epifascially (7%) and subfascially (93%) with histological grading I (13%), II (24%) and III (63%) and a mean maximum diameter of 90 (10–300) mm were treated by resection, chemotherapy and radiation therapy. 97 women and 135 men were evaluated in a retrospective study. In group 1 un-

planned inadequate initial or repeated resection was performed in 61% of patients followed by revision surgery at our institution in mean 21 (0–241) months after the first surgical intervention. In group II biopsy and planned adequate surgery was performed in 91 patients (39%). The histological evaluation showed intralesional resection in 91%, marginal resection in 8% and radical resection in 1% of patients after unplanned initial resection. After planned resection histologically radical margins were found in 20%, whereas the resection was wide in 49%, marginal in 22% and intralesional in only 9% of the patients. After a mean follow up of 61 (1–360) months. 42% of patients had died because of the disease, 26% showed no evidence of disease, 14% were continuously disease free, 12% were alive with disease and 7% of patients had died because of other diseases. We found a higher survival rate in patients with tumors smaller than 50 mm in diameter, low tumor-grading and after wide and marginal resection. There was no difference in the survival time in both groups with regard to initial type of surgery.

From these results we conclude that in case of adequate reexcision of a soft-tissue sarcoma despite of a primary inadequate excision, equally good survival rates may be achieved as compared to planned biopsy and resection although a deterioration in the functional outcome—not evaluated in this study—has to be expected after repeated resections.

37. Vertebrectomy—en-bloc resection for primary malignant bone tumors of the spine

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As wide surgical margins have been proven to be adequate for the treatment of primary malignant tumors of the extremities, efforts have been made to apply this oncological principle to the treatment of primary malignant tumors of the spine.

Methods: En-bloc resection of one or more vertebrae is regarded feasible when at least one lamina is not affected by the tumor. In prone position a median doorwing-like enlarged skin incision under excision of the biopsy tract is performed. From the dorsal approach the affected vertebral vertebral body and the adjacent vertebrae are exposed partially resecting the ribs on both sides. A laminectomy of the tumor-bearing vertebrae on the depicted healthy side is performed before the anterior and posterior ligament and the discs are dissected proximally and distally. Now the specimen can be removed by rotating the bloc around the longitudinal axis of the spinal cord. Finally stabilization is performed ventrally titanium cages and dorsally with CD or ISOLA instrumentation.

Results: 7 patients (3 men, 4 women; mean age 24 (6–37) years) with primary malignant tumors of the spine (3 osteogenic sarcomas, 1 chondrosarcoma, 1 schwannoma, 1 spindle cell sarcoma, 1 Ewing sarcoma) have been treated at our institution by the surgical procedure described above since 1993. The mean evaluation period was 25 (6–52) months.

The tumor was located in the lumbar spine in two patients and five times in the thoracic spine. All patients underwent pre- and postoperative polychemotherapy and in two cases preoperative radiation was done. The operation time ranged from 7.3 to 17.5 hours (mean 11.3 hours). Only one revision due to deep wound necrosis was necessary. One patient died seven months postoperatively because of cerebral complications. In another patient a breakage of a pedicle screw occurred. No permanent neurological complication could be found.

Discussion: Although the number of patients is too small and the follow up period too short to evaluate the long term influence on the systemic tumor control, we look forward to achieve with this method equal outcome results as they can be obtained in patients with primary malignant tumors of the extremities.

38. Knee allograft arthrodeses in limb salvage surgery and their clinical outcome after 3 years

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Substantial bony defects around the knee may be left after resection of malignant bone- and soft tissue tumors. In these situations allograft-arthrodeses often can salvage the limb. Especially in long defects and difficult soft tissue situations this slim reconstruction helps to avoid amputation. For graft fixation intramedullary nailing and plating is possible.

Objective: The 3 year follow up results of intramedullary and extramedullary fixed allograft arthrodeses are analyzed regarding their complications and functional outcome.

Material and methods: Between 1991 and 1993, 21 patients with an average age of 26 years sustained defects around the knee after malignant tumor resection and underwent reconstructive limb salvage surgery with allograft-arthrodeses. The main tumor diagnose was osteosarcoma in 80% of the patients. The length of the defects ranged from 12 to 28 cm with an average of 21 cm. 14 of the allograft arthrodeses were primary reconstructions, the other 7 had prior reconstructions that failed due to infection. The fixation was performed 13 times by intramedullary nailing and 8 times with plating. The majority of the patients was treated with chemotherapy in addition.

Results: The median follow up time was 3 years. 3 of the 21 patients died of disease, local recurrence occurred once and one patient died of old age without evidence of tumor recurrence. 16 patients were continuously disease free. Of the 17 patients 11 had intramedullary fixed allografts and 6 were fixed by plate. In both groups nearly half of the reconstructions with 4/11 and 3/6 did not need any revision so far, 5 patients underwent further surgery once, 3/11 and 2/6 patients had more than one secondary procedure. 8/11 intramedullary- and 4/6 plate fixed allograft arthrodeses survived after 3 years. In 3/11 and 1/6 graft removal was carried out. The main reason for revision was nonunion in both groups (4/11; 2/6) which was treated with autogenous iliac

crest grafting. Functional evaluation of 13 patients after 3 years showed 2/3 of the normal function by the MSTS/ISOLS Score.

Discussion: Allograft arthrodeses allow primary limb salvage procedures as well as reconstructions after infected situations. According to the complications and functional results there is no significant difference between intramedullary nailing and plating.

39. Resection of the malignant soft tissue tumors with marginal resection or excisional biopsy

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Reresection is indicated to provide safe margins in the treatment of soft tissue sarcomas treated by marginal resection or pathological examination revealed contaminated margins. Radiation therapy could be applied to sterilize the area contaminated by hematoma before resection.

Patients and method: 14 patients (9 men and 5 women) with malignant soft tissue sarcomas were resected in our institution between 1990 and 1996. Mean age was 37 (11–56). Histologically, the tumors were synovial sarcoma in 6, malignant fibrous histiocytoma in 3, liposarcoma in 3, spindle-cell sarcoma in 2 patients. Anatomically, the tumors were located at thigh in 6, ankle in 2, shoulder in 1, elbow in 1, thoracic wall in 1 and buttock in 1 patient, cruris in 1, popliteal space in 1 patient. All patients had received a marginal resection or excisional biopsy with contaminated margins. Preoperative Rxt performed in 7 patients with high grade soft tissue sarcomas. Surgical margins after resection were negative in all patients. Histological examination revealed alive tumour cells in 11 patients. 6 patients were examined by MRI and 8 patients were examined by CT scans. No tumor was found at the multiple sections of the old incision in 3 of 6 patients with gadolinium positive MRI before the resection. False positive images were due to gadolinium uptake of scar tissue in 2 patients and muscular hyperplasia in 1 patient. Mean follow-up was 36 (6–76) months. Local recurrence was observed in 1 patient and treated by 3 d local wide excision with safe margins.

Discussion: Reresection with 1.5 cm wide normal tissue around the incision including all layers of skin, fascia, muscle and periosteum provided satisfactory local control in high grade and low grade soft tissue sarcomas. Preoperative radiation therapy was found to be effective only in half of patients regarding sterilization of the incision site and hematoma before resection of high grade sarcomas. Three patients had alive tumour cells in the resected specimen out of 7 Rxt-received patients, 6 patients out of 7 without Rxt had alive residual tumour cells. Early postoperative MRI sometimes could be misleading with gadolinium binding scar tissue and muscular hyperplasia. The presence of live tumour cells even in irradiated contaminated resections

was thought to be justifying local resections in all patients with marginal resections unrelated to the grade of the tumor.

40. Prognostic significance of tumor site in osteosarcoma of the humerus

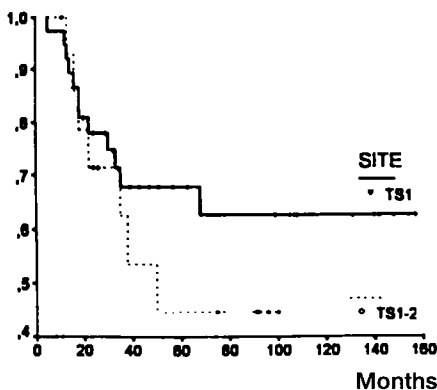
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To date, no specific analysis on prognosis of osteosarcoma in the humerus is reported. The aim of this study is to analyze the role played by location and volume when the tumor is located in the proximal dia- and metaphyseal region of the humerus.

Material and methods: This review presents the experience of 63 patients with osteosarcoma of the humerus, who between 1983-1995 at the Rizzoli Institute, were eligible for the chemotherapy protocols and surgery. The cohort was divided according to tumor location into proximal 1/3 (TS1, n=37), proximal and mid 1/3's (TS1-2, n=15), mid 1/3 (n=3), distal 1/3 (n=3), or whole bone (n=5) based on x-ray evaluation. For statistical analysis only the first 2 groups could be compared. The absolute tumor volume (ATV) was calculated from bi-planar, post-chemotherapy radiographs using the ellipsoid estimation. The relative tumor volume (RTV) was defined as the ATV divided by the volume of the whole humerus. The ratio of extra- to intracompartmental tumor volume was also measured. The effect of tumor volume, age, gender, height, grade, histology, necrosis, surgical margins, preoperative fracture, serologic parameters (LDH, AP) and chemotherapy protocol on disease free survival (DFS) and overall survival with respect to tumor site (TS) was assessed by Kaplan-Meier univariate analysis. Small sample size did not permit meaningful Cox regression multivariate analysis.

Survival function (DFS)



Results and conclusions: The disease free survival (DFS) was better in the TS 1 group than in the TS1-2 group, independent of ATV. The difference did not reach statistical significance, perhaps due to small sample size. ATV and RTV did not affect outcome. No other prognostic variables were detected. Metanalysis with pooled data from other oncological centres in patients with similar tumor location may permit more meaningful interpretation of the significance of tumor site in regard to other independent DFS (months) dependent variables.

41. Rapidly recycled intensive induction chemotherapy without methotrexate in adult patients with osteosarcoma—a prospective study

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High dose methotrexate (HD MTX) in adult patients (pts) with osteosarcoma (OS) is highly toxic. In order to improve the outcome of this disease and limit the duration of preoperative chemotherapy (CT), in 1993 we designed an intensive regimen without HD MTX for nonmetastatic OS. Two cycles of induction CT (API-AI regimen) consisting of doxorubicin 60 mg/m² (day 1 and 15), cisplatin 100 mg/m² (day 1), and ifosfamide 5 g/m² (day 2 and 15) and an equivalent dose of mesna were to be administered with an interval of 28 days before surgery. G-CSF was given after each course (day 4–11 and day 18–25). Good responders (grade III and IV according to the Huvos classification) were to receive two further APO courses and poor responders (grade I and II) a salvage regimen of etoposide 100 mg/m² (day 1–3) and ifosfamide 4 g/m² with G-CSF.

20 consecutive untreated adult patients with nonmetastatic histologically proven OS have been included in this study. The median age is 27 (15–50). 40 APO-AI cycles have been administered without dose reduction before surgery. 12 courses were delayed due to hematological toxicity. 18 patients experienced grade 3–4 neutropenia, 14 grade 3–4 thrombocytopenia and 4 grade 3–4 anemia. Functional symptoms resolved in all 20 patients before surgery.

After a median follow up of 27 (8–45) months 17 patients have remained in complete remission. 2 patients died due to metastases, one whose disease progressed during initial chemotherapy and one who relapsed 6 months after surgery (histologic grade II responder). One patient is alive with pulmonary metastases at 20 months. All good responders have remained disease free after a median follow up of 32 months.

The API-AI regimen is feasible, safe and seems as effective as regimens containing HD MTX. The induction CT period was considerably shortened by this rapidly recycled API-AI regimen.

42. Surgical or percutaneous treatment of osteoid osteoma

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Osteoid osteomas are common benign pediatric bone tumors. However, radiographic diagnosis and location of the tumor nidus can be difficult.

When present in a child, the clinical and radiographic picture is not that clear and often misdiagnosed. Routine radiographs do not offer a complete diagnosis in young patients and additional studies are indicated. CT provide more information in determining the presence of absence of bone lesion in the child. In some case the preoperative MRI demonstrates a well-margined lesion in the medullary canal but no tumor nidus. This was confusing and misleading. Correct diagnosis was made with a CT scan and mammographic radiographs. MRI give us more knowledge about bone marrow changes.

A surgical procedure was performed to excise the lesion in 21 patients and replace it with bone graft. 12 cases were examined by intraoperative CT and mammography scan. This application was used to avoid a large amount of bone resection and weaken the bone. We performed CT guided intraoperative drilling of the lesion and injection a formol in 3 cases

Patients have been followed for 5 years and have remained asymptomatic.

Recent progress in radiology for management of osteoid osteoma have given greater accuracy in the preoperative and intraoperative examination.

43. High dose therapy for primary metastatic Ewing tumours—experiences from 38 EICESS patients

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Primary metastatic (stage 4) Ewing tumour patients have a poor prognosis for event free survival (EFS). Therefore these pts are treated in high risk protocols and/or receive myeloablative high-dose chemotherapy (HDT) with stem cell rescue.

Patients and methods: 38 of 177 primary metastatic patients, registered in European Intergroup Cooperative Ewing Sarcoma Study 1990 through 1995, received HDT. Stem cell rescue was applied as allogeneic bone marrow (BM), autologous BM, or peripheral blood stem cells. Results are demonstrated by Kaplan-Meier analysis and by uni- and multivariate procedures.

Results: After a median observation time of 19 (4–75) months, 89/177 patients have died. EFS 4 years after diagnosis was 0.23 in patients with HDT, and 0.28 for those without. HDT was of some benefit in patients with multiple bone/BM and pulmonary metastases (0.30 versus 0.08, $p=0.02$). Source of progenitor cells, or myeloablative treatment regimen did not influence outcome.

Conclusions: Intensified treatment by HDT may improve outcome in a subset of patients with primary metastatic Ewing tumors, but prospective randomized studies are warranted.

44. Rotationplasty (Type B III A)—a preliminary report

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We report on seven patients who underwent a rotationplasty (WINKELMANN-type B IIIa). This surgical technique is performed in young children with a malignant bone tumor of the middle or proximal part of the femur. After wide resection of the tumor including the whole femur, the tibia is rotated 180° and the former lateral tibial plateau is placed into the acetabulum, therefore a new joint between the tibia and the acetabulum is artificially constructed. The ankle joint functions as the new knee joint.

Method: 7 children, mean age 5.4 (3–9) years old, underwent a wide resection of tumor of the femur and a type B IIIa reconstruction. 5 patients were operated on for Ewing sarcoma, 1 for neuroectodermal tumor and 1 for osteosarcoma. The mean follow up was 3.6 (2–6) years. The radiographic and MRI findings after rehabilitation are presented in details. Furthermore we present the functional results according to the ENNEKING-score.

Results: None of the patients had local recurrence or metastasis. We observed neurologic complications in 2 cases after soft tissue swelling or bleeding. In 1 patient the neurologic symptoms reversed, 1 patient still has paresis. Only one further operation was necessary because of postoperative bleeding. As far as the ENNEKING-score is concerned, the patient showed good to satisfying rehabilitation (pain: mean 4.9 (4–5), function: mean 4.3 (3–5), emotional acceptance: mean 4 (3–5), supports: mean 3 (3–3), walking: mean 3.8 (3–4), and gait: mean 2.3 (1–3). Radiographs in patients ($n=4$) with a follow up longer than 4 years showed a remodelling of the medial aspect of the rotated tibial cartilaginous epiphysis in the sense of a neo-hip-joint according to Wolf's law.

Conclusion: We conclude that the rotationplasty type B IIIa offers a convincing solution for biologic reconstruction after tumor resection of the middle and the proximal femur in young children. Furthermore we recognized during the child's growth a new bone or so called joint formation of the neo-tibio-acetabular joint with good functional results.

45. Osteoblastoma with renal hypophosphatemia

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We present a case with diagnostic and treatment problems. The 5-year-old boy had a pathologic fracture of the right humerus after trauma. Postnatal development of this boy was normal. During 2 months after trauma we observed bone tumor growth, the right upper extremity became 3 cm shorter and deformed. Radiographic diagnosis was osteosarcoma? Histopathological diagnosis (based on biopsy) was chondrosteodysplasia with osteoblastoma. In the next 2 months the enlarging tumor was operated on with bone transplantation. Postoperative histopathologic diagnosis was osteosarcoma. Parents did not decide for chemotherapy and amputation. In the next few months the boy did not grow and felt diffuse osteocopic pain. Finally he stopped to walk. In laboratory tests we observed renal hypophosphatemia. Radiography, CT, NMR control showed focal osteomalacia in the bone transplant. The therapy with alpha-calcidol (2 µg per day) was started. After 2 years the boy grew 11 cm, and the bone tumor was constantly 5 cm in diameter. The boy is 8 years old now, and waits for bone transplantation or endoprosthesis. He learns in school very well.

46. Metastases in osteogenic sarcoma in children and adolescents—results of treatment

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Between 1985 and 1994, 158 osteogenic sarcoma children were treated. The age ranged from 3–25 years. Distant metastases were detected in 34 patients: at diagnosis in 7, during the course of treatment in 13 (within 6 months from diagnosis in 6 and after in 7), after the treatment in 14 (between 6 and 36 months). Lung metastases were found in 32 cases (in 10 bilateral). In this group additional sites of distant spread were detected: femur in 3, rib in 1, neck spine in 1, and lumbar spine in 1.

Isolated bone metastases were shown in 2 cases (pelvis-femur, mandible) and according to different protocols. There were 3 groups of patients: group I – chemotherapy + surgery of the primary + adjuvant chemotherapy, group II – chemotherapy (only in 1 patient the surgical approach for pulmonary lesions), and group III – chemotherapy + thoracotomy + chemotherapy.

The following types of thoracic surgery was performed in 18 patients: unilateral thoracotomy in 8 patients (3 times in 1 patient): sternotomy in 5 (2 times in patients). Bone metastatic lesions were resected in 2 patients. Laminectomy was done in 2 cases and brain metastasis removal in 1 patient.

Results: In the group of 16 children, where conservative treatment was employed only, 2 patients survived, while in

15 operated ones, 10 patients were survivors. Surgery is planned in 4 patients.

Conclusion: Removal of metastases at the time of partial remission or stabilization after neoadjuvant chemotherapy seems to be the treatment of choice in osteogenic sarcoma. Repeated lung metastatectomies (2–3 times) can prolong survival.

47. Limb-sparing surgery for bone sarcomas of the lower extremity in children and the role of custom-made expandable implants—our experience with 25 cases (31 implants) during the last 9 years

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Amputation surgery was always considered to be the rule for gaining local control in bone sarcomas of the lower extremity in children under the age of 10–12 years. The reason was the huge problem of coping with later growth and limb length discrepancies which cause chronic dangerous repeated morbidities until maturity.

During the last 9 years (1988–1997) 25 children (5–12–14 years) with osteosarcoma or Ewing's sarcoma of the femur or tibia were treated with a variety of custom-made expandable endoprostheses. 31 different implants were introduced (including revisions). About 15 expansions were already performed. 5 children reached maturity during this period and are alive. The follow-up time is 1–8 years.

The complications, especially the prosthesis related ones, and late functional results are described in details. The rate of limb preservation until now is almost 100% (no limb was yet amputated during all the morbidities. One limb was amputated due to local recurrence after 2 years). The rate of a functional joint preservation is lower, around 75%.

It seems that the goal of maintaining a limb, its length and its function (the joint) until maturity in these very young children is an achievable one but with a high price in terms of morbidity.

48. The association massive allograft/vascularized fibula for reconstructing children long bones

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Various options are available for reconstructing long bones after tumor resection. Massive allografts (MA) have been successfully used, however bone resorption and non union are frequently observed. Vascularized fibula (VF) is an alternative: immediate restoration of a physiological blood supply may result in rapid union and hypertrophy of the graft. The authors have been using the combination of a MA and a

VF in the reconstruction of long bones since 1988,

In an homogeneous group of 24 children (14 girls, 11 boys; mean age 10.5 (4–14) treated in the period 1989–1997, VF was inserted into a longitudinal trough, cut in the MA. All patients were affected by bone sarcomas (18 osteosarcomas, 5 Ewing's sarcoma and 1 MFH) and 23 received neoadjuvant chemotherapy. The association of MA and VF was used for reconstructing various resected segments (mean length 15 (8–26) cm): diaphyseal intercalary femur (5 cases), proximal tibia knee arthrodesis (1 case), intercalary intraepiphyseal proximal tibia (10 cases), diaphyseal intercalary tibia (5 cases), tibiotalar arthrodesis (2 cases) and intercalary diaphyseal humerus (1 case). The authors investigated the nature of biological interactions between the MA and the inlaid VFA by serial CT examinations performed with the same CT Unit over a 7 year period.

VF fused to the host bone at both osteotomies at a maximum of 4 months from the surgery. Allograft-host fusion was evident on standard radiography in 92% of osteotomies by one year. Fracture of the implant occurred in 14 cases (58%): in 6 patients the fracture healed after conservative treatment while 8 other ones were treated by: new osteosynthesis and bone autografts (7 cases) or substitution of the implant (1 case). One case of postoperative deep infection was treated by amputation. At a mean follow-up of 42 (6–99) months, only 1 patient presented a local recurrence and was amputated, all the others are alive (4 after the treatment of distant metastasis) with no signs of disease. Excellent or good functional results were obtained in 16/21 patients with more than 1 year of follow-up (76%). The results of the CT study demonstrated significant changes in VF diameters, area and cortical thickness ($p < 0.001$). The tissue interposed between VF and MA showed a progressive maturation with axial bridges between VF and MA. A layer of ossification on the inner surface of the allograft was the starter of the bony bridges.

The association of a MA with an inlaid VF allows to obtain a biological long lasting bone reconstruction with a high rate of functional success. The serial CT scan analysis demonstrated the biological activity of the VF and suggested a new way of MA remodelling induced by the VF.

49. Hip reconstruction after limb salvage surgery for high grade bone sarcomas of the proximal femur in childhood

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Between 1975 and 1995, 20 patients under age 13 affected by an high grade bone sarcoma of the proximal femur were surgically managed at our institution.

There were 8 boys and 12 girls; the mean age was 8.9 (3–12) years. Diagnosis was osteogenic sarcoma (OGS) in 13 cases and Ewing sarcoma (ES) in 7 cases; according to Enneking Surgical Staging System there were 19 stage IIA or B and one stage III disease. All the patients received chemo-

therapy along with surgery. A limb salvage procedure was elected in 18 cases while an amputation was chosen in 2 cases. In the limb salvage group, a hip rotationplasty was performed once whereas 17 patients underwent a major reconstruction; these included 7 prosthetic replacements, 3 allograft-prosthetic composite implants and 7 arthrodesis.

3 of the 7 prostheses were nonmodular cemented custom made devices while the remaining 4 were modular uncemented implants; 2 of the 4 modular replacements were an expandable total femur.

All the arthrodeses were ilio-femoral and followed in 4 cases an intraarticular resection and in 3 cases an extraarticular resection. Surgical margins were adequate in 18 cases (17 wide, 1 radical) and inadequate in 2 cases (1 wide/contaminated, 1 intralesional). Mean follow-up was 55 (12–230) months. Complications included 3 deep infections and 4 aseptic mechanical and/or biologic failure, accounting for a reoperation rate of 25%. The most common complication was proximal nonunion, observed in the arthrodesis group (3 of 7); however, only one of these 3 cases required further surgery.

2 patients developed local recurrence while 6 patients relapsed with lung metastasis. Oncologic outcome at a mean follow-up of 4.5 years showed 11 patients being continuously disease free (CDF), 1 alive and disease free after distant relapse, 4 deceased from disease, 1 alive with untreatable disease, one deceased because of adriamycin toxicity and 2 currently lost to follow-up.

Overall functional results were unsatisfactory; in fact, even evaluating the relatively homogeneous CDF group with a minimum of 18 months (9 cases) only 3 patients were found having a good result.

Limb salvage surgery for high grade bone sarcomas of the proximal femur in pediatric age is a challenging problem; because of residual skeletal growth and subsequent limb length discrepancy, functional results are in fact poorer than in adults and children over age 13. Several reconstructive options are currently available and include arthrodesis, rotationplasty, prosthesis and allograft-prosthetic composite. In regard to the more recent choices, a larger experience and a longer follow-up is needed to assess their reliability and long-term outcome.

50. Desmoid tumors in children

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Desmoid tumors (DT) belong to fibromatosis, and in TNM classification to G1 fibrosarcomas. Their rate among soft tissue sarcomas is about 25%, and among all benign and malignant soft tissue tumors 3%.

From 1960–1996 we followed up 64 children aged 1–18 years, which is about 18% of all DT patients (3–52). There were 26 boys and 38 girls. Eleven children had abdominal desmoids (AD), 51 had extraabdominal desmoids (ED), and 2 children had a combination of AD and ED. Congenital DTs

were registered in 12 children, mothers of three of them had DT as well as diffuse polyposis of the colon. Primary DTs were in 37 children, 27 presented with recurrences, 20 of them with multiple ones. DT sites were femur (26), gluteal area (18), abdominal wall (11), shin (10), foot (8), thoracic wall (7), hand (6), neck (5), shoulder (4), lumbar area (4), perineum (2), abdominal wall and femur (2), cheek and lower jaw (2). The total number of desmoid lesions was 105. The size of DT ranged from 5–35 cm, its maximum weight was 3.8 kg.

105 DTs in 61 children underwent surgery, 42 had surgery with radiotherapy and 3 patients did not undergo surgery. After surgical treatment relapses occurred in 60% of the cases. In cases of combined modality they occurred two times rarer and after a longer period of time. Remote results are known in all the patients: 14 patients are alive for 3–5 years, 6 for 6–10 years, 18 for 11–15 years, 13 for 16–20 years after the first operation. Of all the children, only one girl has an inoperable tumor. The rest are healthy. We observe neither transformation of DT into fibrosarcoma nor metastasizing. One girl had a spontaneous regression of DT at the beginning of menses and subsequent two childbirths. The mother and her children are healthy.

51. Treatment results in rhabdomyosarcoma

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In the period 1981–1994, 71 patients with rhabdomyosarcoma were treated. Age distribution was: up to 3 years 20 children, from 3–10 years 30, from 10–14 years 15 and over 14 years 6 adolescents. The ratio males:females were 1.5: 1.

The primary tumors originated from: head and neck 39%, urogenital 25%, extremities 14%, abdomen 16% and others 6%. The treatment of all patients was complex surgery, radio- and chemotherapy. In the tumor region the realizable local dose was 60–64 Gy (8.5–9 Gy for week).

The chemotherapy was done according to protocol VACA (Vinc, Adria, Cyclo, Acti D). The survival rate analysis determined: 1-year survival 85%, 2-years survival 70%, 3-years survival 51%, 5-years survival 50%. From 30 patients who died (42%), 28 died from tumor progression and 2 from complications (peritonitis and viral hepatitis). From cl. stage I 100% survived, from cl. stage II 82%, from cl. stage III 36%, while from cl. stage IV nobody survived. The reported treatment results confirmed the necessity of complex treatment.

52. Recurrent gains and losses in Ewing's sarcomas by comparative genomic hybridization

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Ewing's sarcomas (ES) are characterized by the (11;22)(q5>4-q12) translocation. Secondary chromosomal aberrations occur, but less is known about their frequencies and clinical correlation. Here, comparative genomic hybridization (CGH) was utilized to In this study the frequency of DNA sequence copy number changes in ES, and the findings were correlated to the clinical outcome.

DNA was extracted from 20 tumor samples and CGH was performed as described (1). The clinical follow-up was updated.

15 tumors (75%) showed copy number changes, gains of DNA sequences being more frequent than losses. Recurrent findings included copy number increase for chromosomes 8 (35%), 1q (25%) and 12 (25%). The minimal common regions of these gains were the whole chromosomes 8 and 12, and 1q21-22. High-level amplifications affected 8q13-24, 1q and 1q21-22. The correlation between copy number increases and the 5-year overall survival showed only a statistical trend, the strongest for chromosome 8 ($p=0.16$).

Conclusion: The most common secondary changes in ES are trisomy 8, trisomy 12 and a gain of DNA sequences in 1q. The possible prognostic significance of chromosome 8 trisomy has to be tested on a larger material.

Reference: 1. Br J Cancer 75.1403-1409

53. Bmi-1 protooncogene links skeletal development and osteosarcoma genesis

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The bmi-1 gene encodes a nuclear protein of 324 amino acids which is homologous to certain members of the *Polycomb* family of proteins that regulate homeotic gene expression through alteration of chromatin structure in *Drosophila*. By using a differential display approach to identify genes that are overexpressed at the RNA level in high-grade osteosarcoma as compared to low-grade osteosarcoma we found one of the isolated clones to have sequence identity with bmi-1. Transgenic mice overexpressing Bmi-1 exhibit a dose-dependent anterior transformation of vertebral identity along the complete anteroposterior axis, while at the other end of the spectrum mice with a targeted deletion of the bmi-1 gene show a posterior transformation. This regulation is mediated by repression of specific *hox* genes caused by interaction of Bmi-1 with other members of a mammalian *Polycomb* complex during development. To further characterize the role of Bmi-1 in bone tumorigenesis we used specific antibodies to analyze Bmi-1 expression by immunob-

lotting and confocal microscopy in all 3 types of normal bone cells as well as in bone tumor cells *in vitro* and *in vivo*.

We found equally low levels of Bmi-1 expression in both, osteoblasts and chondrocytes, as well as very low to non-detectable levels in osteoclasts. Expression levels were slightly elevated in preosteoblastic MC3T3 cells. However, expression was significantly increased in primary cells from 2 high-grade central osteosarcomas as well as in the osteosarcoma cell lines U2OS and HOS TE85. In sharp contrast no increase was observed in chondrosarcoma cells. Furthermore and most interestingly, confocal imaging revealed a speckled Bmi-1 pattern in the nucleus of U2OS cells, which was specific for osteosarcoma cells, while all other cells investigated, including osteoblasts, osteoclasts, chondrocytes and chondrosarcoma cells showed only a homogeneous nuclear staining pattern, excluding the nucleolus.

We therefore conclude that with respect to bone tumors Bmi-1 is specifically overexpressed in osteosarcoma but not in chondrosarcoma. Furthermore the specific subnuclear localization in osteosarcoma suggests a functional mechanism by which Bmi-1 contributes to tumorigenesis in osteosarcoma.

54. $\alpha 4\beta 1$ (VLA-4) integrin specifically mediates osteosarcoma cell adhesion to thrombospondin

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Thrombospondin (TSP) is an extracellular matrix (ECM) glycoprotein that can regulate a variety of processes associated with cell motility and tissue turnover, including tumor cell adhesion, invasion and metastasis. Here we investigated the interaction of 5 different human osteosarcoma (OS) cell lines with purified TSP immobilized on culture plates, and analyzed the receptor(s) involved in TSP recognition by flowcytometry and antibody-blocking studies.

OS cells adhered to TSP in a time- and dose-dependent manner, with maximal adhesion after 60 min and at 1.8 $\mu\text{g}/\text{sqcm}$. Adhesion of the 5 OS cell lines was in the potency order U2OS \approx SAOS \gg MNNG-HOS \approx MG-63; cell line OST hardly adhered to TSP. Pretreatment of OS cells with soluble TSP prevented their subsequent adhesion to immobilized TSP. In this context, a reciprocal relationship between OS cell TSP production and TSP adhesion was evident. By using several monoclonal antibodies (mAbs) against integrin and non-integrin adhesion receptors it was revealed that the integrin $\alpha 4\beta 1$ (VLA-4) functions as the sole TSP receptor in OS cells. The relative fluorescence intensity for anti-VLA4 mAb/goat-anti mouse FITC for the cell lines was in the order U2OS \approx SAOS \gg MNNG-HOS \approx MG-63; cell line OST was devoid of VLA-4 receptor. Since VLA-4 is an alternate ECM receptor for fibronectin (FN) through the CS-1 peptide, it was examined whether VLA-4 could function as a dual receptor for TSP and FN. Though OS cells firmly adhered onto

FN, the cells did not adhere to immobilized CS-1 peptide EILDVPST. Also, the adhesion to FN was not prevented after preincubation of cells with EILDVPST.

Collectively, these results demonstrate that VLA-4 integrin on OS cells specifically recognizes ECM protein TSP, which may play a critical role in OS cell function. The failure of OS cells to adhere onto TSP is due to the absence of VLA4 receptors rather than the production of TSP by these cells.

55. Role of PTHrP and Bcl-2 in chondrogenetic tumors

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Human chondrosarcomas (CS) are a frequent form of malignant bone tumors. The accurate distinction between benign solitary enchondroma and conventional CS of bones is a major diagnostic goal. Although the histological characteristics of chondrogenic tumors and the grading of CS (G1 to G3) have been defined by several authors, immunohistochemical markers for the different entities and grades are still missing and the mechanisms of tumorigenesis remain poorly understood. In addition to the emerging evidence that parathyroid hormone-related peptide (PTHrP) plays a critical role in endochondral bone formation, we have recently reported that Bcl-2 lies downstream of PTHrP in the regulation of chondrocyte maturation.

Methods: To further characterize chondrogenic tumors and to determine whether PTHrP and the regulation of Bcl-2 expression is of relevance to tumorigenesis in these tumors, we analyzed the expression of both PTHrP and Bcl-2 on a series of 23 cases of solitary enchondroma (9 cases) and primary CS (14 cases) using light and confocal microscopy.

Results: While all 9 enchondromas exhibited detectable levels of PTHrP expression, only 2 showed low levels of immunoreactivity for Bcl-2. In sharp contrast, strong coexpression of Bcl-2 and PTHrP was found in 11 (composed of 3 CS G3, 7 CS G2, and one dedifferentiated CS) out of 14 CS, while the expression level of these proteins was below the detection limit in two CS G1 and one dedifferentiated CS. To verify this data 3 cases each of enchondroma, CS G2, and CS G3 respectively, were subjected to quantitative confocal analysis, after double labeling for PTHrP and Bcl-2. The results showed a significant increase in the expression of both PTHrP and Bcl-2, in malignant CS versus the benign enchondromas. Most interestingly, the levels of coexpression of both PTHrP and Bcl-2 correlated with the degree of malignancy of the chondrogenic tumors.

Conclusion: These results therefore suggest that both PTHrP and Bcl-2 play a role in the tumorigenesis of chondrogenic tumors and further indicate that both proteins may participate in the same pathway regulating chondrocyte differentiation.

56. The pattern of CD44 expression and clinical outcome of synovial sarcomas

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The purpose of this study was to determine the pattern of CD44 expression within synovial sarcomas, and the clinical outcome of patients with these tumours. CD44 is a cell adhesion molecule that has been shown to correlate with the ability of certain tumours to metastasise. Previous studies have shown that CD44 expression is an independent prognostic indicator for several types of adenocarcinoma. No work to date has shown the pattern of CD44 expression within synovial sarcomas. Previous studies on synovial sarcomas have shown, size, mitotic rate and degree of necrosis to be significant prognostic indicators.

43 cases of synovial sarcoma from the Birmingham Orthopaedic Oncology Service were assessed. The clinical outcome of each case was reviewed, entered into a database, and related to established prognostic indicators. Stored tissue from each case was investigated for CD44 expression using immunohistochemistry. The monoclonal antibodies to CD44 and variants v3, v5, v6 and v7 were used. The pattern of CD44 expression was compared with the established prognostic indicators and the clinical outcome.

Results of the study have shown size, grade and stage to have statistical significance on clinical outcome. CD44 expression, depth of tumour, and surgical margin were not shown to have statistical significance on clinical outcome. It would appear that the clinical aggressiveness of synovial sarcomas is not dependent on CD44 expression.

57. DNA cytometry in the diagnosis of bone neoplasms—results from 249 cases of the Hamburg Bone Tumor Registry

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The DNA ploidy of bone neoplasms and tumorlike lesions of different histogenetic origin was investigated to test DNA cytometry, as a diagnostic tool. Feulgen stained imprints of biopsy samples or single cell preparations of paraffin embedded material in osteoidosteomas (9), osteoblastomas (4), high-grade central osteosarcomas (83), low-grade central osteosarcomas (26), solitary bone cysts (22), aneurysmal bone cysts (38), giant cell tumors of bone (10), fibrous dysplasias (5), nonossifying fibromas (10), malignant fibrous histiocytomas of bone (4), chondromas (11), chondrosarcomas G1–G3 (16) and chondroblastomas (11) were used.

The evaluation of the DNA histograms was carried out according to the principles of stemline interpretation or single cell interpretation. The benign cystic fibrous and fibrohistiocytic lesions showed only diploid DNA patterns. Between the osteoidosteomas and osteoblastomas only 1 atypical osteoblastoma had aneuploid single cells. The majority of the high grade central osteosarcomas (70/83 cases) dis-

played a DNA-aneuploid stemline and only 8 cases had tetraploid stemlines. The occurrence of diploid osteosarcomas in the high-grade subgroup was rare and restricted to 5 cases of special histologic types (osteoblastoma-like and fibroblastic). In contrast, the low-grade central osteosarcomas showed DNA-diploid stemlines except for 1 case resembling a parosteal osteosarcoma. In 5 cases there was evidence for a DNA-euploid polyploidisation but in another 5 cases single aneuploid nuclei as a sign for genetic instability within the population of tumor cells were detectable. In chondrosarcomas there was a correlation between DNA-ploidy and histological grade of malignancy. In G2-chondrosarcomas either a DNA-diploid pattern, single cell aneuploidy or a DNA-tetraploidy was found. DNA aneuploid stemlines were detected only in G3-chondrosarcomas. A distinction between chondromas and G1-chondrosarcomas was not possible. The chondroblastomas were DNA-diploid. However 1 case of chondroblastoma with malignant transformation showed single cell aneuploidy. In giant cell tumors of bone a DNA-diploid pattern as well as DNA-euploid polyploidisation was detectable.

DNA cytometry is a useful additional tool in the diagnosis of bone neoplasms. The identification of an aneuploid stemline is a sign for a neoplastic process and does not occur in tumorlike lesions. Furthermore in osteoblastic and chondroblastic tumors this feature indicates a highly malignant process. However, to avoid false interpretation of DNA-cytometric results the histological type of the lesion has to be considered.

58. P-glycoprotein expression in musculo-skeletal tumors in relation to p53 status

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Overexpression of P-glycoprotein (PGP), encoded by the MDRI gene, has been reported to have an adverse prognostic value in osteosarcoma (OS) and soft-tissue sarcomas (STS). Recent in vitro experiments have demonstrated that transcription of the human MDRI gene can be increased by mutations of p53 gene. By using immunohistochemistry, we evaluated the expression of PGP and p53 status in 64 primary and 11 metastatic OS, and in 45 STS, including 30 primaries and 15 local recurrences. Among OS, overexpression of PGP was found in 31/64 primary tumors (48%) and in 7/11 (64%) metastatic lesions, and appeared to be associated with a worse clinical outcome. Among STS, increased expression of PGP was revealed in 23/45 cases (51%) and no significant difference was observed between primary and recurrent lesions. Nuclear accumulation of p53, which corresponds to mutation of p53 gene, was found in 7/64 primary OS (11%), but not in metastatic OS. Among STS, p53 positivity was found in 4/45 samples (9%), 3 of which were from recurrent lesions. PGP-overexpression was associated with nuclear

accumulation of p53 in 5/7 OS and in 2/4 STS. These observations confirm the adverse prognostic value of PGP in OS and suggest that PGP is overexpressed in a significant proportion of patients with STS. Moreover, our data suggest that p53 mutations may influence the expression of PGP in OS, although they do not clarify whether these two parameters are associated in STS.

59. Immunohistochemistry of growth factors and growth factor receptors in chondrosarcomas

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Chondrosarcomas are traditionally treated with surgery alone. The prognosis of high grade chondrosarcomas is often poor. Chondrosarcomas may show more or less differentiation into cartilaginous tissue. As capable of forming cartilage chondrosarcomas display some of the effects of the growth process. Growth factors and their receptors are important mediators of growth.

Materials and methods: Tissue specimen were obtained fresh from the operating room, frozen in liquid nitrogen and stored at -80 °C until processing. For comparison some benign cartilage tumors and tumorlike conditions were also sampled. Normal epiphyseal and articular cartilage served as references. The patient material included 26 chondrosarcomas, 5 chondroblastomas, 1 osteochondroma, 1 synovial chondromatosis and 1 reactive cartilage proliferation in osteoarthritis. Antibodies directed against PDGF-BB, TGFβ-1, TGFβ-2, IGF1, IGF2, αFGF, βFGF, EGF, TGFA and their corresponding receptors were obtained from commercial suppliers.

Results: Generally chondrosarcomas showed positive staining for IGFI, αFGF, βFGF, PDGF-BB, TGFβ-1, TGFβ-2 and the corresponding receptors. High grade chondrosarcomas often showed more staining than low grade tumors. Benign tumors, reactive cartilage proliferation and normal epiphyseal and articular cartilage generally showed less positive staining.

Conclusions: The results imply the possibility of self stimulation by autocrine mechanisms, so called autocrine loops, previously implied in Ewing sarcomas. The production of growth factors by the tumor cells remains to be established. A study with RT-PCR methodology is underway to investigate this.

60. Tumor cell differentiation and extracellular matrix composition in enchondromas and chondrosarcomas

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At present, there is little information available about the biology of cartilaginous tumors. In this study, we attempted to extend these data by subtyping the various components of the extracellular tumor matrix. Additionally, we tried to monitor differentiation pattern of the neoplastic chondrocytes using collagen subtypes as differentiation markers.

Materials and methods: 7 enchondromas and 14 chondrosarcomas (various grades) were analyzed by histochemical, immunohistochemical (collagen types I, II, III, X), and in situ hybridization (collagen types I, II, III, IX, X, and XI; aggrecan core and link protein) techniques.

Results: All tumors were subdivided into chondroid, chondromyxoid, and myxoid areas: Chondroid areas showed strong expression for collagen types II, IX, and XI as well as cartilage proteoglycan. Focally, also expression of collagen types X and I were detected. Interestingly, in enchondromas significantly less expression of type X and I collagens was found than in chondrosarcomas. In chondromyxoid areas, less expression of cartilage components was found and collagen types I and type III appeared in the extracellular tumor matrix. In myxoid areas, the neoplastic cells expressed typically collagen types I and III.

Discussion: Our study demonstrates the full differentiation capacity of neoplastic chondrocytes showing features of the mature, hypertrophic, posthypertrophic and dedifferentiated phenotypes. The striking heterogeneity of the extracellular matrix appearance—a so far badly explained characteristic feature of chondroid neoplasms—can be largely explained by the extensive phenotypic modulations of the neoplastic cells. The higher phenotypic instability of malignant cells, which is documented by the overall more frequent expression of collagen types I, III and X compared to the benign varieties, explains why matrix appearance can serve as one criterion of malignancy and grading.

61. Cytotoxic effect of methotrexate and 1-methyl-2-pyrrolidone in osteosarcoma cells in vitro

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One of the main problems in treatment of malignant bone tumors is the local recurrence of the tumor even after wide surgical excision and systemic chemotherapy. Since acrylic bone cement is filling defects and stabilizing reconstructive prosthesis in many instances, some investigations proposed a local chemotherapy by loading the cement with a cytostatic agent as methotrexate (MTX). Although there are a few animal experiments and first clinical studies showing encouraging results in using MTX for local chemotherapy, little is known about the cytotoxic effect of MTX eluted from acrylic

ic cement on bone tumor cells in vitro. Therefore to gain cytobiological data on the cytotoxic effect of MTX and its solvent 1-methyl-2-pyrrolidone (NMP) eluted from acrylic bone cement (Merck, Darmstadt) the dose response relationship of MTX and NMP in various osteosarcoma cell lines MG-63, MNNG-IIOS, OST, SaOS and U2OS was determined by MTT assay. Sensitivity to NMP was similar for all five osteosarcoma cell lines: cell viability was not affected by concentrations ranging from 10^{-9} M to 0.01 M. NMP concentrations > 0.1 M displayed high cytotoxic effects. The cell lines showed different sensitivity to MTX correlating on their growth rate. The time-dependent dose response curves exhibit a cytotoxic effect at concentrations $> 10^{-7}$ M of MTX. Collectively, the current data should be valuable for estimating the optimal MTX dose eluted from bone cement for inhibition of osteosarcoma cell proliferation.

62. Experience with inner hemipelvectomy and endoprosthetic replacement in primary and secondary malignant pelvic tumors

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Inner hemipelvectomy with endoprosthetic replacement is a very large orthopedic operation asking for an elaborate concept of planning, materials, techniques and postoperative rehabilitation. Even with optimal preparation using preoperative planning with 3-D solid models in real life scale (1:1) and combined custom-made/modular endoprostheses, postoperative rehabilitation is difficult considering the important bone and soft tissue loss leading to a higher risk of dislocation and muscular instability. This concept is defined and the experiences gained during its use are described.

Material and methods: In 12 patients an inner hemipelvectomy with endoprosthetic replacement was carried out in from 1993–1996. In 9 patients this operation was due to primary or secondary malignant pelvic tumors, in 3 patients due to situations with massive bone loss and pelvic discontinuity with a THA in situ (in 2 of these patients the primary THA implantations followed the resection of tumors).

Results: The planning was carried out using 3-D solid models in real life scale (1:1) manufactured using 3-D CT data. These models allow for a preoperative surgery and implantation control of the custom-made/modular endoprosthetic components and represent an intraoperative guide. The endoprostheses were partly custom-made, partly modular. In all cases a special intramedullary peg fixation in the iliac bone (cemented or cementless) was used. In the postoperative rehabilitation phase a complete pelvis-to-foot cast was used in the first 6 weeks, followed by a pelvis-to-foot orthosis with three joints for another 6–12 weeks depending on the individual patient. Nevertheless, the very pronounced bone and soft tissue loss caused muscular instability and a dislocation in 6 patients at the beginning of the concept elaboration. Further complications included infection, wound necrosis and hematoma, which were treated surgically.

Conclusions: Inner hemipelvectomy with endoprosthetic replacement allows for the salvage of a lower limb, but implies very large and difficult orthopedic surgery, a high complication rate as well as a large bone and soft tissue loss with consecutive muscular instability. An elaborate concept with planning, special endoprostheses and carefully monitored rehabilitation (with the use of an individually built orthoses) is necessary to overcome those difficulties.

63. Patella allograft with patellar tendon in prosthetic reconstructions of the upper tibia after en bloc resection and gastrocnemius flap

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After en bloc resection of the upper tibia for bone sarcomas, the functional results hang mostly on the strength of patellar tendon reattachment and the quality of skin healing.

Material: From 1982–1995, 50 upper tibial reconstructions were made by the authors after en bloc resection for primary bone tumors (osteosarcoma 35, Ewing 5, chondrosarcoma 3, fibrosarcoma 2, NWH 2, osteoclastoma 2, chondroblastoma 1). 13 patients had a direct skin closure, 37 others benefited of gastrocnemius flap. In 5 cases, reconstruction procedures used stainless steel long prostheses coated with stem polyethylene. In others, we used long stem custom made titanium prosthesis coated with massive bank allograft. In 8 cases, we used only bone graft. Patellar tendon was reinserted either direct, through bone or with patient tibial tuberosity. In other cases, bank allograft was harvested with patellar tendon and patella, and patient's patellar tendon was reattached to the patella and the graft. Weight bearing was immediate in all cases but active motion was restricted during 45 days to help muscle's reattachment. All patients have been followed by the authors. Median follow up is 72 (18–144) months.

Results: Complications are frequent: 10 loosening and 12 infections compelling to reoperate 18 patients and leading to 8 secondary amputations. The gastrocnemius flap is the best prevention of infection: we obtained 9/13 infections without flap, versus 3/37 with flap. Massive stainless steel prosthesis coated with polyethylene doesn't provide a reliable reattachment of patellar tendon: extension lag appears in all 5 cases after 6–10 months. Bone allograft permits a real reinsertion of patellar tendon, but is exposed to shortening of the tendon (that limits flexion) and is threatened by secondary fracture. Best results were obtained with graft of tibia, tendon and patella. Such procedure provides the good length of patellar tendon and permits suture through patella.

Conclusions: 1) Upper tibia allograft should be harvested with patella and patellar tendon. Such allograft permits a much reliable reconstruction of patellar tendon avoiding extensor lag while allowing acceptable knee flexion. 2) Gastrocnemius flap is the best prevention of deep infection after upper tibial reconstruction using prostheses.

64. "Hand on" prosthesis reconstruction after periacetabular resection for malignant bone tumors—our experience

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After periacetabular resection for bone malignancies, a reconstructive procedure is necessary to stabilize the hip, avoid limb discrepancy, and permit full weight bearing. But as resection of this area is time and blood consuming, this procedure should be easy to perform. In this case, we used an "hand on" prosthesis.

Methods: Our reconstructive prosthesis uses a titanium cup with long screw in remaining bone (sacrum or spine). Once the cup is finely fixed to the bone, the gap between the cup and the bone is filled with cement loaded with antibiotics and the polyethylene component, cemented on the cup. Then, the femoral component of an usual total hip prosthesis is implanted.

Material: Since 1990, we used such a reconstructive procedure in 27 patients with bone sarcoma involving the acetabulum (7 chondrosarcomas, 6 osteosarcomas, 5 bone metastases, 6 Ewing's sarcomas and 3 other sarcomas). The average duration of the reconstructive procedure was 45 minutes. Walking started 4–10 days after operation but full weight bearing was usually authorized after 6 weeks.

Results: Postoperative complications were frequent: 5 deep infections required ablation of the prosthesis (one could secondary benefited of a saddle prosthesis). 9 patients had postoperative luxation requiring reduction and plaster with no further complication.

Oncologic results: With a median follow up of 5 years, 7 patients died of disease and 1 from unrelated disease. The others are event free survivors.

The orthopedic result graded according to Society for Musculoskeletal Oncology criteria is excellent in 4, good in 13, fair in 5, bad in 5. Only 2 loosening have been observed till now.

Best functional results are observed after resection of the acetabular and the anterior ring. The rapidity (average length: 45 minutes) and the efficacy of this procedure plea for this reconstructive way. The use of cement to fill the iliac gap permits the adjunction of antibiotics often needed in these complicated cases.

Conclusion: "Hand on" acetabular prosthesis seems to be very promising for reconstruction after en bloc resection of primary bone sarcoma. A longer follow up and more cases are necessary for better analysis

65. Angiographic evaluation of response to preoperative chemotherapy in bone and soft tissue sarcomas

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Evaluation of the effect of preoperative treatment on bone and soft tissue sarcomas is important. This study investigated the accuracy of angiography in evaluating tumor response to preoperative chemotherapy.

Methods: 31 patients with bone and soft tissue sarcoma who received preoperative chemotherapy were studied. There were 18 patients with osteosarcoma, 4 with synovial sarcoma, 2 with MFH, and 7 others. The Seldinger technique was used to perform digital subtraction angiography under local anesthesia. The angiograms before and after preoperative chemotherapy were compared based on vascularity and existence of tumor stain. Angiographic findings were divided into 4 grades; grade 1: increase or no change in size or vascularity of tumor, grade 2: decrease in tumor vascularity and tumor stain, grade 3: total disappearance of tumor vascularity with slightly persistent tumor stain, grade 4: complete disappearance of hypervascularity and tumor stain. Grade 3 or 4 was defined as an angiographically positive response. Tumor necrosis over 90% was considered effective.

Results: Angiograms before preoperative chemotherapy showed both hypervascularity and tumor stain in 30 of 31 patients. 17 patients were considered as responders on angiography. On histological examination, all of 10 cases (100%) showing angiographic grade 4 and 5 of 7 cases (70%) showing grade 3 demonstrated affective preoperative chemotherapy. Correlation between angiographic and histological results revealed 15 true-positive, 2 false-positive, 11 true-negative, and 3 false-negative.

Discussion and conclusion: This study demonstrated that the angiographic assessment has a sensitivity of 83%, a specificity of 85%, and an accuracy of 84%.

66. Endoprosthetic replacement of the proximal tibia—long-term results

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Limb salvage surgery for bone tumours of the proximal tibia is complex because of the combined problems of obtaining soft tissue cover and repairing the extensor mechanism whilst maintaining a stable functioning limb.

Methods: 151 adult patients have had endoprosthetic replacements of the proximal tibia over the past 20 years. The initial implant used was based on a hinged Stanmore knee. The mean age was 28 years. 100 are still alive at a mean of 80 months. All patients have been reviewed and assessed.

Results: Up to 1988 the infection rate was 31% but since the routine use of a gastrocnemius muscle flap since then this has dropped to 12% ($p = 0.005$). Infection was not related to age, length of bone replaced, previous surgery or chemotherapy. The local recurrence rate was 10%. These two causes accounted for 25 of the 26 amputations. The risk of revision for aseptic loosening or implant failure was 70% by

20 years. This risk has decreased dramatically since a rotating hinge knee has been used. The overall functional score was 77% with emotional acceptance being 84% but functional activity being 62%. Knee flexion averaged 104° but with a mean 30° extensor lag. One in four had changed or lost their job following the operation.

Conclusion: Endoprosthesis replacement of the proximal tibia is still a high risk procedure with significant complications. These results need to be strictly compared with alternative procedures such as allografts or even amputation.

67. Clinical outcome of intercalary allograft reconstructions in the lower extremity after 3 years

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Resection of malignant bone and soft tissue tumors in the diaphysis of long bones causes substantial bony defects. Intercalary allografts can salvage the limb in such situations. Intramedullary nailing, plating or screws can be utilized for fixation.

Objective: The 3 year follow up results of different intercalary reconstructions in the lower limb are analyzed regarding their complications and functional outcome.

Material and methods: Between 1991 and 1993, 29 patients with an average age of 23 years sustained intercalary defects of the lower limb after malignant tumor resection and underwent reconstructive limb salvage surgery with intercalary allografts (15 femoral and 14 tibial defects). The tumor diagnose was Ewing's sarcoma in 15 and osteosarcoma in 9 patients, 5 had soft tissue sarcomas. The length of the defects were from 11 to 28 cm with an average of 18 cm. 23 of the femoral and tibial defects were primary reconstructions, the other 6 had prior reconstructions that failed due to infection, loosening or fracture. The majority of the patients was treated with chemo- and/or radiotherapy.

Results: The median follow up time was 3 years. Three of the 29 patients died of disease, local recurrence occurred once and two patients were lost to follow up. 23 patients were continuously disease free. Out of 23 patients 13 had intercalary femoral allografts and 10 had intercalary tibial allograft reconstructions. Eleven patients underwent further surgery once, six patients had more than one secondary procedure. 9/13 femoral grafts and 8/10 tibial grafts survived after three years. In all but one cases of graft removal, secondary limb salvage procedures were carried out. One patient was amputated due to persistent infection. The main reason for revision was nonunion in both groups which was treated with autogenous iliac crest grafting. Functional evaluation of 18 patients after 3 years showed 57% for femoral lesions and 73% for tibial lesions.

Discussion: The three years follow up of intercalary reconstructions in the lower limb shows acceptable survival rates with 69% for femoral and 80% for tibial grafts. During

this time 2/3 needed grafting for nonunion to achieve healing of the junction. In cases of graft failure secondary reconstructions are possible. Once healing is achieved revisions are rare. The functional rates are comparable to other modalities. Therefore intercalary allograft reconstructions can be recommended after diaphyseal tumor resection as a biological substitute of the bone defect.

68. One-stage ablation and reconstruction by free flap transfer in extremities due to malignant tumors

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Ablative surgery with simultaneous microsurgical repair was performed in 42 patients with primary or metastatic malignant tumors of the extremities, we divided them into 3 groups.

Group A consisted of 10 cases where ablation created large (15 cm or more) bone defect sparing the same time of soft tissues. Vascularized fibular grafting undertaken in all cases in one operative session with the bone resection provided vital bone substitute in every case. Group B consisted of 12 patients with primarily soft tissues affection. Bones were either intact or needed no reconstruction. Thoracodorsal myocutaneous flap sufficed to solve the reconstructive problem in four cases. In two patients free serratus muscle was transferred to the defect and covered by meshed skin graft. In two remaining patients large defects were covered by the combined—scapular + serratus—flaps on either common or separate vascular pedicles. Good results were obtained in each case. Group C (20 patients) had complex—bone and soft tissues—extensive defects which required refilling for the limb salvage. Combined transplants consisted of fibular bone with peroneal muscles and overlying skin or separate island fascio-cutaneous flap on the same vascular pedicle were used in all cases. Free vascularized tissue transfer allows to save extremities bearing advanced tumor by means of full replacement of all affected tissues in the scarred irradiated surroundings which would have been absolutely impossible to salvage otherwise. Above that the postoperative irradiation treatment can be carried out due to stable reconstructed integument.

69. Periosteal host response during chemotherapy as a prognostic factor in osteosarcoma

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Various prognostic factors in osteosarcoma have been looked at in the past. It is well known that the effect of chemotherapy on the primary tumor, so called tumor-response, is most predictive on the final outcome. Little attention has

been directed to the tumor-host relationship, so called patient response. Local reaction by the host towards the tumor has three aspects known as mesenchymal, vascular and inflammatory response.

Material and methods: We have developed a grading system for patient response toward the osteosarcoma after preoperative chemotherapy including distinct histologic patterns, formation and quality of the pseudocapsule, presence and size of satellite metastases, amount of reactive bone formation around the lesion and amount of soft tissue reactive zone around the lesion. We graded the patient's response in 4 distinct grades. Grade 1 describes a poorly formed loosely arranged pseudocapsule with fingerlike projections of viable tumor cells with satellite lesions and/or skip metastases and little vascular and inflammatory response. Grade 2 describes a loose poorly defined pseudocapsule without fingerlike projections of viable tumor cells without satellites. Grade 3 shows a capsule of mature fibrous tissue around the lesions with vascular and inflammatory reaction beyond it. Grade 4 host reaction implicates a capsule of reactive bone around the lesion with non reactive muscle around it. Forty-four patients with stage IIB osteosarcomas of the knee were treated at a single institution with preoperative chemotherapy and were studied to determine the effect of the patients response towards the lesion. The above grading system was applied to postoperative histology slides and macrosection slides that showed representative features host to tumor reaction. The histologic slides were blindly reviewed by four experienced musculoskeletal physicians (3 surgeons, 1 pathologist) to assign a grade of response. The results were correlated to histologic tumor response and overall oncologic outcome.

Results: Correlation has been found between post chemotherapy tumor necrosis grade and patient response grade towards the osteosarcoma. A Grade 3 and 4 patient response was predictive for long term survival.

Conclusion: The tumor-host relationship, so called patient response, has prognostic impact on oncological outcome. Histomorphometric studies focusing on patients response might help tailoring therapeutic planning in the future. These results suggest that effective preoperative adjuvant treatment on osteosarcoma clarifies the border between the tumor and the normal tissues in the extraosseous part, especially in the peri- and parosteal region.

70. Oncologic outcome in dermatofibrosarcoma protuberans involving the musculoskeletal system

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Dermatofibrosarcoma protuberans occurs over a broad age range and equally among females and males, most commonly involves the trunk and proximal extremities without any particular pattern. The disease usually runs an indolent

course and is too often regarded lightly by patients as well as physicians leading to delayed and often too conservative treatment.

The dilemma of a high recurrence rate due to frequent inadequate treatment stimulated this study to provide current sufficient data on Dermatofibrosarcoma protuberans in the oncologic literature.

Methods: The clinical course and histopathologic factors of all patients surgically treated for dermatofibrosarcoma protuberans at the University of Florida from 1975 to 1996 were retrospectively reviewed. Inclusion criteria were the history of dermatofibrosarcoma protuberans that required surgery at our institution. The medical records of 35 consecutive patients treated at our hospital within the last 21 years were searched for characteristics like age, sex, primary tumor or number of recurrences, anatomic site and diameter and extend of the tumor, time of previous surgery before reexcision, years of symptoms, surgical margins, reconstructive procedures. Adjuvant therapy and follow up status. A review of the world literature, comparing the treatment and results is presented.

Results: Inadequate marginal or intralesional surgery leads to 100% local recurrence without adjuvant radiotherapy. The final oncologic outcome was continuously disease free (CDF) in 17 cases and no evidence of disease (NED) in 17 cases. Of the followed 18 patients that presented with an untreated primary lesion or an immediate reexcision of the primary lesion are 17 patients CDF. All seventeen cases that were treated after a local recurrence have no evidence of disease. No patient developed lymphatic spread of distant metastases.

Conclusion: To avoid mutilating surgery later in the course, the initial treatment must be wide surgical excision including a surrounding margin of at least 2 cm normal tissue. The removal of underlying deep fascia is essential and adequate resection will require a skin graft replacement in nearly every instance.

71. Limb salvage, clinical and oncological outcome of osteosarcoma—the University of Münster experience

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136 consecutive patients with stage II osteosarcoma of the skeleton treated from 1978–1994 were studied to identify clinical and oncological outcome.

Design: All patients referred to our center with a primary osteosarcoma of high grade were eligible for the study. All these patients with histopathological diagnosis of osteosarcoma were treated with a multidisciplinary approach including intravenous neoadjuvant chemotherapy according to the COSS scheme and limb salvage or amputation. There were 74 men and 62 women. There were 15 tumors in the humer-

us, 2 in the forearm, 6 in the pelvis, 66 in the femur, 32 in the tibia, 12 in the fibula and one in the foot, rib and xiphoid. 50 tumors were considered osteoblastic, 26 chondroblastic, 10 fibroblastic, 7 telangiectatic, 7 anaplastic, 7 small cell and 36 were not further specified. The tumor volume was calculated based on MRI and postoperative pathology. In 93 cases surgical margins were wide, 25 were radical, 12 marginal and 6 intralesional, having revision surgery in three cases to enhance the margin. 33 patients underwent an amputation, 20 had a rotationplasty, and 79 underwent limb salvage. Limb salvage consisted of 32 endoprosthetic 26 allograft, 19 autograft and 2 shortening procedures. Postoperative complications were documented as well as functional and oncological outcome.

Results: 77 patients are continuously disease free, 3 are alive after local recurrence, 14 patients are living with pulmonary metastases, 5 are alive with local tumor present and 33 died of disease, 4 died of other causes. 48 patients developed pulmonary metastases, 14 osseous and 3 abdominal, 2 lymphatic and 8 skip metastases. 23 patients showed grade 4 response to chemotherapy, 37 grade III, 34 grade II and 16 grade I. Prognosis was correlated with chemotherapy response. 68 patients have their original reconstruction in place, 23 their second and 9 their third and 2 their fourth. 3 patients have persistent infection. Minor complication rate in limb salvage was 75% and major complication rate was 18%. Amputations had a 51% minor complication rate and 21% major complication rate. Rotationplasties had a 30% minor and 20% complication rate. Functional evaluation after limb salvage showed 10 excellent, 32 good, 12 fair and 4 poor results concerning to the MSTS system.

Discussion: The improvement in accurate preoperative local staging techniques allows salvage of healthy tissue to obtain best functional results. Amputation has to be carried out if a adequate margin is not compatible with limb salvage. Modern orthopedic oncology ensures local control leading to a higher prognostic impact in systemic therapy in prevention of oncologic failures in the future.

72. Metastatic carcinoma of the extremities—a new protocol of treatment

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Up to now, the treatment of bone metastases from carcinoma did not follow a well codified therapeutic protocol and the competence was shared between the orthopedic surgeon, the oncologist and the radiotherapist. In addition, the surgical treatment followed personal indications and several techniques and devices were employed without any specific rule of choice. For these reasons the authors defined a protocol of treatment of metastatic carcinoma of the extremities in order to integrate the roles of the different specialists and to identify the better therapeutic solution for each single patient.

4 different classes of patients are identified: solitary le-

sion with good prognosis (class 1); pathologic fracture (class 2); impending fracture in major bones (class 3); all other cases (class 4). Class 1, 2 and 3 have an orthopaedic priority and the surgical solution is the first choice. After surgery the patient has to be referred to the oncologist (chemo- and/or hormone-therapy) and/or to the radiotherapist. Class 4 patients have to be treated in first instance by the oncologist and/or radiotherapist, and in case of mechanical failure (class 2) or persistent pain and/or local progression (class 3) must be referred to the orthopaedic surgeon.

The metaepiphyseal area is divided in 3 segments and, depending on tumoral extension, the reconstructive choice is between long stem prostheses and megaprotheses. For metadiaphyseal defects a scoring system has been defined taking in account four parameters: expected survival; site of lesion; defect size; response to adjuvants. Depending on the score, the reconstructive choices are: simple osteosynthesis (reconstructive rod or single plate + cement); reinforced osteosynthesis (reconstructive rod + cement or double plating + cement); megaprotheses; intercalary spacers.

At present, a multicentric study on this therapeutic protocol is under trial, and encouraging results on the treatment of the metastatic bone carcinoma are expected.

73. The social impact of amputated patients versus patients treated with limb salvage

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If compared with amputation (A), conservative surgical procedures are often associated with a higher incidence of local recurrences and surgical complications, whose subsequent surgical treatments can cause a reduction of the dose/intensity of the associated chemotherapy. Moreover, conservative treatment do not always give functional results superior to those obtained with amputation

It is generally believed that these risks are worth running in order to allow patients the much better quality of life given by limb salvage (LS) rather than by amputation. To verify this assumption, a study on 520 cases of osteosarcoma (OS) of the extremity treated in our Institute from 1984–1994 with LS or A, was carried out.

Methods: We tried to evaluate the quality of life of these patients through a questionnaire investigating on levels of education, of job and salary, of personal achievement, the everyday activities (and their limits), the psychologic adaptation etc.

Results: As expected, we found that personal satisfaction after surgery, was much higher for patients who had a LS. Nonetheless, these patients denounced more limits in everyday activities (housework, autonomy in movements, etc.;) than amputated patients.

Conclusion: Today, for the treatment of OS of the extremity, various surgical procedures can be chosen (amputation,

rotationplasty, limb salvage followed by various reconstructions) which give different results and time to recovery. On the basis of our data we believe that, when deciding on the kind of surgery and reconstruction to be performed, the surgeon, together with all the medical staff, should evaluate not only the surgical feasibility but also the specific features of every single patient (style of life, age, sex, expectations, family environment, etc.) in order to provide the best quality of life after the treatment.

74. The prognostic value of chemotherapy induced necrosis in localized Ewing's sarcoma of the extremities—evaluation on 118 cases

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The specimens from 118 patients with localized Ewing's sarcoma of the extremities treated with preoperative chemotherapy in the years 1983–1993 were accurately mapped and reviewed to assess the amount of necrosis. The method used, previously described, is based on the absolute amount viable tissue detected and not as a percentage of viable tissue in comparison to the tumor before preoperative treatment. With this method necrosis was classified as Grade I (persistence of macroscopic nodules), grade II (persistence of microscopic nodules), and grade III (no evidence of nodules). All the possible prognostic factors were investigated by univariate and multivariate analyses. These included gender and age of the patients, tumor site and volume, type of surgery, surgical margins, addition of radiation therapy, chemotherapy protocol, and grade of chemotherapy induced necrosis. The follow-up averaged 86 (30–158) months.

Results: 46 specimens showed a grade I response, 35 a grade II, and 37 a grade III. The overall estimated 5-year disease-free survival rate was 62%. At univariate analysis a strong correlation with prognosis was found for the grade of necrosis and a weaker correlation was also found for age and tumor volume. At multivariate analysis the grade of necrosis maintained its prognostic value ($p=0.0001$), whereas age was at borderline level ($p=0.04$). Tumor volume lost its prognostic value.

Conclusion: The estimated 5-year disease-free survival was 95% for patients with total necrosis in comparison to 68% for patients with microscopic foci, and 34% for patients with macroscopic foci. These results will have to be considered when designing new therapeutic protocols for Ewing's sarcoma.

75. Prevention of recurrent giant cell tumor of long bones—a new surgical technique

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Giant-cell tumors of the long bones have been reported to have up to a 20% recurrence rate when locally resected, even when advanced techniques, such as high-speed burring, cryosurgery and polymethyl methacrylate packing are employed. Wide en bloc resection has a lower recurrence rate, but carries a far greater local morbidity.

We present a modification for local resection based on dye-staining the tumor cavity wall to a known depth, enabling controlled, uniform removal of bone and facilitating removal of tumorous remnant without unwarranted damage to healthy bone.

Our results, after a 2-year follow-up period during which there were no recurrences, are highly favorable when compared to the literature.

76. Giant cell tumor of the axial skeleton—the Gothenburg experience

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Giant cell tumor (GCT) of the axial skeleton may have disastrous consequences. Modern treatment with high speed bur, phenol, bone cement or liquid nitrogen is difficult to apply efficiently in the spine and sacrum. What is the outcome with more conventional treatment?

Patients: 14 patients were treated in our department; mean age 32 years. 9 had vertebral tumors, 5 had sacral tumors. 11 had neurologic symptoms. Intralesional procedures were done in 12 patients and an extra lesional resection in 1. 5 patients had radiotherapy.

Results: 4 patients developed a local recurrence. All were reoperated and radiotherapy was added in 2 patients. 1 vertebral tumor recurred in spite of this and had additional surgery. Radiotherapy and ligatures of the internal iliac arteries controlled one sacral tumor. At follow-up (average 12.5 years) all were without evidence of disease.

Conclusion: The results indicate that patients with GCT of the axial skeleton appear to have an almost equal chance for local control as is nowadays achieved in GCT of the extremities, where the mentioned modern treatment reduced recurrence rate from 50% or more to 15%.

77. Synchronous and metachronous radio-sensitive myxoid liposarcoma—a clinicopathologic study of 2 cases

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There is limited information in the literature regarding the effectiveness of radiotherapy in liposarcomas. However, well differentiated and myxoid types are generally regarded as unresponsive to radiotherapy.

Material and methods: 2 patients with 3 and 6 synchronous and metachronous myxoid liposarcomas were reviewed. Cytogenetic analysis was performed. 1 patient had a family history of lipomatous tumors. The other patient had a strong family history of malignancy (no constitutional p53 mutation was detected). All tumors were surgically removed. 5 tumors were treated preoperatively with radiotherapy.

Results: The 4 nonirradiated tumors were classified as myxoid liposarcoma. 4 of 5 irradiated tumors decreased in size; all 5 demonstrated maturation similar to a benign lipoma with occasional foci of hypocellular myxoid liposarcoma. 1 patient is free of disease (follow-up 12 months). The other patient developed 9 further extrapulmonary tumors, which are currently under treatment (follow-up 29 months).

Conclusion: The observations of radiation-induced maturation of myxoid liposarcoma to mature adipose tissue, (which have not been previously described), suggest that preoperative radiotherapy is a useful complement in surgical treatment of certain types of liposarcoma. Whether this response to radiation is unique to multicentric, familial cases of myxoid liposarcomas, or potentially useful in isolated cases of myxoid liposarcomas, or potentially useful in isolated cases of myxoid liposarcoma remains unclear.

78. Extraskelletal osteosarcoma—the Gothenburg experience

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Extraskelletal osteosarcoma is a rare malignancy which accounts for about 1% of all soft tissue sarcomas and most often occurs in middle aged and elderly patients. 9 patients with extraskelletal osteosarcomas, treated at Sahlgren University Hospital, were reviewed.

Patients and methods: 4 male and 5 female patients (mean age 54 years) with extraskelletal osteosarcomas involving the thigh (5), breast (2), abdomen (1) and head and neck region (1) were treated 1974–1993. Preoperative investigations included plain radiography, sonography, scintigraphy, CT, angiography, fine needle aspiration cytology (6) and incisional biopsy (1). All tumor were excised, 4 patients

had chemotherapy postoperatively.

Results: All but 2 patients died of tumor related disease 9–34 months after diagnosis. 1 patient died of cardiac failure 13 years after diagnosis. He was operated on 11 times because of a grade III recurrent tumor of the thigh. The remaining patient, who also had a thigh tumor, is alive 48 months after diagnosis without evidence of disease.

Conclusion: Extraskelletal osteosarcoma is a highly malignant tumor. The literature, as well as our experience points to a very poor prognosis. However, the application of modern diagnostic principles, surgery with adequate margins and adjuvant therapy according to updated protocols might improve survival.

79. Reasons for abstaining from radiotherapy after a poor surgical margin in soft tissue sarcoma—a SSG Register study

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Although adjuvant radiotherapy is recommended after a marginal margin in soft tissue sarcoma, only approximately half of such patients are actually treated. We tried to determine why patients were not referred for radiotherapy. 7 sarcoma centers participated in this retrospective study of patients treated 1990–1995. 197 patients with an intralesional or marginal margin, operated for primary tumor at a center, were identified. Other inclusion criteria were: age older than 15 years, no metastases at diagnosis, situated to the trunk wall or extremities, and not Kaposi's sarcoma or sarcoma protuberans. Among these 197 patients, 88 did not receive adjuvant radiotherapy. Data for reasons not to treat was available in 82 of these 88 patients. In another 7 cases, recorded data was incorrect: 5 had a wide margin and 1 patient had been treated.

The most common reason for nontreatment was low-grade (I–II) lesions, 36 cases. Other common reasons were old age and concomitant disease or sarcoma secondary to radiotherapy. Among the whole group of 88 patients, follow-up data was available in 87 with a mean follow-up time of 3 years. The 3-year local recurrence rate was 0.27 (Kaplan-Meier). After exclusion of 27 patients with Grade I lesions, among whom there was only one recurrence, the rate was 0.38. For comparison, the recurrence rate was 0.19 for the group of 109 patients that received radiotherapy ($p=0.005$ Mantel-Haenszel).

Although follow-up is still short, the study shows a high local recurrence rate. The results imply that more patients, despite old age or unfavorable anatomic location, should receive adjuvant radiotherapy after a poor surgical margin in soft tissue sarcoma.

80. Relative importance of response and methotrexate intensity on prognosis of osteosarcoma

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Since the Huvos and Rosen publication on prognostic value of tumoral response, most neoadjuvant protocols following Rosen TIO scheme give less methotrexate and more other drugs to bad responders than to good responders. For that reason, the relative impact of response and drug intensity often remains unclear. This literature analysis tries to provide an objective quantification of factors.

Methods: Literature assembly: a computerized research encompassing January 1976 to March 1997 was conducted to identify all available published reports of clinical trials using HDMTX in treating osteosarcoma. This research was supplemented by a systematic examination in all retrieved articles and major congress abstracts.

Inclusion criteria were: 1) Stage II limb osteosarcoma in patient younger than 40 years of age, 2) at least 20 patients treated by the same chemotherapy regimen, 3) multidrug chemotherapy including HDMTX (≥ 7.5 g/mL per course), 4) chemotherapy treatments with the dose and schedule clearly specified for good and bad responders, and 5) clear quantification of 5 years DFS of patient in each treatment.

Statistical analysis: To identify the most plausible hypothesis we used a linear multivariate analysis according to the model: $DFS(\%) = \sum A (D.I. \text{ drug } A) + \sum d (\text{dose drug } A) + \sum x (\text{response}) + \sum Y (\text{other factors}) + Z$.

Response was rated +1 for good; 0 for unknown, -1 for bad.

This model permits to determine the independent weight of each factor on DFS. It allows to compare adjuvant and neoadjuvant protocols. It measures the relative importance of response and of eventual switching of drugs for good and bad responders.

Results: 37 protocols including 2,471 patients fulfilled our including criteria. The average length of treatment was 39 (19–72) weeks, the average dose of methotrexate: 115 (32–240) g/m², doxo.: 384 (0–600) mg/m², platinum: 309 (0–720) mg/m² and the average DFS: 59 (24–95)%.

In this data base, the only independent significant factor was the response ($p < 0.001$) and the dose intensity of methotrexate ($p < 0.0001$). The best fitting model for DFS was:

$$DFS: 40\% + 6.6 (DI \text{ MTX}) + 6.5 (\text{response})$$

A good response gives an independent increase of 6.5% on DFS and a bad response a loss of 6.5%. Comparatively, an increase of 2 g/m²/week of methotrexate gives an independent increase of 13%. Influence of doxorubicine and platinum were not significant.

Conclusion: The prognostic value of dose intensity of methotrexate is independent of response and weights more than response on DFS. Increasing DI of methotrexate gives more gain in DFS than increasing the rate of good responders alone.

81. Forequarter amputation for high grade malignant tumours of the shoulder girdle

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The purpose of this study was to assess the role of forequarter amputation in the light of recent success of limb salvage surgeries for musculoskeletal tumours. We reviewed 20 forequarter amputations performed for high grade malignant tumours around the shoulder girdle (grade IIB–III) from 1979–1994, classifying them as palliative or curative according to the resection margins and/or the presence of disseminated disease at the time of the surgery.

There were 5 palliative and 15 curative procedures. 2 patients died of unrelated causes—septicaemia and suicide. 8 patients died in the first 2 years due to disease, 4 of whom had had a palliative operation. 4 patients died between 2 and 5 years, 1 following a palliative operation. 5 patients are alive, and average of 89 months from surgery, 4 of whom are disease free. The median survival after palliative amputation was 21 months and the 5-year survival rate for curative cases was 30%. Overall, 5-year survival (palliative and curative cases) was 21%. None of the patients use an artificial prosthesis.

We conclude that this operation, although disfiguring, still has a useful role to play in the management of high grade malignant tumours of the upper limb.

82. Impact of surgery and length of preoperative chemotherapy on outcome of Ewing's sarcoma—a monocentric study

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With the improvement of the outcome of patients with Ewing's sarcoma, local recurrence following radiotherapy have become a major concern advocating the wider use of surgery. Nevertheless, many questions remain open. Which resection? Which time for surgery and for postoperative chemotherapy? What is the best chemotherapy induction?

Patients and methods: From 1979–1995, we have seen 110 patients with Ewing's sarcoma who were operated on by our surgeon. Locations were ilium (24), spine (10), rib (7), femur (30), tibial (15), fibula (6), humerus (6), and other (10). Metastases were present at the initial evaluation in 19 cases. 24 patients were seen for local relapse. Tumoral volume was > 100 mL in 54 cases.

The induction chemotherapy varied; 1979–1984 it was vincristine, adriamycin–cyclophosphamide–actinomycin 3 months, 1982–1985 cyclophosphamide, tetrahydropyranil–adriamycin 3 months, 1985–1993 cyclophosphamide–tet-

rahydropyranil–adriamycin 6 weeks. We added ifosfamide and cisplatin from 1985 in the postoperative phase.

Surgery was tumoral reduction in 17, en bloc resection in 93 (61 extratumoral, 32 contaminated). Radiotherapy was administered in 61.

Results: Surgery was easier and DFS higher after short induction chemotherapy (<2 months), compared to long preoperative phase including radiotherapy. 9 local relapses were seen: 7 after contaminated or incomplete resection in spite of radiotherapy and 2 after en bloc extratumoral resection. Surgery is not able to salvage patients with local relapses after radiotherapy and appears to be only palliative in such cases. Perioperative chemotherapy is feasible in the 24 hours following surgery. To avoid wound healing problems, ifosfamide 6 g/m² is better tolerated than Doxo containing regimen.

Conclusion: Local control of the primary tumor is better obtained by en bloc extratumoral resection than after radiotherapy. Contaminated or incomplete resection must be avoided. The easiest way to permit extratumoral resection is a short Hayes's induction. Analyses of effect of local surgical control must separate clearly extratumoral or contaminated surgery, to avoid wrong conclusions on the role of surgery in Ewing's sarcoma.

83. Experience of treatment of dedifferentiated chondrosarcoma

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This study is a retrospective review of the results of treatment of dedifferentiated chondrosarcoma using limb-salvage surgery and adjuvant chemotherapy.

Material: 22 patient with dedifferentiated chondrosarcoma were identified in 15 men and 7 women, 7% of all chondrosarcomas. Mean age was 55 years. 45% of these tumours occurred in the femur. An accurate preoperative diagnosis was obtained in 8 patients. Treatment was amputation in 4 cases, limb-salvage with endoprosthesis replacement (EPR) in 11 and local excisions in 3. Margins were wide or radical in 8, marginal in 3 and intralesional in 7. 11 patients received chemotherapy.

Results: 32% were alive at 1 year, all under 60 years old. Improved survival was seen in women, younger patients and patients in whom the tumour had been diagnosed preoperatively. In contrast, if preoperative diagnosis was not precise the mean survival was 8% at 1 year. Mean survival after amputation was 32.5 weeks, after EPR 104 weeks and recurrence occurred after 54% of EPRs and 50% of amputations, but never after radical amputation. Survival after surgery without chemotherapy was 29 weeks. With chemotherapy, 67% of patients survived 37 weeks. Age differences may account for this.

Conclusion: A high index of suspicion, accurate preoperative diagnosis and wide excision margins are shown to be important factors in the prognosis of dedifferentiated chondrosarcoma. A beneficial response to chemotherapy can not be ruled out.