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EMSOS study—epithelioid sarcoma

M Salzer-Kuntschik, Ö Berlin, A v Hochstetter, G Contesso, T A Alvegård, A Lecesne

Vienna Bone Tumor Registry, Austria, the Scandinavian Sarcoma Group, Lund, Sweden, University of Switzerland, Zurich, and Institut Gustave Roussy, Villejuif, France.

I. Pathology

47 cases of epithelioid sarcoma (ES) from France, Scandinavia, Switzerland and Austria were submitted for retrospective analysis. There were 26 male and 21 female patients, ranging in age from 10 to 67 years at the time of first histologic diagnosis, with a mean in the 3rd decade. Sites of predilection were the upper extremity (32 cases), below the elbow in most cases; lower extremity (11); shoulder (2); gluteal region (2). 5 ES occurred primarily as clinical multiple lesions. Tumor size varied between 0.5 and 12 cm. ES in superficial site mostly did not exceed more than 3.5 cm, whereas the diameters of deep seated ES usually were more than 3.5 cm. 5 patients had multiple lesions. The diagnosis was based on histologic features and confirmed by immunohistochemistry, including positive reactions with antibodies to cytokeratin, EMA, vimentin; negative reactions with antibodies to HMB45 and endothelial markers. The histologic types were: predominant (pd) epithelioid 25/47, 2 of them presented as the angiosarcoma like variant, pd spindle-cell 7/47, and mixed 15/47. The mitotic rate varied between 0 and more than 20 mitotic figures per 10 hpf, mostly it was below 10. Most ES had infiltrative margins. According to the French system of grading 21/34 ES were G II, 13/34 G III. By a different grading system used for 11 of the Swiss cases, there were 4 G I, 4 G II and 3 G III. In a grading trial with a 4 grade scale on the Austrian and Scandinavian cases 5/25 ES were G II, 8/25 G III, 12/25 G IV. The initial histologic diagnosis is known in 35 cases and was correct in 12 only; 10 of the 35 ES were evaluated as benign, 13 as various types of sarcoma. This delay in establishing the correct histologic diagnosis is certainly a major limiting factor in determining the clinical outcome.

II. Clinical and prognostic features

45 patients had surgical treatment; 39 local excision and 6 amputation as the first surgical procedure. The surgical margins were inadequate (intralesional or marginal) in 33 primary procedures, while 12 were adequate (wide or radical). An additional 10 patients had ablative surgery due to inadequate

margins or later local recurrences. Neither radiotherapy (6), nor chemotherapy (9) have been used extensively in the treatment of these epithelioid sarcomas.

At the time of preliminary follow-up 21 patients had local recurrences; 18 had surgical treatment of which 10 were inadequate, and 8 adequate. An average of 2 operations (excluding surgery for the primary tumor) were performed among the patients with local recurrence. Of 42 patients with reliable but varying follow-up, 14 had no evidence of disease, 7 were disease-free after treatment for local recurrence and 7 were survivors with local recurrence or distant metastases. 14 patients had a tumor-related death. Vascular and lymphatic dissemination dominated.

The impact of molecular pathology in diagnosis of sarcomas

B Dockhorn-Dworniczak, K-L Schäfer, S Biasius, W Winkelmann¹, W Böcker, H Jürgens²

Gerhard-Domagk-Institute of Pathology, Depts. of ¹Orthopedic Surgery and ²Pediatric Hematology and Oncology, Westfälische-Wilhelms-University, Münster, Germany

We analyzed 96 pediatric solid tumors comprising 40 Ewing's tumors (ET) 20 rhabdomyosarcomas (RMS), 20 osteosarcomas (OS), 10 neuroblastomas (NB), 2 synovial sarcoma, 2 esthesioneuroblastoma, 1 desmoplastic small round cell tumor (DSRCT) and 1 extraskelatal myxoid chondrosarcoma for the occurrence of the major recurrent translocations (11;22) (q24;q12), (21;22) (q22;q12), (11;22) (p13;q12), (9;22) (q22;q12), (2;13) (q35;q14), (1;13) (p36;q14), and (X;18) (p11;q11).

Methods: Frozen tissue material were analyzed by Reverse Transcription followed by PCR and nested PCR-(RT-PCR). Specificity of obtained PCR products were confirmed by non-isotopic Southern-Blot analysis with gene specific probes and/or automated direct sequence analysis.

Results: 37 ETs have been shown to carry either a 11;22 or 21;22 translocation by identification of chimeric EWS/FLI-1 or EWS/ERG gene fusion transcripts respectively. In 1 OS with the morphology of a small cell osteosarcoma a EWS/FLI-1 fusion product was detected. 3 ETs were lacking EWS/FLI-1 or EWS/ERG fusion products. However, these tumors were shown on review to have unusual features for ETs. All of non-ETs were negative for 11;22 or 21;22 trans-

locations. 4/20 RMS were initially diagnosed as alveolar RMS. In these 4 and further 3 RMS a 2;13 translocation exhibiting chimeric PAX3/FKH fusion transcripts or a 1;13 translocation with PAX7/FKH chimeric gene products were found. The X;18 translocation was detected in both synovial sarcomas; 11;22 translocation causing a EWS/WT1 gene fusion product was found in the DSRCT; a 9;22 translocation could be shown in an extraskeletal myxoid chondrosarcoma. All Nbs and the two esthesioneuroblastomas were negative.

Conclusions: Our results support the concept that the major recurrent translocations are histogenetic specific for a subset of a of sarcomas. Their detection increases the diagnostic precision and allocate individual cases to the appropriate groups of sarcomas.

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Oncogene alterations in bone tumors

MS Benassi, MR Sollazzo, G Gamberi, P Ragazzini,
L Molendini, M Merli, P Picci

Oncology Lab., Orthopedic Rizzoli Institute, Bologna, Italy

C-myc and c-fos proto-oncogenes code nuclear proteins which appear implicated in various biological functions such as cell differentiation and proliferation. The overexpression of c-myc detected in a variety of sarcomas was associated with a poor prognosis.

Materials and methods: The prognostic significance of c-myc and c-fos expression was analyzed with methods of molecular biology and immunohistochemistry. The series comprised human bone tumor tissues of localized osteosarcoma (LOS-16), metastatic osteosarcoma (MOS-13) and giant cell tumor (GCT-25) of which 12 developed metastasis.

Results: In most OSs and metastatic GCTs a significant and uniform expression of c-myc, at the protein and mRNA level, was found. However, in 5 cases the protein was detected in absence of corresponding mRNA. In GCT from disease-free patients the intensity of labelling was less significant and the staining heterogeneous. RT-PCR analysis demonstrated an overexpression of c-myc and c-fos respectively in 46% and 38% of MOS compared to 6% and 13% of LOS. Concerning GCT, both oncogenes were overexpressed only in patients who developed metastasis.

Conclusions: These findings suggest that c-myc and c-fos alterations occur more frequently in poor prognosis patients candidates for more aggressive therapies and play an important role in the induction and progression of bone tumors.

A new p53 germline mutation in a Li-Fraumeni family

L Sangiorgi^{1,3}, M Weintraub², KG Bhatia², P Picci³,
LJ Helman¹

¹Molecular Oncology Section and ²Lymphoma Biology Section, Pediatric Branch, NCI, NIH, Bethesda, MD and

³Lab. of Oncologic Research, Rizzoli Orthopedic Institute, Bologna, Italy

Germline mutations of the p53 gene have been described in the Li-Fraumeni Cancer Family Syndrome and occur in patients with osteosarcoma, particularly those with a history of a metachronous cancer or a family history of cancer. We investigated tumor samples from 2 sisters, affected by osteosarcoma of the extremities, in a phenotypic Li-Fraumeni family (mother died of breast carcinoma at the age of 35, brother died of leukemia at the age of 3). One sister presented with a bilateral osteosarcoma at the age of 5 and ultimately died 6 years later while the second presented with a very aggressive pelvic tumor at the age of 14 and died 2 years later, despite aggressive chemotherapy and surgery in both cases. PCR based Single Strand Conformation Polymorphism (SSCP) for exons 4 through 11 was used to screen DNA tumor samples for p53 mutations. The analysis revealed a pattern consistent with the presence of a homozygous mutation in exon 6 of both of the samples. DNA sequence analysis confirmed the presence of a p53 mutation, a transversion from adenine to cytosine at codon 220. This mutation results in an amino acid change, from tyrosine to serine. Usually p53 mutations in Li-Fraumeni families occur in exons 7 and 8, in codons 245, 248, 273 and 282 or less frequently in codons 133, 175 and 193. Six previous mutations have been described in exon 6 and none involved codon 220. Studies to evaluate the presence of this mutation in the other family members are planned.

Overexpression of p53 protein and its prognostic significance in Ewing's sarcoma of bone

SR Carter, A Abudu, DC Mangham, GM Reynolds,
P Pynsent, RM Tillman, RJ Grimer

Royal Orthopaedic Hospital Oncology Service, Birmingham, United Kingdom

p53 gene mutation is the most common genetic abnormality associated with malignancy and results in over-expression of the gene product which can be detected by histochemical methods. We used immunohistochemical methods to study mutations of the p53 gene in patients with Ewing's sarcoma to determine their significance in the diagnosis and prognosis of the disease.

Results: Biopsy tissues of 52 patients with Ewing's sarcoma were studied. The mean age was 17 years and the minimum follow-up was 30 months. Expression of p53 protein was demonstrated in 7 patients. There was no relationship

between expression of p53 and tumour stage, site, patients age and necrosis following chemotherapy ($p>0.5$). The 5-year relapse-free survival and overall survival in patients without metastases at diagnosis were 66% and 71% respectively in p53 protein negative patients compared to 20% relapse-free and overall survival in those with p53 protein expression ($p=0.01$). The poorer prognosis in p53 protein positive patients was independent of site, local treatment or necrosis of the tumours ($p=0.02$).

Conclusion: Expression of p53 protein is an independent poor prognostic factor in Ewing's sarcoma of bone.

Neuroglial markers in relation to EWS gene fusion type in MIC2/CD99-positive tumors of the Ewing family

G Amann¹, M Salzer-Kuntschik¹, A Zoubek², R Windhager³, H Kovar²

Depts. of ¹Clinical Pathology, ³Orthopedic Surgery, Univ. of Vienna, and ²CCRI, St. Anna Children's Hospital, Vienna, Austria

MIC2/CD99 positive small blue round cell tumors, referred to as the Ewing family of tumors (ET), are characterized by EWS gene rearrangements. A division into peripheral primitive neuroectodermal tumours and Ewing's sarcoma is still a matter of debate. We investigated 37 ET for the presence of neuroglial markers (pNSE, mNSE, S-100, chromogranin A, synaptophysin, Leu-7, GFAP and neurofilament) and the type of EWS chimeric transcripts expressed. Positivity with pNSE was found in 14 but with mNSE only in 8 tumors. 3 cases showed a positive reaction with the Leu-7 marker. 8 tumors were positive for S-100 protein and 2 for synaptophysin. In one tumor reactivity with an antibody against neurofilament was focally present. No positive reaction could be detected using chromogranin A or GFAP antibodies. Excluding pNSE, 23 tumors showed no positivity for any of the neuroglial markers we used. Reactivity with one neural marker was detected in 10 and with 2 or more in only 4 tumors. In 25 tumors fusion between EWS exon 7 and FLI-1 exon 6 (type I) and in 9 tumors between EWS exon 7 and FLI-1 exon 5 (type II) were detected. Rare chimeric transcripts were present in 3 tumors. Among cases with 2 or more neuroglial markers 3/4 tumors showed other than type I chimeric transcripts. Our results indicate that when pNSE is replaced by mNSE only very few tumors display reactivity with more than one neuroglial marker. Since in this small group type I fusion transcripts were underrepresented compared to all others, further comparative immunohistochemical and molecular investigation is warranted to define the biological significance of these preliminary findings.

Imaging low grade osteosarcoma—report of 7 cases

D Vanel, G Missenard, J M Guinebretiere, A Le Cesne

Institut Gustave-Roussy, Villejuif, France

Low grade osteosarcoma is a rare malignant primary bone tumor. Histological diagnosis is usually difficult and the lesion is often initially considered as benign. The radiological pattern of seven cases is presented, with emphasis on the discrete signs suggesting aggressiveness.

Materials and methods: All 7 cases had plain films, CT and histological correlation. 3 had an MRI.

Results: All tumors involved long bones. There were 3 women and 4 men, aged from 5 to 58 years. On plain films 4 lesions were very well limited, suggesting benign tumors and 3 were sclerotic and irregular. CT was the diagnostic key revealing at least one aggressive sign in each case; limited perpendicular bone formation ($n=4$), cortical lysis ($n=4$), irregular sclerosis ($n=3$). Soft tissue involvement was absent ($n=4$) or very limited ($n=3$) and only marked in one case, but after biopsy. MRI was less useful than CT, especially for periosteal reactions. 3 histological diagnoses were modified after radiological confrontation.

Conclusion: Even a limited aggressive radiological sign in an apparently non aggressive lesion must suggest low grade osteosarcoma. CT is the most reliable diagnostic technique.

Giant cell tumor of bone—post-surgical detection of recurrent or residual tumor with fast dynamic contrast-enhanced MRI

HJ van der Woude, KL Verstraete, JL Bloem, PCW Hogendoorn, AHM Taminiau

Depts. of Diagnostic Radiology, Pathology and Orthopedics, Leiden University Hospital, Leiden, The Netherlands

We assessed the value of fast dynamic contrast-enhanced MRI in the pre- and postoperative evaluation of giant cell tumor (GCT).

Materials and methods: Fast dynamic contrast-enhanced sequences (temporal resolution, 1–3 sec) were performed in 20 patients with histologically proved GCT at diagnosis and/or during follow-up. Subtraction images were made and time-signal intensity curves of tumor relative to artery and reference tissues were obtained.

Results: All patients with primary GCT showed early and rapidly progressive enhancement (<5 sec after arterial enhancement), usually with early washout, consistent with highly vascularized and cellular tumor with scarce intercellular matrix. An identical enhancement pattern was seen in all 8 recurrences. Late and slowly progressive wash-in without early washout of contrast medium was consistent with postoperative reactive changes and progressive incorporation of bone grafts, in absence of residual tumor.

Conclusion: The characteristic enhancement curve assessed with dynamic MR of primary GCT is also a typical feature in recurrent tumor and allows differentiation from reactive tissue postoperatively. In this respect, it is also useful to assess the incorporation of bone grafts.

Fast dynamic contrast-enhanced subtraction MRI allows differentiation between benign and low-grade malignant cartilaginous tumors

AHM Taminiau, HJA Geirnaerd, JL Blaem, KJ Van der Woude

Depts. of Diagnostic Radiology, Pathology and Orthopedics, Leiden University Hospital, Leiden The Netherlands

Purpose: To differentiate between benign and low-grade malignant cartilaginous tumors with fast dynamic contrast-enhanced subtraction MRI.

Materials and methods: Fast dynamic contrast-enhanced subtraction MRI's with temporal resolution of 0.9 to 3 seconds were obtained in 7 enchondromas, 10 osteochondromas and 14 chondrosarcomas. Start and pattern of enhancing areas were correlated with histology of surgical specimen.

Results: Early (<10 sec after arterial enhancement) septal and nodular enhancement was seen in 12 chondrosarcomas and delayed enhancement was seen in 2. 8 showed rapid progression of enhancement, 6 gradual. A rapidly progressing early enhancement was only seen in 1 osteochondroma of a 4 year old boy. In 2 osteochondromas in patients with unfused growth plates, a rapid onset with gradual progressive curve was seen. In 2 others with fused growth plates a delayed enhancement with gradual progressive curve was seen. Only 2 enchondromas showed dynamic enhancement, both delayed and in a gradual pattern.

Conclusion: Early onset of usually rapidly progressive enhancement is seen in low-grade chondrosarcomas and in osteochondromas of patients with unfused growth plates (sensitivity 100%, specificity 94%).

Unusual MRI finding in follow-up of synovial sarcoma

M Üzel, K Kanberoglu, Ö Aydingöz, S Dervisoglu, M Hiz

Cerrahpasa Faculty of Medicine, Depts. of Orthopedics, Radiology and Pathology, Istanbul, Turkey

MR imaging is established in the follow-up of soft tissue tumour recurrence. We question the reliability of evaluation criteria based on the Gadolinium-DTPA enhancement of local recurrences because of discordance between MRI and histopathological finding in some cases.

Patients and method: 21 patients who had undergone resections for synovial sarcoma between 1990 and 1996 were examined for local recurrences by MRI.

Results: 6 patients with previous marginal resections were evaluated to have tumour recurrence by MRI imaging. 5 patients had reresection of the previous operation site including the recurrent mass with wide margins. CT-guided biopsy was performed in the last patient. Extensive histopathological cross sections revealed no recurrence in 4 of these patients. Instead, fibrosis, muscle degeneration and muscle hyperplasia were found.

Conclusion: Gadolinium-DTPA enhancing masses near the old operation site of marginally resected synovial sarcomas indicates local recurrence. Contrast enhancing masses, which appear after a wide excision, might be the result of other causes rather than local recurrence. CT-guided biopsy could be considered in such equivocal cases.

3-D computer tomography for planning operative treatment in bone tumors

H R Duerr, A Lienemann, F-W Hagen, H J Refior

University of Munich, Dept. of Orthopedics, Klinikum Grosshadern, München, Germany

With adjuvant therapy in malignant bone tumors more often limb and function-preserving resection is possible. For optimizing the operative planning we have used 3-D CT surface reconstruction since 1990.

Patients and methods: 3-D reconstruction was performed in 10 patients because of pelvic defects (6 malignant tumors and 4 postendoprothetic defects), in 4 primary sarcomas of the distal femur, the distal ulna, and the scapula and different benign tumors of proximal humerus and scapula. An individual pelvic reconstruction system was implanted in 10 cases. In addition to the 3-D CD, a simultaneous angiography with 3-D reconstruction was performed in 3 cases.

Results: 3-D computer tomography does not only allow an anatomic reconstruction of pelvic and hip geometry but also visualizes the tumor volume and position especially with simultaneous angiography. With pelvic reconstruction limb preserving was possible in all cases. Only 1 case, needed an amputation 38 months after primary surgery because of systemic progression of metastatic disease. Local tumor progression was not observed, 2 patients died of systemic disease.

Discussion: Especially osteoid-producing tumors could be visualized in any 3-D direction with relation to adjacent osseous structures and also vessels. In combination with MR for visualization of the soft tissue structures, tumor and resection levels could be precisely fixed. Furthermore it helps the patient to receive a workable demonstration of the operative procedure.

Influence of intraoperative brachytherapy on surgery of Ewing's sarcoma

M Hein¹, T Ozaki¹, R Rödl¹, A Hillmann¹, W Winkelmann¹, FJ Prott², N Willich²

Depts. of ¹Orthopedics, and ²Radiotherapy, University of Münster, Germany

We compared the results of 20 patients who received brachytherapy to those of 42 patients who didn't get brachytherapy.

Results: Local relapse developed in 1 of 20 patients who received brachytherapy and in 1 of 42 patients without brachytherapy. The average operation time was longer in 20 cases with brachytherapy than in 42 cases without brachytherapy (7.9 versus 4.3 hours). After the brachytherapy time was excluded from surgery time, the average time was significantly longer in patients with brachytherapy than in patients without brachytherapy (5.6 versus 4.3 hours). The average blood loss in both groups was not different. The surgical complication rate in patients between with and without brachytherapy was not different.

Conclusion: We conclude that in case of the surgical margin being close to the tumor, brachytherapy is of value.

Accelerated irradiation (A-RT) for osteosarcoma

F Lombardi, G Cefalo, F Fossati Bellani, MC Gianni, R Luksch, S Mapelli¹, M Massimino, P Navarria, M Oliva¹, L Gandola

Istituto Nazionale Tumori and ¹Istituto Ortopedico G. Pini, Milano, Italy

We evaluated the efficacy of A-RT in controlling bone lesions from osteosarcoma (OS).

Patients and methods: From 1984 to 1995, 44 pts (age 5-40 yrs) with OS were irradiated to the primary tumor site or to skeletal metastases with an accelerated fractionation modality: 36 Gy divided in 6 frts of 6 Gy, 3 frts/wk (39 pts), or 48 Gy divided in 3 Gy bi-daily frts, 5 frts/wk (5 pts). 18 pts (Group I) were irradiated for palliation of progressive OS to 26 sites (7 primary tumor, 19 skeletal metastases). 26 pts were irradiated to the primary tumor site, in combination with CT, as an alternative to immediate surgery in presence of synchronous metastases (10 pts Group II), or to improve response to CT in order to avoid amputation (5 pts Group III), or as complementary treatment after intralesional surgery (11 pts Group IV).

Results: In the 18 Group I pts, a clinical and/or radiological response was achieved in 23/26 irradiated sites for a median of 7 mos, corresponding to median time of survival. Except for 3 non responders, in no case tumor progression occurred in the irradiated bone. In the 10 group II pts, only 1 local relapse 67 mos from RT occurred before surgery (2 pts) or death due to progressive disease elsewhere (7 pts). In the 5 Group III pts surgery was performed 3 to 17 mos from RT and histologic evaluation showed 100% OS necrosis in all. A limb sparing surgery was feasible in only 3/5 pts but all had

to be later amputated because of infective complications. In the 11 Group IV pts only 1 local relapse occurred 6 mos after RT, 5 pts remained progression free after a median of 30 mos, 5 pts died because of metastatic spread after a median of 24 mos.

Conclusion: A-RT was highly effective in providing durable response in 30/33 pts with evaluable OS. Furthermore, only in 2/30 responders OS relapsed in the irradiated site before surgery or death. Due to high normal tissue morbidity, A-RT is not recommended for primary OS candidate to limb sparing surgery.

Errors in diagnosing musculoskeletal tumors

R Grimer, S Carter, R Sneath

The Royal Orthopaedic Hospital Oncology, Service, Birmingham, U.K.

In May 1993 errors in diagnosing musculoskeletal tumours were identified at The Birmingham Bone Tumour Service. As a result all 1996 cases treated over the previous 8 years were submitted to peer review.

Results: There were 87 errors in diagnosis (4.4%) of which 33 were not clinically significant. In 54 cases (2.7%) there was some detriment to the patient. In 32 cases this was "minor" (e.g. a second unnecessary biopsy), in 18 cases "intermediate" (e.g. one or more cycles of unnecessary chemotherapy (7 cases), radiotherapy (7 cases) or surgery). In 4 cases there was a major detriment where there had been loss of life or limb as a result of misdiagnosis. The error rate was found to have increased over the years. The overall error rate compares favorably with published figures.

Conclusion: Diagnosing musculoskeletal tumours is difficult and even in specialist centres errors can occur. Pathologists should not work in isolation and the whole clinical team must be confident to share a diagnosis ideally following a multidisciplinary clinicopathological conference. There should be a low threshold for seeking a further opinion.

Reactive zone, does it exist?

G A Baflıdemir, D Sabah, R Arkun, G Yüçetürk, M Hekimgil, A Memiş, Z Burak, Z Özcan, F Öztop

Medical Faculty of Ege University, Musculo-Skeletal Oncology Council, Izmir, Turkey

We have observed that Enneking's system for surgical grading, staging and classification or surgical procedures was inadequate for estimating the prognosis and for planning the surgery. In this study we examined the tumor borders for "reactive zone", capsules or pseudocapsules and their reflections on imaging techniques.

36 cases with musculoskeletal lesions including 15 osteosarcomas, 3 chondrosarcomas, 2 dedifferentiated chond-

rosarcomas, 2 mesenchymal chondrosarcomas, 2 liposarcomas, 3 malignant fibrous histiocytomas, one rhabdomyosarcoma, 2 synovial sarcoma, 2 Ewing's sarcomas, 1 adenocarcinoma metastasis, 1 PNET, 2 benign aggressive lesions were studied. The resection materials of all cases were examined with the conventional mapping method and multiple samples of tumor borders were studied. Histopathologic findings were correlated with results of MRI and bone scintigraphy.

Encapsulation was common in low grade lesions but in high grade lesions it was scarce and mostly restricted to the natural barriers, mainly dense fascia. A reactive zone surrounding the whole tumor mass was identified in 3 high grade sarcomas. MRI was superior to bone scan in distinguishing tumor borders, capsules and reactive zones.

In conclusion, we believe that reactive zone is exceptional rather than a rule in malignant tumors. As a result our study group has decided to change the classification of surgical procedures to "intralesional", "wide resection with tumor-free margins" and "wide resection with positive margins" instead of intracapsular, marginal, wide and radical.

Function after limb saving surgery and amputation of malignant bone tumors—evaluation of three classification systems

H Ervasti, A Kivioja, E Karaharju

Dept. of Orthopedics and Traumatology, Helsinki University Central Hospital, Helsinki, Finland

A standardized system of reporting the functional result in various surgical alternatives has been modified through years and the quite complicate initial system of Enneking (1987 and 1989) has been simplified to more practical version (Enneking 1993) adopted by the Musculoskeletal Tumor Society (MSTS). The Scandinavian Sarcoma Group (SSG) has revised the system further: Post Operative Functional Assessment (POFA, 1993). In this study we analyzed the outcome by these versions of functional analysis.

Patients and methods: 62 patients treated between 1974 and 1995 because of primary malignant bone tumor were included. 25 were amputees and 37 were limb salvages. The follow up of amputees was 8,6 years and that of limb salvages was 4.1 years.

The 7 parameters of the initial Enneking analysis were motion, pain, stability, deformity, strength, functional activities and emotional acceptance. In advanced Enneking analysis there were factors pertinent to the patient as a whole (pin, functional activity and emotional acceptance) and factors specific either to upper extremity (positioning of the hand, manual dexterity and lifting ability) or the lower limb (use of external supports, walking ability and gait). The POFA analysis is similar but without scoring the emotional acceptance. A numerical score and percent rating was calculated (Total score: Maximum score= % Rating). The descriptive terms of the initial system were converted to numerical ones (excellent= 5, good= 3, fair= 1, poor= 0).

Results: The percent rating was:

Type of analysis	I. Initial Enneking	II. New Enneking	III. POFA
Ablative surgery	57 %	64 %	63 %
Limb salvage	61 %	62 %	63 %

Sports activities were multiple and variable after ablative surgery, when the external prosthesis could even be thrown away during physical activity (squash, slalom). Patients who had limb saving surgery had more pain than amputees. The emotional acceptance of amputation was better than that of limb saving surgery. The amputees managed functionally worse, when motion, strength, stability and deformity were scored according to old Enneking system, and the difference was clearly significant comparing with modern Enneking system and the POFA.

Conclusion: In this study the amputees managed themselves statistically worse when motion, stability, deformity and strength were measured, but they had less pain and their emotional acceptance was better than that of limb salvages. The functional result of both groups was equal using POFA and it was very similar using any analysis.

Palliative major amputation and quality of life in musculoskeletal cancer patients

O Merimsky, Y Kollender, S Chaichik and I Meller

Dept. of Oncology, and The National Unit of Orthopedic Oncology, The TelAviv Sourasky Medical Center, Tel-Aviv, Israel

Limb sparing surgery has replaced amputation for limb sarcomas. Recurrent or persistent disease constitute a major problem. Local symptoms as agonizing pain, fractures, tumor fungation, inability to walk and to maintain the daily activities, further impair the patient's quality of life. In this clinical setup palliative amputation of the limb should be considered.

Patients: 18 patients with soft-tissue or bone sarcomas underwent palliative major amputation. Hip disarticulation was performed in 10, knee disarticulation or below-knee amputation in 2, shoulder disarticulation in 1, forequarter amputation in 2, and hemipelvectomy in 3 patients. The length of hospitalization was 5 to 7 days in cases of forequarter amputation, 10 to 14 days in cases of simple hemipelvectomy, and 3 to 6 weeks in cases of extended hemipelvectomy.

Results: Local control of the disease and pain, and improvement of the performance status were observed in 16 evaluable patients. The mobility was restored in 14 patients with lower limb surgery. The median survival following the procedure was 9 months. There was only one case of immediate postoperative death. Severe phantom pains were not reported by any of the patients.

Conclusion: Our data point to the fact that palliative amputation surgery is feasible, not associated with increased mortality, and is worth performing in low-performance status cancer patients with locally advanced disease. Local symptoms and signs were controlled, and quality of life was restored. In our opinion, pain alone does constitute an indication for palliative major amputation, especially if it is accompanied by pain-related limb dysfunction or low performance status.

Spinal tumor surgery—functional prognosis and treatment—a report of 127 new cases

H R Dürr, A Krödel, C Plessnar, H J Refior

Dept. of Orthopedics, Klinikum Grosshadern, University of Munich, München, Germany

Spinal tumors are mainly metastases. We analyzed which patients benefitted from spinal surgery.

Methods: Between 1980 and 1995, 127 patients were surgically treated for spinal tumors (76 men, mean 56 years; 51 women, mean 53 years). Evaluation of surviving, neurologic outcome (Frankel), mobility and quality of life (Karnofsky, Roser) was performed.

Results: 10% patients had a benign, 23% a primary malignant lesion of the spine and in 67% metastases. In 345 lesions a cervical localization was seen in 13%, a thoracic in 52% and a lumbar in 35%. In half of the cases a ventral or combined ventro-dorsal treatment was chosen, a stabilizing instrumentation was necessary in three quarters of remaining cases. From a preoperative Karnofsky-score of 42% the surviving patients reached 50% after 1 month and 61% after 1 year. Improvement in neurologic outcome (Frankel-Score) was seen especially for survivors of the first 6 months.

Discussion: Except for curative approaches for benign or certain malignant lesions the evaluation of palliative spinal surgery is rather difficult. In this study an improvement in life quality or neurologic outcome was only obvious for 75% of patients surviving at least 6 months. Despite gradual improve or clinical stabilization after acute surgical intervention for neurologic complications the extension of the procedure should be carefully matched to the overall prognosis.

Surgical treatment for metastatic epidural compression in the thoracic and lumbar spine

HCF Bauer

Oncology Service, Dept. of Orthopedics, Karolinska Hospital, S-171 76 Stockholm, Sweden

Patients and methods: 137 cancer patients with neurologic symptoms of epidural compression due to spinal metastases were operated 1990-95. There were 90 men and 47 women with a median age of 64 years. The most common primary tumors were cancer of the prostate in 37% and of the breast

in 17%. The spinal lesion was a solitary metastasis in 14% of the patients, 63% had multiple skeletal metastases and 23% had visceral or brain metastases as well. The epidural compression was thoracic in 72% and lumbar in 28%. Preoperative neurologic function assessed according to Frankel (A-E) showed that 47% were bedridden (A-C), 38% could walk with aid (D), and 13% were neurologically intact (E). A posterior decompression and stabilization was performed in 126 patients, 7 had posterior decompression alone, and 4 had anterior decompression and reconstruction of the vertebral body.

Results: There were 13% local wound complications (9% infections). The perioperative mortality rate (within 2 weeks of surgery) was 4%. The 6 months survival rate was 0.51 and 1 year 0.28. The neurologic function improved immediately postoperatively in 85 patients, was unchanged in 29 and worsened in 3. Altogether, 120 patients (88%) became walkers (Frankel D-E) during follow-up. 17 patients were reoperated; 7 for epidural compression at a new spinal level, and 10 for recurrence of compression or failure of stabilization.

Conclusion: Posterior decompression and stabilization restores neurologic function in cancer patients with epidural compression and is associated with a relatively low systemic morbidity.

A new technique for treatment of intraacetabular metastatic carcinomas in lieu of major arthroplasty reconstruction—composite polyethylene and bone cement reconstruction without THR

Y Kollender, I Meller, O Merimsky and MM Malawer

The National Unit of Orthopedic Oncology and The Department of Oncology Tel-Aviv Sourasky Medical Center, Israel and The Washington Cancer Institute at the WHC, Washington D.C., U.S.A.

Metastatic periacetabular tumors are difficult to treat and may require extensive surgery for reconstruction. The aim of treatment is palliative as a means of pain control and ambulation. The usual treatment for these patients is curettage of the tumor and total hip replacement with reconstruction of the acetabulum with bone cement and pins, or a saddle prosthesis. These procedures have significant blood loss, operative time, morbidity and prolonged rehabilitation. We have developed a new simpler and reliable technique of periacetabular reconstruction without THR for metastatic cancer.

Patients and methods: 8 patients with periacetabular metastatic carcinomas were treated between 1993 and 1995. Our method includes: Preoperative angiogram with embolization (not in all patients) followed by curettage of tumor mass and reconstruction of defect with silastic or a custom polyethylene block for the periacetabular roof and augmentation of the remaining defect with bone cement and pins or plates connected to the remaining ilium.

Average blood loss was 945 mL and the operative time 2-2.5 hrs. Good pain control was achieved in all patients. The patients ambulated 48-72 hrs post operatively. No intra

or perioperative mortality occurred and no infections recorded.

Discussion: This method is simpler compared to other described techniques and achieves the initial goals of pain control, early ambulation and with a major decrease of morbidity and mortality. We recommend this technique for most cases of metastatic periacetabular tumors resistant to irradiation therapy or as a combination with irradiation therapy especially in cases with a pending fracture.

Wide resection for bone metastases

HCF Bauer, O Brosjö, R Wedin

Oncology Service, Dept. of Orthopedics, Karolinska Hospital, S-171 76 Stockholm, Sweden

Surgical treatment for bone metastases is associated with a high risk of progressive tumor growth and implant failure. The risk of failure increases with the survival time. Resection and reconstruction is indicated in patients with a good prognosis for surviving at least one year.

Patients and treatment: This retrospective analysis includes 19 patients operated 1990–1995 for 20 metastases of the humerus (6) and the femur (14). The median age was 62 years and there were 11 men. The primary tumor was kidney in 10, breast in 4 and various others in 5. 10 patients had bone metastases at diagnosis, where as in 9 metastases appeared 4 (3–11) years after diagnosis of the primary tumor. 9 patients had a solitary and 4 numerous skeletal metastases and 6 had visceral metastases as well. 6 patients had been operated previously and were reoperated because local tumor progression.

The surgical margins were 4 intralesional, 6 marginal, and 10 wide. Reconstructions were custom endoprostheses in 14 cases and allografts in 6 (1 osteochondral and 5 intercalary). There were no perioperative deaths but 5 complications were recorded: 2 hip dislocation, 2 deep venous thrombosis, and 1 radial nerve palsy. 2 patients have been reoperated, both involving allograft reconstructions of the humerus. 1 of these patients had fracture dislocation of the humeral head of the allograft, the other had nonunion of an intercalary graft and plate loosening. The 1 and 2 year survival rates were 0.5 and 0.3, respectively. The reoperation rate for long-term survivors was approximately half of that of patients treated with stabilization of pathologic fracture without resection of the metastatic lesion.

Conclusions: Wide resection and reconstruction, either with endoprostheses or allografts, provides good function and decreases the risk of reoperation in long-term survivors. These patients can be identified by prognostic analysis based on type of primary tumor, extent of skeletal disease and presence of visceral metastases.

Resection-arthrodesis of the humeroscapular joint using autogenous fibular and iliac grafts—excellent results at 9–14-year follow-up

B Stener and B Gunterberg

Dept. of Orthopedics, Sahlgrenska University Hospital, Göteborg, Sweden

Method: After resection of the proximal humerus, the defect (8–14 cm) was substituted by a nonvascularized fibular graft and an iliac graft. The shaft of the fibular graft was inserted into the medullary canal of the humerus, and the articular cartilage of the fibula and the scapula was removed. The fibular head was fixed to the scapula with a steel wire. The iliac graft was interlocked between the humeral shaft and the coracoid process.

Results: In those 3 of our patients with the longest follow-up, the results according to the percent rating system (Enneking et al. 1993) were recorded. Patient 1—boy 15, chondrosarcoma; result after 14 years 93%—has successfully participated in the VASA cross-country ski competition (90 km). Patient 2—woman 21, giant-cell tumor; result after 13 years 97%—has born four children after the operation and is unrestricted in her activities. Patient 3—man 25, aneurysmal bone cyst; result after 9 years 93%—works full-time as an electrician. He enjoys carpentry and has rebuilt his house all by himself.

Reconstruction after resection of forearm-sarcoma

A Hillmann, T Ozaki, R Rödl, W Winkelmann

Dept. of Orthopedics, University of Münster, Germany

Surgical treatment of forearm-sarcomas is sometimes difficult because adequate soft tissue coverage is hard to obtain and the tumors often are close to the neurovascular bands.

Patients and methods: From 1990 to 1995, 12 patients with forearm sarcoma underwent surgical treatment in our hospital. Patients with Ewing's sarcoma, osteosarcoma, chondrosarcoma, or malignant fibrous histiocytoma (MFH) of the soft tissue are included. The median age was 32 (9–65) years. All patients with Ewing's sarcoma, osteosarcoma, or MFH received chemotherapy.

5 tumors were located in the distal radius, 2 in the diaphysis of the radius, 1 in the distal ulna, and 2 in the proximal ulna, and 1 in the soft tissue of the ulnar side and 1 in the soft tissue of the proximal ulna, and 1 in the soft tissue of the ulnar side and 1 in the soft tissue of the radial side of the proximal arm amputation.

Results: Of 10 patients with limb sparing surgery, 8 underwent autogenous fibula graft and 2 only resection of soft tissues including the epicondylus medialis of the humerus. Average length of the grafted fibula was 12 cm. 2 patients had pseudoarthroses. 1 patient had a minor skin problem and 2 ulnar or radial nerve palsy. Function seems to be satisfactory in most of patients.

Reconstruction of the extensor knee mechanism after proximal tibial resection and prosthetic replacement by using a part of the quadriceps muscle tendon

Y Kolender, J Bickels, R Oren, O Merimsky and I Meller

The National Unit of Orthopedic Oncology and Dept. of Oncology, Tel-Aviv Sourasky Medical Center, Israel

The primary attempt for reconstruction of the extensor mechanism includes transfer of the gastrocnemius muscle (which is done anyway for soft tissue coverage) and suturing it to the stump of the patellar tendon with augmentation by Dacron Tapes to the loop which is made in most prostheses.

This method has a high failure rate and almost half of the patients develop an extension lag of 30°. We propose a way of reconstruction of the extension mechanism by using the middle third of the quadriceps muscle tendon + part of the patellar surface and creating a "new" patellar tendon reinforced with "Gortex" implants.

Materials and methods: The procedure was performed on 7 patients, all of them were at least one year after the primary surgery and with extension lag of more than 30°. Age range was 17-23 years. After surgery the limb was in extension for 6 weeks and only then knee flexion was initiated.

Results: All patients gained their active extension again with 0°-20° extension lag. In all patients the flexion ability was not disturbed or changed compared to the pre-operative state. No complications were noted except one prolonged wound healing.

Conclusions: This method is a simple, uncomplicated and reliable way for reconstructing the extension mechanism after proximal tibial resection. We recommend to perform this procedure only if the primary reconstruction failed and at least 1 year after the primary resection.

Treatment of fractures of the tibia or femur after resection and reconstruction with the Howmedica Modular Resection System.

F Gherlinzoni, H Zmerly, D Donati

Istituto Ortopedico Rizzoli, Bologna, Italy

Among 450 patients treated from 1983 to 1995 at the Institute Ortopedico Rizzoli with proximal tibia or distal femur resection and reconstruction with the H.M.R.S., 15 traumatic fractures of the bone where the stem of the prosthesis was implanted were observed.

7 were fractures of the tibia and 8 of the femur. There were 10 men and 5 women ranging in age from 13 to 45 years. There were 12 osteosarcomas; the remaining 3 were MFH, Ewing and chondrosarcoma. All patients (except chondrosarcoma) were administered neoadjuvant chemotherapy. The fractures appeared from 2 to 66 months after resection. 7 patients were treated conservatively with plaster and the fractures healed after 60-80 days. 8 patients were treated with internal fixation and the fracture healed after

90-120 days. Internal fixation of fractures of the tibia or femur with a H.M.R.S. stem implanted is a safe procedure and with shorter healing time and a better function than conservative treatment.

Local failure after interdisciplinary treatment for localized high-grade central extremity osteosarcoma

S Bielack, B Kempf-Bielack, D Epler, K Winkler

for the Cooperative German-Austrian-Swiss Osteosarcoma Study Group COSS. Universitätskinderklinik Hamburg, Germany

An analysis of all 504 protocol patients from the prospective neoadjuvant multicenter trials COSS-80 through COSS-91 entered between 1980 and 1992 was performed in order to search for risk factors for local failure (LF) after seemingly complete surgery plus multiagent chemotherapy.

LF occurred in 24/504 osteosarcoma (OS) patients (5%). 23 of 24 cases developed within 3 years of surgery. Only one of 24 LF patients never had any evidence of systemic spread, while 7 developed metastases before, 10 with, and 6 after LF. Only one patient with LF is currently alive without and two are alive with disease, the remaining 21 died of progressive tumor.

The type of surgery (limb salvage 16/211=8% vs. ablative 8/293=3%) and the extent of histological response to preoperative chemotherapy (poor 15/185=8% vs. good 6/236=3%) influenced the risk to develop LF ($p < .01$). LF developed in 9/63 of cases when limb salvage was attempted despite poor response. Relative tumor size alone did not significantly predict local control ($p = .09$). Large tumor size, however, further increased the LF risk if poorly responding tumors were treated by limb salvage.

Conclusions: In the cooperative COS trials, LF was significantly influenced by both type of surgery and tumor response to primary chemotherapy. As local failure of OS ultimately leads to a fatal outcome in almost all patients, it must be avoided by extra careful surgery in cases of anticipated poor response. Revision surgery after failed limb salvage is not the way to go in OS.

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Revision of failed salvaged limb with prosthesis

M Hiz, Ö Aydingöz, F Erdogan, H Kesmezacar, M Üzel

Cerrahpasa Faculty of Medicine, Dept. of Orthopedics and Traumatology, Istanbul, Turkey

The salvaged limb with endoprosthesis may require revision due to complications such as soft tissue problems, loosening or fatigue fracture of the prosthesis, infection, limb length inequality and local recurrence. Indications and probability

of resalvage achieving the initial functional status are controversial.

Patients and methods: 46 patients (41 IIB and 5 IB tumors) were treated by wide excision and custom-made stainless steel prosthesis reconstruction between 1988 and 1996 with a mean follow up of 42 (6-67) months.

Results: 15 salvaged limbs were revised (skin breakdown and infection: 3, periprosthetic infection: 3, stem breakage: 4, local recurrence: 4, aseptic loosening: 1). 2 IIB recurrent osteosarcomas were attempted to be treated with 2nd line Chx. in patients who refused amputation first. Both progressed and amputation was performed. 2 IB recurrent lesions (1 chondrosarcoma, 1 parosteal osteosarcoma) could be resected with preservation of the prostheses. 3 periprosthetic late infections were treated by debridement and Gentamycin beads + systemic antibiotics. 2 healed but 1 patient required removal of the prosthesis and spacer application followed by a knee arthrodesis prosthesis. Infections due to inadequate soft tissue coverage required removal of the prostheses and temporary antibiotic loaded cement spacer application. These patients underwent free latissimus dorsi transfers. 1 infection persisted and hyperbaric oxygen treatment was begun. All prostheses failures due to stem breakage and aseptic loosening were revised without any problem. 1 patient with a pelvic prosthesis developed infection and secondary femoral aneurysm was converted to hemipelvec-tomy.

Conclusion: Salvage of a local recurrent IIB tumour is only by amputation. IA, B recurrences could be resected. Infection due to skin breakdown or insufficient soft tissue coverage is amenable to removal of prosthesis and antibiotic loaded cement spacer stabilization and subsequent free flap transfer only. Periprosthetic infection early or late could be treated by extensive surgical debridement and Gentamycin beads provided the soft tissue coverage is adequate by local or free muscle flaps. Secondary implantation of a prosthesis is possible subsequent to spacer application provided if the spacer has the initial prosthesis volume or shape to relieve the fibrosis shrinkage or with application of free vascularized flap. The functional outcome regarding all the revisions is inferior to the first achieved range of motion.

Treatment of infections with massive prostheses after limb salvage in 29 cases

G. Delepine¹, N. Delepine², S. Ishak², L. Benkhadra², V. Subovici², D. Goutallier¹, J.C. Desbois²

¹Hop. R. Debre, 48Bd Serrurier, 75019 Paris, and ²Hop. H. Mondor, 93000 Créteil, France

Patients: From 1983 to 1995, 246 patients with bone sarcomas had reconstruction with massive prostheses often combined with massive allograft. Follow up was minimum 6 months. 184 patients received chemotherapy and 45 radiotherapy. The mean follow-up is 5.5 years. 29 (3 initially treated elsewhere) deep infections led to one or more surgical procedures.

Methods: 3 patients were amputated in emergency because of septicemia during a deep aplasia. 26 patients were initially operated on to clean the prosthesis. Antibiotics were adapted to the germ isolated during the surgical procedure. When this method was ineffective, a second cleaning was performed with removal of the prosthesis and replacement with a new prosthesis in the same procedure. When infection remained after these procedures, removal of the prosthesis was performed with interposition of a cement spacer loaded with antibiotics. The new prosthesis was placed in a second procedure, when cutaneous and muscular problems were resolved.

Results: At the last control, 13 were amputated, 3 initially, 10 secondarily, following a mean of 6 ineffective procedures. 16 patients benefitted from conservation surgery but a new prosthesis could be implanted only in 13, following a mean of 4 surgical procedures, and with a result inferior to that obtained with the initial prosthesis.

Conclusion: Infection of massive prostheses leads to amputation in near 40% of the cases. Treatment must be preventive: obtaining a good coverage of the prosthesis using large musculocutaneous flaps, avoiding any radiotherapy, shortening the length and the deepness of aplasias (role of GCSF?) using prostheses able to limit reinterventions. When infections appear, the therapeutic approach depends on other treatments (chemotherapy etc) and of history of the patient. Factors of importance for success are early removal of the prosthesis, effective antibiotherapy, improvement of the muscular coverage, and use of prostheses without cement.

Fractures in allografts for malignant bone tumors

M San Julian, J Canadell

Dept. of Orthopedics, University of Navarra, Pamplona, Spain

We report our experience with fractured allografts.

Patients and methods: We reviewed 169 allografts used since 1986 in limb preserving operations for malignant bone tumors.

Results: There were 14 fractures in 12 patients at a mean time of 22 months from the operation. Most of them were in the metaphyseal area and were related to perforations of the allograft for stabilization with plates, muscular attachment, and so on. All of them occurred when the allograft was consolidated. Consolidation of the fracture after mean 5 months was achieved in 7 cases by osteosynthesis plus autologous bone grafting. In cases of threatening fracture the allograft was changed.

Conclusion: We recommend the use of an intramedullary device in order to avoid fractures, and the use of osteosynthesis and autologous bone grafting to achieve consolidation of the fractures.

Vascularized fibula as salvaging procedure in failed femoral allografts

Manfrini Marco¹, Capana Rodolfo², Ceruso Massimo², Gasbarrini Alessandro¹, Caldora Patrizio²

¹Istituto Ortopedico Rizzoli, Bologna, and ²C.T.O., Firenze, Italy

Between 1989 and 1994, 10 patients underwent a vascularized fibula autograft (VFA) as salvage procedure for a failed intercalary femoral allograft.

2 patients had had a previous reconstruction: Küntscher rod and cement and autogenous bone grafts. The allograft had been implanted as secondary procedure because of mechanical failure or local recurrence. The remaining 8 patients had the allograft reconstruction performed at the same time as the tumor resection.

In all allograft reconstructions, osteosynthesis had been achieved by an intramedullary locking nail, and 8 patients had received postoperative chemotherapy.

The allograft failed because of nonunion of the proximal (7), distal (2) or both (1) osteotomy lines. 3 patients also presented a mechanical failure with breakage of the rod in one case, and fracture of the allograft in two cases. Partial resorption of the allograft was observed in 6 cases.

VFA was performed after mean 23 months from the allograft reconstruction. In all but 1 patient, the fibula was transplanted as medial support to the failed allograft without any modification of the previous osteosynthesis. In the bipolar nonunion associated with rod breakage, the original implant was completely removed and a new diaphyseal allograft with a lateral long plate and a medial VFA bridging the graft was applied.

The vascular pedicle of the fibula was always anastomized to the terminal branches of the deep femoral artery and vein.

No postoperative complications were observed. Union of the VFA was achieved in all patients. One patient sustained a mechanical failure of the implant (at 30 months) treated by a new massive allograft and a new osteosynthesis. At a mean follow-up of 40 months from the VFA, all other patients reached a satisfactory function, walking without external support with full weight bearing.

Limb salvage for malignant tumors of the knee joint with large soft tissue involvement by wide resection, endoprosthetic/allograft replacement and free microvascular latissimus dorsi muscle transfer

G U Exner¹, K Schütz², J Middendorp

¹BALGRIST, Dept. of Orthopedics, and ²Dept. of Hand, Plastic and Reconstructive Surgery, University of Zürich, Switzerland

Because of the critical soft tissue anatomy below the knee joint proximal tibia reconstructions after bone tumor resec-

tions even without extraosseous soft tissue involvement raise technical problems with skin closure. The minimum required for adequate soft tissue coverage of the reconstruction usually is a medial gastrocnemius muscle pedicle flap. Tumors in this area with soft tissue involvement commonly are treated by amputation. Free vascularized muscle transposition however may allow for limb salvage in such cases and we wish to report our experience in 4 such patients.

Patients and methods: 4 patients (aged 17 to 60 years) with malignant tumors about the knee joint and significant soft tissue involvement needed en bloc resection of the knee joint, in two of them including the complete extensor apparatus (patella, patellar ligament, quadriceps tendon) to achieve wide margins. The reconstruction of the osseous and joint defects was performed either by endoprosthesis alone or the combination of an allograft and an endoprosthesis. The soft tissue defect was reconstructed by a free latissimus dorsi muscle transfer to provide a continuous vital extensor apparatus reconstruction and replacement of the skin defect.

Results: In all patients a functional reconstruction could be achieved and continues at a follow-up of presently 2–5 years.

Active tibial and femoral titanium growing prostheses in limb sparing salvage for children's bone sarcomas—10-years experience

N Delepine, G Delepine, JC Desbois

Hopital R. Debré, 48 Bd Serrurier, 75019 Paris, France

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 tried to use an expandable and adjustable prosthesis. We review here our 10 years experience with tibial and femoral prosthesis and our successive models, the last growing without open surgery.

Methods: Prostheses are produced in titanium, chosen for its better mechanical properties. The prosthesis is manufactured following the recommendations of the surgeon for each patient with individualized size. The prosthesis is done with three elements: one special growing part, one epiphyseal part, one tibial or femoral stem. The size of the epiphyseal part is small enough to be inserted from age 5 y and its smooth edges avoid any soft tissue damage. The lengthening of the prosthesis is performed when the discrepancy is ≥ 3 cm. The increase of the prosthesis has no limits, can be > 15 cm, even if the resection was inferior to 15 cm.

Patients: From 1984 to 1995 we used 27 growing prostheses for children aged 4.5 y to 13 y. 3 tibial growing prostheses, 3 superior femoral prostheses, 5 total femur replacements, 16 inferior femur prostheses. The patients had Ewing's sarcoma (6) or osteosarcomas (19).

Results: 5 patients died from the illness. 23 had lengthening of the prosthesis, mean 6.2 (2.4–12) cm, which improved function. Only 2 patients received a definitive prosthesis.

Following EMSOS criteria, functional results are rated: excellent or very good (15), fair (7), bad (5). 3 patients had an infection following the operation to increase the limb. 1 was amputated. 2 had a new reconstructive surgery.

Conclusion: The expandable prosthesis has provided an excellent alternative to amputation in young children. Nevertheless, the infection risk appended to multiple surgical procedures leads us to develop a new generation of growing prostheses which will not need open surgery for lengthening.

Complications after reconstruction surgery of pelvic sarcomas

A Hillmann, R Rödl, T Ozaki, W Winkelmann

Dept. of Orthopedics, University of Münster, Germany

Patients and methods: From 1990 to 1995, 61 patients with pelvic sarcoma underwent a pelvic resection in our hospital. 32 patients had Ewing's sarcomas, 23 chondrosarcomas, and 6 osteosarcomas. Tumors originating in the sacrum were excluded in this study. 30% of patients underwent iliac resection, 30% periacetabular resection, 30% both iliac and periacetabular or hemipelvic resection, and 10% anterior arch resection. Reconstruction was performed as follows; sacroiliac arthrodesis with allograft or autograft (fibula), acetabular reconstruction with total hip arthroplasties with allograft, prosthetic replacement of hemipelvis, and hip transposition. In several patients, skeletal reconstruction was not performed and only soft tissue reconstruction including joint capsule was done.

Results: Complications developed in over half of the patients. The complication rate after pelvic reconstruction is higher than that after reconstruction at other sites. Minor complications were as follows; skin necrosis, superficial infection, abscess, and hematoma. Nerve damage and vascular or visceral complications were also observed. Deep infections, implant fracture, and local tumor recurrence were severe complications which lead to reconstruction failures. Complications were commoner in patients reconstructed with allografts than in patients with other materials. Patients after prosthetic replacement of the pelvis or patients without skeletal reconstruction seem to have few complications.

Long-term follow-up of massive osteochondral allografts in limb salvage procedures for bone tumors

I Andreeff

State University Hospital of Orthopedics. Sofia, Bulgaria

I analyzed the complications and fate of massive allografts implanted to replace the articular ends of long bones after tumor resection.

Materials and methods: Since 1960, 25 patients with giant cell tumor and 26 with bone sarcoma, mean age 31 (12–64) years, were operated on. The most common location of the lesions was the knee region (32). After resection of the tumor bearing bone the allograft was anchored by screws, metal plates or Küntscher nail.

Results: 9 patients were lost to follow-up. The mean follow-up period for the 42 patients was 13 (0.5–34) years. In 29 of them 36 complications developed. 8 died of disease and 2 of other causes. The overall tumor-free survival was 76%. The radiographic examination finally reveals changes, similar to those observed in neuropathic arthropathies. Vast new bone deposition around the allograft, as well as para-articular ossifications are noted in some cases. Nevertheless, in most patients the knee joint is stable with good range of painless motions. On the contrary, mobility of the shoulder joint is markedly restricted.

Conclusion: Massive bone allografts ensure a good function in the joint after resection of the tumor bearing bone, and represent an alternative to amputation and prosthetic replacement in young adults with long life expectancy.

Allografts surrounding stems of hip and knee massive prostheses

B Tomeno

Ph. Anract Hospital Cochin, Paris, France

Since many years we used massive prostheses for tumors including conventional devices (metal, or metal + polyethylene), and composite devices (with an allograft around the stem).

Out of 28 composite hip replacement 12 patients presented a progressive resorption or fragmentation of the graft (specially 6 of the 8 cases with more than 5 years follow up!) but with better functional results compared to the conventional prostheses (21 cases).

In 13 cases of composite prostheses of the distal femur we noted only a single minor fragmentation of the graft. The functional results were exactly the same for reconstructions with (13 cases) or without allograft (53 cases).

For the 26 composite arthroplasties of the proximal tibia. 16 have had a total or partial resorption-fragmentation of the graft. The functional results were worse than with the conventional replacement without allograft (10 cases). Failure of the graft usually lead to the loosening of the tibial component.

Conclusion: Allografts surrounding stems were functionally useful in massive hip replacements in spite of some radiological unsatisfactory features.

For knee reconstructions no improvement (and no disadvantage) was observed for the lower femur, but in the upper tibia the allografts appeared harmful.

Osteoarticular allograft in bone tumor surgery—analysis of complications

D Donati, M Di Liddo, M Zavatta, P Caldora¹, M Mercuri, R Capanna¹, M Campanacci

Bone Tumor Center, Istituto Ortopedico Rizzoli, Bologna, and ¹C.T.O., Firenze, Italy

Since 1989 we have used osteoarticular allograft in 65 patients, upper limb in 36 cases and lower limb in 11. Mean age 22, resection length 13.5 cm.

Results: In 57 cases we were able to achieve a follow-up longer than 12 months (mean 42). Infection occurred in 3 patients but with only 1 graft failure. Nonunion occurred in 17 patients, no failed. The major complication was fracture in 21 patients. In 8 patients no operation was done (6 in the upper limb), among 13 patients operated, 12 grafts failed and were substituted in 3 with a modular prosthesis, in 3 with a new graft and in 6 with a conventional prosthesis achieving an allograft composite prosthesis. Failure occurred in 17 patients (4 local recurrences), while 40 patients still have the graft. 24 did not experience any complication. Function at follow-up scored was excellent in 21 patients, good in 17, fair or poor in 2.

Conclusion: Osteoarticular grafts still have indication in upper limb, with cement inside and in children aged 10–14 years. In the lower limb, in adult patients, we prefer endoprostheses.

Intercalary reconstructions of the femur

D Donati, L Campanacci, C Ercolani, M Mercuri, R Capanna¹, Campanacci M

Bone Tumor Center, Istituto Ortopedica Rizzoli, Bologna, and ¹C.T.O., Firenze, Italy

As prosthetic devices are not very effective in diaphyseal reconstructions, bone graft has been widely used. Femoral diaphysis is one of the most challenging sites. Since the early 1980s we used autograft in 20 cases, but only 7 in femur. After a mean follow-up of 109 months results were quite unsatisfactory with 3 cases complicated (2 deep infection and 1 fracture). Time of surgery (6 hours mean) and infection were considered too high. From 1985 we could use intercalary allograft in 53 femurs. The first 6 cases were high grade malignant tumor receiving chemotherapy. Outcome was poor with 3 cases infected and 1 fracture. Later, we used locked nail for fixation in 11 cases. Limited rotational stability led to 10 nonunions (8 failure of the device) and in 4 cases a fracture occurred. Plate as a mean of fixation was again re-applied and in 21 cases yielded 8 nonunions and 3 fractures. The latest experience included 15 cases in which graft was filled with cement. No fracture occurred but 9 patients had nonunion.

Conclusion: Allograft surgery in intercalary resection of the femur is still the first option of choice presenting excellent results after healing of the graft. Failure of the graft can

be avoided with the use of cement and double plating at the cortical site of osteotomy. In very extensive resection the use of vascularized fibula has to be considered.

Ewing's tumor—outcome according to tumour volume—a report of the German CESS 86 trial

M Paulussen¹, S Ahrens¹, C Hoffmann, K Wörtler, A Schuck, H Jürgens¹

¹Dept. of Pediatric Oncology, and Hematology, University of Münster, Germany

153 CESS-86 patients (pts) with locoregional Ewing's sarcoma of PNET treated on neoadjuvant systemic chemotherapy, plus local surgery and/or radiotherapy were compared for relapse-free survival probability (rfs) according to tumor volume (tv) at diagnosis.

Patients and methods: In a previous study (CESS-81) tv of ≥ 100 mL had been an indicator of poor prognosis. In CESS-86 pts with tv ≥ 100 mL received ifosfamide instead of cyclophosphamide with otherwise identical chemotherapy and individualised local therapy. Rfs were calculated by Kaplan-Meier analysis, comparisons done by logrank test and Cox analysis.

Results and Discussion: Rfs was 0.63 for pts with tv < 100 mL, 0.51 for pts with tv ≥ 100 mL ($p=0.57$), but was 0.65 for tv < 200 mL and 0.34 for tv ≥ 200 mL, $p=0.033$. Within the high-risk group of pts rfs was 0.69 for tv of 100–199 mL vs 0.34 for tv ≥ 200 mL, $p=0.037$. However, tv ≥ 100 mL was more often reported in CESS-86 (67%) than in CESS-81 (41%). Due to more exact imaging techniques tv of ≥ 200 mL in CESS-86 may assemble tv of > 100 mL in CESS-81. It needs to be examined, if adaptation of risk groups to a tv of 200 mL could balance outcome.

Conclusion: In locoregional Ewing's tumour, tumour volume at diagnosis is a prognostic factor.

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High dose chemotherapy with bone marrow or peripheral stem cell rescue for metastatic or recurrent Ewing's sarcoma

JS Whelan, K Denby, AM-Cassoni, RL Souhami

The London Bone Tumour Service, Meyerstein Institute of Oncology, UCL Hospitals, London, U.K.

Improved survival of patients with recurrent or metastatic ES may be achieved by dose intensification. Appropriate selection of patients and the best regimen have to be determined.

Patients: 16 patients with Ewing's sarcoma (ES) or primitive neuroectodermal tumours received high dose therapy (HDT) supported with either bone marrow (3 patients) or peripheral stem cells (PSCR; 11) or both (2). There were 7

females and 9 males aged between 13 and 37 years (median 21). Primary sites were extremity, 7; pelvis, 5; extraosseous, 3; scapula, 1. All received initial chemotherapy with ifosfamide, doxorubicin, vincristine and actinomycin D. Indications for HDT were: metastases at diagnosis, 9; recurrent disease, 7. Status at time of HDT was 1st remission, 8; 2nd remission, 6; 3rd remission, 1; progressive disease, 1. Treatment was busulphan (B) 16 mg/kg (600 mg/m² if less than 16 years) and melphalan (M), 140 mg/m² (7 patients); M 110 mg/m² and 12 Gy total body irradiation (TBI; 3 patients); etoposide (E), 40 mg/kg and M 120 mg/m² (5 patients); E+M+TBI, 1 patient. Two of three patients with sufficient CD 34+ cells had tandem treatments with E+M, the third had insufficient platelet recovery after one treatment.

Results: Median number of days to neutrophils $> 0.5 \times 10^9/L$ and platelets $> 20 \times 10^9/L$ were 12 (10–26) and 9 (0–50), respectively. All patients experienced grade 3–4 mucositis and infection but there were no treatment related deaths. Impaired platelet recovery was frequent after B+M with PSCR. Other toxicities of B+M included seizures (2 pts), hemorrhagic cystitis (1), veno-occlusive disease (1) and pulmonary fibrosis (1). There were no additional toxicities associated with E+M or E+M+TBI. Two patients have died of ES, 9 and 21 months after HDT. Two patients have developed progressive disease after 5 and 7 months, one of these is again disease free 7 months after surgical resection of a single pulmonary metastasis. Twelve patients remain disease-free between 1 and 49 months (median, 9) after HDT.

Conclusion: This is a tolerable and effective strategy for poor risk ES with toxicity of B+M exceeding that of E+M. Future, multicenter, studies must determine appropriate criteria for selecting patients.

Importance of early extratumoral surgery on outcome of Ewing's sarcoma of pelvic bone

G Delepine, N Delepine, H Cornille, S Alkallaf, B Markowska, JC Desbois

Oncologic Pediatric service, Hôpital R. Debré, 48 Bd Serurier, 75019 Paris, France

Local treatment of Ewing's sarcoma is difficult and still debated. High dose radiotherapy is followed by 20 to 40% local recurrence and the patients are threatened by secondary sarcoma. Surgery is a challenge. To precise the impact of surgery and its modalities on outcome we reviewed our file.

Patients: From 1977 to 1995, we have treated 21 patients for Ewing's sarcoma or PNET of the innominate bone, 6 of them were primary metastatic to lungs and or bone.

All patients received polychemotherapy. Local treatment consisted of radiotherapy alone (5 cases), surgery and radiotherapy (19), surgery alone (6 cases). Surgery was done in 16 patients (extratumoral in 9, contaminated in 7) either early, (before the 60 th day of biopsy) or late. All patients experimented limb salvage with no reconstruction (2 cases) or reconstructive procedures adapted to anatomic site of tumor. In extraacetabular tumors, we used composite reconstruction

with acrylic cementations and screws or allograft (9). For periacetabular location, we used combined total hip prosthesis (5).

Result: With a median follow up of 66 months, we have seen 6 local recurrences (all followed by metastases) and 8 primary metastatic evolution. Only 7 patients are alive and well. Patients with primary metastases, big tumors and bad response to induction chemotherapy did worst. All 7 patients treated with radiotherapy alone or debulking surgery followed by radiotherapy subsequently died, without local control in 5. 5 of 6 patients with early extratumoral surgery are alive and well but 2 of those with late surgery relapsed.

Conclusion: Our results confirm the EMSOS-EAMTS 95 study: 1) surgery increases the disease free survival rate of patients with Ewing's sarcoma of pelvis, and 2) surgery must be by extratumoral.

Malignant fibrous histiocytoma of bone—combined chemotherapeutic and surgical approach

S Mapelli¹, V Zucchi¹, M Oliva¹, A Parafioriti¹, E Armiraglio¹, P Casali¹, R Bertulli²

¹G. Pini, Orthopaedic Institute and ²National Cancer Institute, Milano, Italy

Since 1986, 18 pts with MFH-of bone have been treated (M/F=7/11; average age 45 (17–81). The data of the first 7 pts (1986–1989) were presented at the 3 rd EMSOS meeting in Stockholm in 1990; in this group the combined treatment (CT-SURG-CT) achieved good homogeneous results (necrosis $>90\%$ in 5/7; conservative surgery and CDF survival in 7/7) that are still valid except for 1 pt that had resections of lung metastases in 7/90 and in 1/94 and now is DF. The following 11 pts (1990–1996) represent a less homogeneous group. 3 pts received only a surgical treatment (age 71, 80, 81). 1 pt will receive CT only after surgery. The others 7 pts received combined treatment (CT-SURG-CT): necrosis $>90\%$ was found only in 2/7 pts. Ablative surgery was performed in 4/11 pts because of primary or secondary extension of the tumor. Oncological results include 2 pts died, 3 pts CDF and 1 pt DF after resection of lung metastasis (F.U. < 3 y. in the others 5 pts)

The overall results of the complete series are: 7/14 pts with necrosis $> 90\%$; 14/18 pts with conservative surgery; 9/13 pts CDF, 2/13 DF after resection of lung metastases; 2/13 died; 0/18 recurrences.

Conclusions: The results of the treatment of the recent 11 cases of MFH of bone are not so favorable as the first 7 presented in 1990; however the overall results seems to confirm, in our experience, the chemoresponsiveness of the MFH of bone to the same drugs effective in the osteosarcoma. Nevertheless the rarity of this tumor requires more extensive and cooperative studies to reach reliable results.

A randomized trial (COSS-86C) comparing two cisplatin (DDP) schedules within multiagent chemotherapy for osteosarcoma

S Bielack, B Kempf-Bielack, D Epler, N Fuchs, G Delling, N Graf, H Jürgens, O Koch, R Kotz, M Salzer-Kuntschik, K Winkler

Cooperative Osteosarcoma Study Group COSS, Germany, Austria, Switzerland

With complete surgery, 4-drug chemotherapy for osteosarcoma (OS) according to protocol COSS-86 (doxorubicin (DOX), high-dose methotrexate, ifosfamide, DDP) led to 73% projected metastasis free-survival (MFS) at 7 years. Cardiotoxicity, though severe initially, was reduced by giving DOX as continuous infusion (CI). Ototoxicity, however, remained to be a significant problem.

The objective was to evaluate if, by altering DDP scheduling, ototoxicity can be reduced without compromising treatment efficacy.

Methods: Randomized trial of 72h-CI vs. 5h infusion of DDP (120 mg/m² per cycle, 2 x pre- and 2 x postoperatively) within otherwise identical 4-drug therapy for primary, localized extremity OS.

Endpoints: Histological good response rate (RR, % with >90% necrosis), MFS, toxicity.

Results: With a median follow up of 1.82 (5h-DDP) and 1.52 years (72h-DDP) for patients (pts.) at risk (CCR= continuous clinical remission, SE= standard error):

Schedule	Response			Projected 3-year MFS			
	n	Good	RR	n	CCR	MFS	SE
5h-DDP	75	47	63%	58	49	80%	6%
72h-DDP	73	41	56%	52	47	83%	7%
p-value	0.42; Chi-Square			0.47; logrank			

Ototoxicity was much less severe in the 72-hour arm. Severe nephrotoxicity was very rare, myelotoxicity was not influenced by DDP scheduling.

Conclusion: Prolongation of DDP-infusions from 5h to 72h resulted in reduced ototoxicity without compromising the antimetastatic efficacy of combination therapy for OS.

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Histological response of osteosarcoma of the extremities to intraarterial vs. intravenous Cisplatin—results of 2 randomized studies in which Cisplatin was preoperatively administered within a 3-drug and a 4-drug regimen

G Bacci, E Figus, S Ferrari, M Mercuri, P Picci, F Bertoni, D Donati, M Manfredi, C Forni, E Rulli, Smerli and M Campanacci

Dept. of Chemotherapy, Istituto Ortopedico Rizzoli, Italy

We report the Rizzoli experience about intraarterial (IA) vs intravenous (IV) CDP-in multiagent preoperative chemotherapy for osteosarcoma of the extremities (OE). It consists of 2 randomized studies: the 3rd Rizzoli Neoadjuvant Study (7/90-9/91) in which, preoperatively, CDP was used within a 3-drug regimen (HDMTX, CDP, ADM) and the 5th Rizzoli Neoadjuvant Study (5/94-3/96) in which, before surgery, CDP was administered within a 4-drug regimen (HDMTX, CDP, ADM, IFO).

With the 3-drug regimen (IOR/OS-N3 protocol) the rate of good histological response to chemotherapy (defined as 90% or more tumor cells necrosis) was significantly higher in the 40 pts who received CDP intraarterially than in the 39 pts who received CDP-intravenously (77% vs 46%: P .004).

In contrast, in the study in which a 4-drug regimen of chemotherapy (IOR/OS-Neo5 protocol) was applied before surgery, the rate of good histological response was the same in the 60 pts who received CDP IA and in the 59 patients who received this drug IV (76.6% vs 72.8%: P ns). We conclude that in neoadjuvant treatment of osteosarcoma of the extremities, a 4-drug regimen of preoperative chemotherapy is more effective, at least on the primary tumor, than a 4-drug regimen and that if a 4-drug regimen is used before surgery there are no advantages in delivering CDP intraarterially.

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Osteosarcoma of the extremity with detectable lung metastases at presentation—results in 23 patients treated with chemotherapy followed by simultaneous resection of primary and metastatic lesions

G Bacci, E Figus, A Briccoli, S Ferrari, M Mercuri, P Picci, C Forni, F Bertoni, M Campanacci

Dept. of Chemotherapy, Istituto Ortopedico Rizzoli-Bologna, and Istituto di Patologia Chirurgica dell'Università di Modena, Italy

For patients with extremity osteosarcoma and long metastases at presentation (OEM), the efficacy of chemotherapy coupled with aggressive surgery is not well established. The present study evaluates the efficacy of neoadjuvant chemotherapy associated with simultaneous resection of primary and metastatic lesions (SRPSL) in patients with OEM. Patients with OEM received chemotherapy (high dose Methotrexate, Cisplatin, Adriamycin and Ifosfamide) followed, when feasible, by SRPSL. Between January 1993 and June 1995, 23 patients entered the study. After primary chemotherapy, in 3 patients lung metastases disappeared, whereas in 4 patients they remained surgically unresectable. All these 7 patients received surgical treatment of the primary tumor only. In the remaining 16 patients, after chemotherapy, a SRPSL was performed. The resection of metastatic lesions resulted complete in 15 cases and incomplete in one. All the 5 patients who never achieved a tumor-free status died in a few months. Of the 18 patients who achieved radiological

remission at a 30-month follow-up (14–50), 10 (43%) remained continuously free of disease, 12 relapsed with new metastases and 1 died of toxicity.

In 13 pts out of the 15 who had a complete SRPSL, a strong correlation between the degree of necrosis of the primary and metastatic tumor was found.

We conclude that in patients with OEM the combination of aggressive chemotherapy with SRPSL improves the traditionally negative outcomes. The strong correlation found between the histological response of the primary and metastatic tumors support the strategy, largely used nowadays in the neoadjuvant treatment of osteosarcoma, of tailoring postoperative chemotherapy on the basis of the primary tumor histologic response to chemotherapy.

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Hyperthermic isolated limb perfusion with tumor necrosis factor and melphalan for unresectable bone sarcomas of the lower extremity—our experience in 5 consecutive cases

I Meller, J Bickels, Y Kollender, M Gutman, JM Klausner, and M Mozes

The National Unit of Orthopedic Oncology and Department of Surgery, B. Tel-Aviv Sourasky Medical Center, Israel

From December 1993 to December 1995, 5 consecutive patients with bone sarcomas of the lower extremity who were candidates for immediate major amputation, underwent isolated limb perfusion (ILP) of the affected limb with tumor necrosis factor (TNF) and melphalan.

No major complications related to the procedure developed. Partial response was observed in 4 patients and no response in 1. The average follow-up period was 13 (6–34) months at the end of which 2 patients are alive with no evidence of disease and 3 patients had died. In 3 patients the amputation was avoided.

Isolated limb perfusion with TNF α + melphalan $\pm$ IFN γ for locally advanced extremity soft tissue sarcoma—the cumulative multicenter european experience

AMM Eggermont¹, H Schraffordt Koops², JM Klausner³, BBR Kroon⁴, PM Schlag⁵, G Ben-Ari⁶, JC Pector⁷, FJ Lejeune⁸

Univ. Hosp. ¹Rotterdam, ²Univ. Hosp. Groningen, and ⁴Cancer Inst., Netherlands; ³Ichilov Hosp., Tel Aviv, Israel; ⁵Robert Rissle Cancer Center, Berlin, Germany; ⁶Medical Center Tel Hashomer, Israel; and ⁸C.P.O. Lausanne, Switzerland

Long terms results of the treatment of giant-cell tumor of bone with cryosurgery—a retrospective multi-institutional study of 102 cases

Y Kollender, R Buch, M M Malawer and I Meller

The National Unit of Orthopedic Oncology, Tel-Aviv Sourasky Medical Center, Israel; Dallas TX, U.S.A.; and The Washington Cancer Institute at the WHC, Washington DC, U.S.A.

We review our experience in the use of cryosurgery as a physical adjuvant in the treatment of giant-cell tumor of bone.

Patients and methods: Three institutions contributed 102 cases. There were 52 female and 50 male patients. Age: 15–72 (3–13.5) years.

Anatomical locations were scapula - 1, distal radius - 6, wrist bones - 6, hand and foot bones - 7, pelvis - 5, sacrum - 1, proximal femur - 12, distal femur - 28, proximal tibia - 20, proximal fibula - 5, and distal fibula - 11.

According to Campanacci's Staging System there were 15 cases in stage I, 47 in stage II and 40 in stage III. 16% (17pts) were already local recurrences after previous treatment in other places. Curettage was combined with high speed burr drilling followed by 1–3 cycles cryosurgery (open system) according to the techniques of Marcov modified by Malawer. Reconstruction of the bone defects was performed using different methods and materials such as: autologous bone graft, allograft, internal fixation, implants, and bone cement.

Results: There were 8 local recurrences (7.9%), 7 in bone and 1 in soft tissue. 6 were treated by recurettage and cryosurgery with no evidence of disease until now. The other 2 underwent resection and prosthetic replacement. There were 6 fractures (5.9%). 5 were undisplaced and treated conservatively to healing. 1 had a displaced fracture and needed open reduction and internal fixation. There were no deep wound infections, nerve palsies or vascular injuries. There were 5 cases of skin damage from the liquid nitrogen that healed without further operations.

Conclusions: Cryosurgery is a powerful physical adjuvant to curettage for G.C.T. of bone. No relationship was found between local recurrence and stage, anatomical location of type of reconstruction. Composite fixation techniques succeeded in preserving the joints and reduced dramatically the fracture rate that was previously reported. Careful attention to the cryosurgery technique and skin protection reduced the infection rate and skin damage.