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Diagnosis, treatment and prognosis of desmoid tumors—a joint European Musculoskeletal Oncology Society (EMSOS) study

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A retrospective EMSOS study to assess risk factors for local recurrence in desmoid tumors was initiated in 1991.

Patients and methods. 151 patients treated at 11 EMSOS institutions were studied. The average age was 33 (1–80) years and 82 were women Tumor locations were: upper extremity 39, lower extremity 40, trunk 49, neck 5, other sites 13, and multiple sites 5. The average tumor size was 7 (1.5–40) cm. 145 patients were operated on. 2 patients received pre- and 6 patients postoperative radiotherapy. 5 patients received medical treatment (1 tamoxifen, 4 chemotherapy). Histopathology review, DNA-cytometry, proliferating cell nuclear antigen (PCNA) and estrogen receptor determination were performed.

Results. The diagnosis was confirmed in all cases. All primary tumors were diploid and estrogen receptor negative. A Cox regression analysis showed a 4.0 relative risk for upper extremity location and a 2.5 relative risk for marginal excision, respectively, for occurrence of first local recurrence. Tumor depth, vascular pattern, cellularity and PCNA index were of no prognostic importance.

Secondary malignant neoplasms after treatment for Ewing sarcoma—EMSOS multicenter study 1994

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13 centers reported 1751 Ewing sarcomas, 289 PNETs, and 80 Askin tumors with a mean follow-up of 18 (2–31) years. The mean age at diagnosis of the primary tumor was 13 (1–24) years. A secondary malignant neoplasm (SMN) was found in 20 cases, 11 women, 9 men. SMN was diagnosed mean 7 (2.5–21) years after the diagnosis of the primary tumor. 10 SMN cases were osteosarcoma, 4 leucemia, 1 MFH, 5 others.

The family history in the 20 SMN cases was in 15 cases negative and in 5 cases positive for a malignancy. All SMN cases had had chemotherapy for the primary tumor; in all Vincristine, in 19 Adriamycin, in 17 Actinomycine, in 15 Cyclofosfamide. The duration of the chemotherapy was 13 (3–24) months. Radiotherapy was given in 18 cases, mean dose 50 (13–65) Gy. 6 patients had been treated by surgery, 3 operations were not radical, 3 were radical.11 patients had the SMN in the radiation field. At follow-up after 4 (0.1–11) years there were 11 survivors (10 NED, 1 AWD). 7 patients died of disseminated disease (1 day-12 years) after the diagnosis of SMN.

Second malignant neoplasms following childhood Ewing's (ES)—the Institut Gustave Roussy experience

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The risk of a second malignant neoplasm (SMN) was evaluated in 111 children diagnosed with ES between 1958 and 1983 and who survived at least 2 years after diagnosis. The mean age at diagnosis was 10 (0.5–27) years. All patients except 17 had received chemotherapy (CT); 84 at diagnosis and 10 only for a relapse. All but 2 had received radiotherapy (RT); median 60 (30–68) Gy.

Results. The median follow-up was 11 (2–33) years. 9 patients developed SMN after median 8 (4–26) years. 2 patients developed AML and 7 developed solid tumors (5 osteosarcomas, 1 MFH and 1 leiomyosarcoma). All the solid tumors occurred within the field of previous RT. We could not establish a relationship between SMN and CT,

since only 17 patients did not receive CT and 1 of them developed AML. The cumulative risk of SMN was 4% at 5 years, 8% at 10 years, 13% at 15 years, and 33% at 25 years (9 patients at risk, confidence interval 20%). The prognosis of SMN was poor; only 2 patients remain free of disease.

Conclusion. Our data confirm the risk of SMN after treatment of ES. To improve the local control and the cure rate we have integrated surgery more and more in our management of ES. Thereby RT may be reduced or avoided to probably minimize the risk of SMN. The possibility of reduction of CT remains questionable.

Radiation-induced sarcomas of bone. Characteristics, survival and management in 19 cases

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We evaluated 10 men and 9 women with radiation-induced sarcoma of bone. The mean age at the first diagnosis was 30 (6–71) years, at diagnosis of the second tumor it was 43 (12–76) years. The median interval between the two lesions was 11 (4–28) years.The first tumor was Ewing's sarcoma (4), cancer of uterus (3) and giant cell tumor of bone (3), respectively, cancer of the brest (2) and a radiographically benign osteolysis (2), and in 1 case each osteosarcoma, soft tissue low-grade fibrosarcoma, histiocytosis X, haemangioendotelioma of bone and Hodgkin's lymphoma.The median RT dose was 51 (27–88) Gy. Only 11 cases had a chemotherapy treatment for the first lesion. The commonest histotype of the second tumor was MFH (10), followed by osteosarcoma (7) and fibrosarcoma (2).The second tumor occurred in femur (6), in pelvic bones (5), in upper girdle (4), in tibia or fibula (3) and in the humerus (1).

8 patients are disease-free after median 6 (1–12) years. The remaining 11 patients died within 4 to 19 months.The type of radiotherapy and the time interval between the primary and secondary tumor did not influence the prognosis. Patients who had surgery with adequate margins had a better prognosis. Considering the small number of cases we cannot draw any definitive conclusions.

Osteosarcoma preceding or following leukemia—an EMSOS cooperative study reporting 12 cases

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12 cases of osteosarcoma and leukemia in the same patient were collected from EMSOS members. 9 cases with primary osteosarcomas developed 3 ALL, 3 AML, 2 undifferentiated leukemia and 1 CML, while 3 cases of secondary osteosarcoma had as the first tumor ALL. The clinical history was suggestive of Li-Fraumeni syndrome in 1 case. Different chemotherapy regimens were used for the primary tumor. Patients with primary osteosarcoma developed ALL after 14–22 months, AML after 25–33 months and undifferentiated leukemia after 4.5 and 8 years; the only case of CML occurred after 8 years. The 3 patients initially treated for an ALL developed an osteosarcoma after 9–10 years. All the patients that developed an ALL after osteosarcoma are disease-free at 26, 44 and 67 months, while 2 of the patients with AML are dead and the remaining one is NED after 7 years. Of the 2 patients with undifferentiated leukemia one is lost to follow-up and the other dead in sepsis after 1 month. The only case of CML is alive with disease after 26 months. Only 1 patient with primary ALL is NED after 17 months, while the others died after 5 and 8 months. The low number of cases prevent any definitive conclusions.

EMSOS joint study on chemotherapy of MFH of bone

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During 1993 EMSOS-members reported patients with MFH of bone to assess whether preoperative chemotherapy was of value. Of 127 patients, 31 were amputated and 96 had a resection of their primary tumor. 9 received postoperative chemotherapy (CT), 90 pre- and postoperative CT and 28 had no CT.

Data on tumor response following preoperative chemotherapy defined as either > 50 % tumor shrinking or > 90 % necrosis histologically were available in 71 patients.

Relapse was reported in 43/127 (34 %) cases (6 local, 30 lung, 7 bone). Relapse was less frequent after resection as opposed to amputation (30 % vs 45 %, ns), in patients receiving any form of CT (31 % vs 46 %, ns), in patients receiving preoperative vs no chemotherapy (25 % vs 46 %, $p < 0.05$), and in patients showing good response following primary chemotherapy (4 % vs 36 %, $p < 0.01$) . No correlation of treatment results with neither the kind of drugs used nor single or cumulative drug dosages could be found. Analysis of histological specimens and radiograhs is in progress.

Conclusion. There is evidence for some efficacy of chemotherapy in MFH of bone. The local response rate of 35 % after a variety of different drug combinations is lower however than that reported from actual preoperative chemotherapy trials in osteosarcoma. The prognostic significance of a good response is comparable to that found in osteosarcoma.

The Scandinavian Sarcoma Group Registry of Musculoskeletal Tumors

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See abstract p 90 in this issue.

Doxorubicin (DOX) schedule, tumor response and survival in the cooperative osteosarcoma studies COSS-86 A-C

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DOX is one of the most active agents against osteosarcoma. Cardiotoxicity, the most dreaded side effect, can be markedly reduced by prolonging DOX infusions. However, the effect of such schedule changes on antitumor efficacy remains less well defined.

Patients and methods. Osteosarcoma patients have been treated with neoadjuvant multiagent chemotherapy according to the COSS-86 protocol (DOX, high-dose methotrexate, cisplatinum, and ifosfamide) since 1986. DOX was originally applied as BOLUS (90 mg/m^2 as 30 minute infusions of 2 x 45mg/m^2 on two consecutive days). One pre- and 4 postoperative courses were given (cumulative DOX 450 mg/m2). As of 1989, DOX was given as continuous 48 hour infusion (CI) in order to diminish cardiac side effects. The histological response rate RR after preoperative chemotherapy and actuarial metastasis free survival MFS were compared for BOLUS and CI.

Results as of May 1994 were as follows:

	Response		Survival	
	n	>90%TCD (%)	n	MFS (%)
BOLUS	140	100 (71)	153 [a]	116 (75)
CI	92	61 (66)	56 [b]	42 (66)

Median year at risk: [a] 5, [b] 3. Differences were not significant.

Conclusion. Changing DOX from BOLUS to CI within a multiagent protocol for osteosarcoma did not lead to significantly inferior results. Minor differences might be acceptable in view of the reduced cardiotoxicity of CI.

Isolated limb perfusion with high dose Tumor Necrosis Factor-alpha, Interferon-gamma and Melphalan for limb salvage in patients with irresectable soft tissue sarcomas

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The results of isolated limb perfusion (ILP) in patients with soft tissue sarcoma is not encouraging. Since 1991 a multicenter study in our institutes assesses the efficacy of ILP with Tumor Necrosis Factor-alpha (TNF-α), Interferon-gamma (IFN-γ) and Melphalan in patients.

Patients and methods. 54 patients, median age 56 (13–78) years, with irresectable STS of the leg (47) or arm (7) were treated with 0.2 mg IFN-γ s.c. on the 2 days prior to a 90 minutes ILP with 0.2 mg IFN-γ, 4 mg (leg) or 3 mg (arm) TNF-α and 10 mg/L limb volume (leg) or 13 mg/L limb volume (arm) Melphalan at tissue temperatures of 39–40 °C. 11 patients had multiple sarcomas in the extremities. The overall median tumor size was 18 x 17 cm. Resection of residual tumor masses took place at the moment of maximal shrinkage after the ILP.

Results. 4 patients have too short follow-up for evaluation. In the remaining 50 patients, with a median follow-up of 9 + (2 ± 36+) months, 19 complete remissions and 26 partial remissions were seen. Remission rates were based on compilation of clinical and histopathological data. A 100% necrosis on histological examination was observed in 15 patients. Acute softening of the tumor and total disappearance of the tumor vascular bed on angiography was often observed. 40 tumors were resected between 2–5 months after ILP. In 10 patients (all cases with partial remissions) the tumor was not resected for various reasons (metastases, multiple tumors). Tumor recurrence (2), irresectability (1), and postoperative complications (2) led to an amputation in 5 patients.

Severe systemic toxicity was only seen in patients with substantial leakage to the general circulation. All patients had fever (37.5–40 °C) and chills and developed a hyperdynamic state after the ILP. In 1 patient there was a grade III liver toxicity and multiple organ failure and in 1 patient prolonged mechanical ventilation and renal dialysis was required. There were no treatment related deaths. Locoregional toxicity was comparable with perfusion using Melphalan alone (edema, redness of the skin, sometimes blistering).

Conclusion. ILP with high dose TNF-α, IFN-γ, and Melphalan appears to be a promising method that can achieve limb salvage in patients with irresectable STS of the extremities.

Does preoperative radiation therapy of Ewing's sarcoma increase the complication rate?

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Since 1991 preoperative radiotherapy in combination with chemotherapy is an important treatment modality for patients with large or unfavorably localised Ewing's sarcoma. From January 1991 to January 1994, 34 patients with Ewing's sarcoma (25) or PNET (9) who had preoperative radiation therapy according to the EICESS protocol were operated on at the bone tumor centre in Münster. 15 tumors were located in the pelvis, 7 in the upper, and 12 in the lower limb.

Patients recieved doses between 30 and 56 Gy in single fractions of 1.6 Gy prior to surgery; all but 2 patients reeieved a hyperfractionated radiation therapy regiment with 2 fractions per day. 7 patients received additional intraoperative brachytherapy because of a narrow resection margin. 30 patients had simultaneus chemotherapy. The preoperative RT had to be interrupted in 3 cases because of dermatitis or enteritis. The time period between radiotherapy and surgery was 17 to 165 days. Auto- and/or allografts were used 24 times, endoprostheses 3 times, and other procedures 7 times. There were no intraoperative complications. Except for cases who received brachytherapy, the operation time was not prolonged (4–10 h), nor was the time of postoperative hospitalisation (8–24 days). An increase of blood transfusions was not seen. 7 postoperative complications were noted: 4 patients had disturbed wound healing, 2 patients developed thrombosis, and 1 patient sustained a fracture 14 months after surgery.

In summary, preoperative radiotherapy and intraoperative brachytherapy do not raise the complication rate of surgery in Ewing's sarcoma.

Revision of custom made prostheses in an irradiated field

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Wide resection and application of a prosthesis in an irradiated limb is controversial because of the risk for wound healing problems and infection, and surgical difficulties due to fibrosis. We report 2 cases of revision surgery with no complications.

Two girls, 13- and 14-year-old, with osteosarcoma received neoadjuvant CRCSC protocol and 3.5 Gy × 10 local irradiation between the first two cycles of chemotherapy. Wide resection of the distal femur and the proximal tibia, respectively, and application of custom made stainless steel hinged prostheses, produced by a local firm, were performed 3 weeks after the completion of irradiation. The stems of prostheses fractured following falls after 11 and 30 months. The prostheses were revised using new components.

There was marked fibrosis in the subcutaneous tissue and fasciae. Closure of the relatively less fibrotic muscles was easy but overlying layers required en bloc approximation stitches in both patients and skin relief incisions in one patient. All wounds healed within 3 weeks and the patients regained the same function as before the revisions.

Intraoperative electron boost (IORT) and postoperative radiotherapy in soft tissue sarcomas of the lower extremity

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We investigated the use of IORT in soft tissue extremity sarcomas to assess local control and functional status. From 1986 to 1992, 27 patients were treated. IORT (10–20 Gy) was delivered to surgically defined high risk areas after tumor resection. 4–6 weeks after surgery postoperative radiotherapy (45–50 Gy) was given provided no previous radiotherapy had been given (2 patients were treated with IORT alone). Chemotherapy (neoadjuvant and/or adjuvant) was given mainly in high grade tumors. 18 patients were treated for primary disease (PD) and 9 for an isolated local recurrence (LR). Tumor stage at diagnosis of the primary tumors was: IB 5; IIB 2; IIIA 1; IIIB 10. Surgical margins were: marginal 4, wide 20, compartmental 2, incomplete resection 1.

Local control inside the IORT field was achieved in 25 patients. Extremity failure occurred in 4 patients and distant failure in 5 (combined in 2 patients). One local failure patient did not receive external irradiation. In patients with close surgical margins, local control was achieved in 9 of 11. Complications included: seroma 3 patients, symptomatic fibrosis 2, soft tissue necrosis 3, delayed wound healing 2, and ischemia leading to amputation in 2 patients. 5 patients developed neuropathy attributed to the treatment. In 4/5 the cone size was >12 cm and IORT dose >15 Gy. Extremity preservation was attained in 24 patients. In the 19 patients living more than 2 years, functional status was considered good to moderate in 13 and 6 patients had a poor outcome. With a median follow-up of 3 (0.5–8) years 20 patients remain alive, 18/20 of the local control patients and 2/4 in patients with local recurrence after treatment.

IORT in soft tissue sarcomas of the lower extremity gives a high local control rate. Tolerance to treatment is accept-

able maintaining good/moderate functional status in the majority of patients. Nerve structures in the IORT field are dose-limiting structures and therefore should be protected in order to avoid neuropathies.

HBA-71 immunostaining and RT-PCR t(11;22) detection for the diagnosis of Ewing's sarcoma

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Two different techniques have been recently suggested for a more accurate identification of Ewing's sarcoma (ES) cells: immunodetection of MIC2 gene product (HBA-71 antigen); and RT-PCR detection of t(11;22) fusion transcripts. We have compared these two methods for the clinical diagnosis of ES and for monitoring ES cells in peripheral blood.

Methods. HBA-71 expression was evaluated with the 013 MAb (1:80). The t(11;22) was detected by RT-PCR. The primers used were able to identify both the expected EWS/FLI fusion and the EWS/ERG variant fusion transcript. We used paraffin-embedded and/or frozen material from 34 musculoskeletal lesions, including ES, osteosarcoma (OS), lymphoma, mesenchymal chondrosarcoma, rhabdomyosarcoma, osteomyelitis, eosinophilic granuloma and metastatic neuroblastoma. Different cell lines of ES and OS were also analyzed, together with peripheral blood from healthy individuals.

Results. Besides ES cell lines, HBA-71 antigen was also expressed in 9/10 OS cell lines and in normal lymphocytes (both T and B). The level of expression was remarkably higher in ES than in OS. The high antigen expression in ES is responsible for the specific detection of HBA-71 in paraffin-embedded sections of ES but not in OS. RT-PCR was highly specific for the detection of ES cells both in vitro and on tissue samples. The presence of the fusion transcripts was detected in all the cases of ES, but not in the other lesions analyzed. In this series, the EWS/ERG transcript was found in one tenth of ES cases.

Conclusion. HBA-71 immunodetection maintains a diagnostic value on histologic sections but appears to be useless for in vitro studies and for monitoring EW cells in the peripheral blood. RT-PCR is highly specific for ES, with a wide range of applications. Moreover, it is able to identify both the EWS/FLI and the EWS/ERG fusion transcripts, possibly reflecting prognostic differences.

Ki-67 predicts metastasis in soft tissue sarcoma

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Thermal alteration in bone adjacent to a cavity filled with PMMA

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We tried to confirm one of the theoretical explanations for the impressive improvement of the local control in giant cell tumor obtained after cementation of the curetted cavity. It has been claimed that the heat generated during the polymerization process extends the margins of the procedure.

We created rectangular cavities of different sizes in the proximal tibial plateau of 12 tibias taken from 6 cadavers. Thermocouples were inserted at different distances from the cement-bone interface. Their output were recorded by a computer equipped with an analog to digital converter card. Our findings confirm the theoretical predictions based on numerical heat flow modelling obtained by other researchers. Necrosis will most likely occur in that region of the bone adjacent to the cement where the temperature time product exceeds the threshold of 300° C min (6 minutes at 50 °C). The boundary of this region extends from 1–4 mm from the cement-bone interface. With a larger cement volume the threshold is reached at a greater distance from the cement-bone interface because more heat is generated by a larger volume of cement. With cement boluses of 8 mL and 24 mL, the depth of necrosis is likely to extend to 2 mm, and 4mm, respectively, from the interface. The maximum predicted margin of necrosis, due to heat generation, will not exceed 5 mm.

Clinical value of P-glycoprotein expression in osteosarcoma

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The heterogeneous response of high-grade osteosarcoma (OS) to chemotherapy, as shown by the occurrence of relapses in 30–40% of the patient despite an aggressive and toxic treatment, may be partially attributed to drug resistance mediated by P- glycoprotein overexpression.

Patients and methods. P-glycoprotein expression was evaluated by indirect immunofluorescence or by immunohistochemistry, using a panel of monoclonal antibodies (JSB-1, C-219, and MRK-16) in 2 different series of patients with high grade OS. Series I included 84 primaries and 27 metastases. Series II included 43 cases of primary OS of the extremities, all treated with the same protocol of multiple-drug chemotherapy (ADM, MTX, CDDP) and limb-salvage surgery, and evaluated at a 5-year minimum follow-up. The histologic response after preoperative chemotherapy was evaluated using 90% necrosis as a cut-off. The disease- free survival curves were analyzed by Kaplan-Meier and log-rank tests.

Results. In series I, resistance was found in 24% of the primaries and 42% of the metastases. Chondroblastic OS was resistant in 58% of the cases, whereas the fibroblastic and the osteoblastic subtypes showed resistance in one fourth of the cases. At 2-year minimum follow-up, both P-glycoprotein-resistant cases and cases with a poor histologic response had a worse, although not statistically significant (p 0.2), prognosis. However, when a longer follow- up was used in series II, the difference in the disease-free survival rate between sensitive and resistant cases was statistically significant by the P-glycopratein method (p 0.05), but not by the percentage of necrosis (p 0.7).

Conclusion. In high grade OS, analysis of P-glycoprotein expression can identify cases responsive to chemotherapy and shows as a better predictor of the clinical outcome than the histologic evaluation of tumor necrosis.

Molecular genetic analysis of long bone adamantinoma—a cytometric, immunohistochemical and p53-mutation analysis

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Adamantinoma of long bones is a rare tumor with histological, immunohistochemical and electron microscopic features of epithelium surrounded by fibrous cells. The epithelial cells show a basal epithelial-cell phenotype. There are strong indications that this tumor is related to the benign osteofibrous dysplasia, which may be designated as precursor lesion of the classic adamantinoma. Evidence whether adamaninoma should be designated as an epithelial bone tumor, or as a biphasic sarcoma with epithelial features is lacking. We employed DNA flow cytometry, image cytometry and p53 immunohistochemistry (antibodies DO7 and CM1) as marker of oncogenic mutation on 34 adamantinomas to obtain more insight in the nature of the neoplasm. Moreover, lung metastases were analyzed for the presence of both epithelial and fibrous components. 6 of 15 tumors of which reliable DNA-histograms could be determined, showed an aneuploid DNA-index. Feulgen-stained paraffin sections of 6 aneuploid and 2 diploid tumors were then analyzed by image cytometry. Using this technique, in tumors that were shown to be aneuploid by flow cytometry, aneuploid nuclei could be detected in cells with an epithelial phenotype only, whereas all fibrous cells were diploid. P53 immunohistochemistry on 23 tumors revealed widespread immunoreactivity restricted to the epithelial cells in 6 tumors as well as focal epithelial reactivity in 6 cases all fibrous cells being negative. Using a PCR technique and micro-satellite markers, loss of heterozygosity of the p53-gene could be confirmed in the epithelial component of an immunohistochemically p53-positive tumor. In lung metastases the (osteo-)fibroblastic cells, present in the primary tumors, could not be detected. We conclude that adamantinoma of lung bones should be regarded as a manophasic epithelial bone tumor, with abundant reactive (osteo-)fibrous stroma.

Our experience with cryosurgery for bone tumors

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50 consecutive cases of bone tumors and tumorlike lesions treated by cryosurgery are included in this study. 35 were "-benign" giant-cell tumors and 5 low grade sarcomas. The age of the patients was 33 (16–61) years. We preferred the funnel method of pouringthe liquid nitrogen. The bone cavity was filled with freezed or demineralized allogeneic bone grafts. In 4 cases an AO condylar plate was applied to increase bone stability and to prevent a fracture. 46 patients have been followed for 5 (0.3–12) years. Within 2 years of treatment local recurrence was found in 13 patients. Eventually local control was achieved in 38 of all patients and in 32 of those with giant-cell tumors. 6 of the 9 patients with bone sarcomas are free of disease from 2–9 years after cryosurgery. Our results are comparable with those of other authors.

Doxorubicin-induced cardiomyopathy and QTc interval evaluation

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Corrected QT Interval (QTc) prolongation has been described in patients with doxorubicin-induced heart failure and it has been interpreted as a marker of doxorubicin induced cardiomyopathy. We retrospectively evaluated its clinical significance.

Patients and methods. 209 electrocardiograms performed 2 months (131), 1 year (35) and 3 years (43) after chemotheraphy completion, and related to 178 patients treated with different cumulative ADM doses, were reviewed by two independent observers. The patients were grouped as A (total ADM 480 mg/m^2; n 92), B (390 mg/m^2; n 52), and C (360 mg/m^2; n 44). The ECGs were classified as normal (QTc 0.38–0.42 msec.), within 1 SD (0.421–0.440), and within 2 SD (0.441–0.460 or more). Serial echocardiograms (ECHO) were available in 70 patients.

Results. At 2 months, normal QTc values were observed in 39% of the group C patients, compared to 15% in the A group. In this last group, a 2 SD QTc was found in 59% of the patients ($p<0.05$). No differences were seen in the ECGs performed after 1 or 3 years after chemotherapy. In serial ECGs, a significant QTc reduction was observed at 1 and 3 years compared with the values obtained at the end of the treatment (2 months: 0.444 msec; 1 year 0.429; 3 years 0.418; $p <.0001$). In absence of clinical signs of heart failure, no QTc differences were seen in patients with or without ECHO alterations (18/52) appearing after chemotherapy. None of the 4 patients with clinical heart failure had a normal QTc at the end of the treatment.

Conclusions. Doxorubicin can cause a treatment-related QTc interval prolongation, and the percentage of patients with prolonged QTc, increases according to the cumulative doxorubicin dose. Qtc prolongation is usually a reversible finding. Since in absence of clinical heart failure, no significant relationship has been observed between QTc prolongation and ECHO alterations, and no normal QTc has been observed in patients with clinical doxorubicin cardiomyopathy, it is possible that QTc prolongation, in patients with clinical heart failure, is a phenomenon secondary to an advanced myocardial dysfunction.

Cardiac function in children survivors of bone tumors

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Anthracyclines (A) are among the most useful antineoplastic agents in childhood malignancies. However, their use is limited by cardiotoxic secondary effects.

Patients and methods. Cardiac pretreatment baseline evaluation and following end of chemotherapy were performed in 34 children with bone tumours (28 osteosarcomas, 6 Ewing sarcomas). Anthracycline was given at 60 mg/m2 every 6 weeks. The mean cumulative dose was 380 (185–579) mg/m^2. The mean follow-up interval was 21 months. The mean age at diagnosis was 13 years and at follow-up 16 years. No patient received mediastinal radiation. Systolic and diastolic function was assessed by serial nucleotide angiocardiography (RNA) and Doppler echocardiogram (DE).

Results. Pretreatment tests were normal in all children. After chemotherapy all were asymptomatic; with DE 9 children had a borderline ejection fraction (EF 55–60%) and 12 had a EF < 55%. 9 children had abnormal shortening fraction (< 28%) and in 5 the ventricular filling velocity index was under 1.1; 2 of these 5 patients with diastolic dysfunction did not have systolic abnormalities. When assessed by RNA 10 children had an EF ≤ 55% and in RNA diastolic evaluation the Peak Filling Rate (PFR) decreased and correlated with the anthracycline dose and follow-up period ($p < 0.01$).

Conclusions. 1. Doppler echocardiogram and RNA are reliable noninvasive means for detecting subclinical left ventricular dysfunction. 2. Diastolic filling abnormalities may precede systolic dysfunction. PFR is a sensitive diastolic cardiac function test. 3. Long term follow-up is needed in children to disclose subclinical cardiac dysfunction.

Low cardiotoxicity of Pirarubicin in the treatment of solid tumors in children—an analysis of 71 cases

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Pirarubicin (4'O-Tetra hydropyranyl doxorubicin: THP) is an adriamycin derivate expected to have much lower cardiotoxicity than adriamycin (ADR). We have used THP instead of ADR since 1985 in our pilot studies on osteosarcoma, Ewing's sarcoma, rhabdomyosarcoma and some other tumor types. Patients who received THP from 1985 were reviewed and compared to other patients who had been treated earlier or elsewhere by ADR.

Patients. 19 patients aged 13 (4.5–19) years received only ADR in a total dose of 241 (60–360) mg/m^2. After mean 66 (21–108) months FU 11 are dead and 8 are in CR. 52 patients aged 6.5 (1.5–34) years received a mean total THP dose of 235 (35–540) mg/m^2. After mean 60 (24–84) months FU 41 patients are in CR, 1 is ED and 10 are dead.

Results. In the ADR group, we observed: 5 grade I, 1 II, 3 III, 1 IV cardiotoxicity (OMS common toxicity criterias) with one death following heart failure in a girl with OS in CR. In the THP group, we observed: 5 I, 2 II, 5 III, 0 IV cardiotoxicity ($p < 0.02$).

Conclusion. THP seems to be safer than ADR as regards cardiotoxicity and the oncological effectiveness is not lower.

MRI of skeletal muscle hemangiomas—a report of 16 cases

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We evaluated how well MRI reproduces the vascular fibrofatty structure of hemangiomas.

Patients and methods. 16 MRI studies of histologically proven skeletal muscle hemangiomas were reviewed retrospectively. Imaging protocols varied since the study was retrospective but included at least scans in 2 planes with T1 and T2 (including fast spin echo) weighted and FIR (fat suppressed) sequences.

Results. All lesions were lobulated or serpinginous. MR signal characteristics for fat were seen in 14 of 16 lesions as lace-like thin fat septa within or surrounding the tumor. All showed a hyperintense T2 weighted image. Post constrast scans showed marked signal enhancement in the lesion in the areas of high T2 signal but not in the same areal extension.

Conclusions. MR appears to display the characteristic vascular structure of hemangiomas and is diagnostic in most cases. Hence, open biopsy does not appear to be necessary in lesions exhibiting MR findings characteristics of skeletal muscle hemangiomas which articulate with clinical findings.

Evaluation of medullary extension and physeal affection in malignant bone tumors—relationship between image methods and anatomopathological findings

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We compared several image methods in the evaluation of the extension and possible physeal affection in 35 osteosarcomas and 13 Ewing's sarcomas in children. The image methods used were in all cases conventional radiography, in 44 cases CT scan, in 30 cases digital angiography, and in 14 cases MRI.

There were no differences between the methods as regards evaluation of the medullary extension. In the anatomopathological study, the physis was affected in 25 of the cases. We correlated the anatomopathological findings and the findings from the different image methods (Table).

	False (–)	False (+)	Total
X-ray (48)	1	5	6
CT (37)	0	5	5
Angiography (25)	1	3	4
MRI (14)	0	1	1

There were more false positive than negative image findings, and in the CT and MRI studies there were no false negatives. The accuracy of MRI (predictive positive value plus predictive negative value) was the best and is the technic that we prefer.

The fact that there are no anasthomoses between epiphyseal and metaphyseal vessels, and the ability, by the image methods, to determine whether the epiphysis is affected, has allowed us to preserve the epiphysis and the joint from the resection in 20 cases by using the physeal distraction according to Cañadell's technic.

MR imaging in the assessment of joint involvement in osteosarcoma

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A proper surgical procedure for osteosarcoma (OS) requires preoperative evaluation of the tumor extent. We assessed the value of MR for diagnosis of joint involvement in OS.

In 46 patients with histologically proven OS, MR was preoperatively performed on 1.5 or 0.5 T units (precontrast T1, T2 SE, postcontrast T1 SE, axial and coronar or sagittal imaging planes). The findings were correlated with histopathologic examinations. All 10 patients with tumorous jolnt involvement were identified with MR. However, in another 11 patients the MR diagnoses were false positive. MR was more accurate in identifying tumor extension into the cruciate ligaments than into the intrasynovial joint space. Post-contrast T1-weighted images were most useful in detecting joint involvement.

Contrast-enhanced multiplanar MR is a sensitive technique for assessment of intraarticular tumor invasion in OS. However, the low specificity imply a risk of overstaging.The presence of a joint effusion is a nonspecific finding.

Fine-needle aspiration of nodular fasciitis—no need for surgery

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Nodular fasciitis (NF) is the commonest of the pseudosarcomatous lesions of soft tissue. Due to its rapid growth and atypical morphology, sarcoma may be misdiagnosed clinically as well as with fine-needle aspiration (FNA). NF has been characterized in aspirate smears and spontaneous regression was first described by Stanley et al. 1991.

Patients. 1985–1995 FNA was performed on 46 patients, 26 men and 20 women, median age 45 (11–59) years. The commonest location was the lower arm (12). In 37 patients the diagnosis was based on clinical data and cytodiagnosis; in 9 the final diagnosis was by histopathological examination of the excised tumor. In the typical case a subcutaneous rapidly growing, firm and tender, 1–2 cm tumor was needled within 1–2 weeks after discovery.

Cytomorphology. The characteristic and repetitive features were high cellularity, mixture of cell clusters and dispersed cells in a myxoid background matrix. Proliferating fibroblast-like cells with ovoid nuclei and pale cytoplasm were mixed with large, cytoplasm-rich uni- or binucleated ganglion cell like cells. In spite of the marked variation in cell size and shape, and prominent nucleoli the chromatin texture was even and the nuclear/cytoplasmic ratio low. Mitoses were present and an admixture with inflammatory cells was comrnon.

Follow-up. All 37 not surgically removed lesions either decreased considerably in size or disappeared completely, usually within 1–2 months after needling.

Conclusion. NF can be diagnosed by FNA. Spontaneous regression is common.

Planning of resection surgery for primary tumors of the spine

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We have set up a system to plan surgical procedures in the spine according to the Enneking criteria of oncological staging. In the transverse plane, the vertebra is divided into 12 radiating zones and into 5 layers. The longitudinal extent of the tumor is recorded. This system should help to standardize the surgical procedures and to evaluate the results according to a computerized system. We have identitied three possibilities to perform an en-bloc resection in the thoraco-lumbar spine:

Vertebrectomy (marginal/wide resection of the vertebral body). A resection of the vertebral body can be perfomed if the tumor is included in the zones 4 to 8 or 9 to 5, that means centrally located, and one pedicle at least is free from tumor. For performing an en bloc resection, a posterior and anterior approach is used in the same operation.

Hemivertebrectomy (marginal/wide excentrical resection of the vertebra). When the tumor occupies the zones 2-5 (or 11- 8), that means arises excentrically from the body, the pedicle or the transverse process, a resection even at more than one level can be performed. This resection can include if necessary one or more ribs and is performed by a single stage procedure allowing a bilateral view on the lateral aspect of the thoraco-lumbar vertebra.

Marqinal/wide resection of the posterior arch. When the tumor is located between the zones 10-3, an en bloc resection can be performed by a posterior approach.

Tumor size as an important prognostic factor in osteosarcoma

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Initial two plain conventional radiograms of 128 study patients (COSS-80 through COSS-86) were retrospectively analysed for 3 tumor diameters as well as extensions of a soft tissue component (n 120). In a subset of 27 patients the measured values were compared to values obtained by CT-scan and a good correlation (0.69) was found. Metastases free survival (MFS) analyses were performed univariately and multivariately with one, two, and three dimensions of the tumor as absolute or relative measures (tumor length, area, and volume referred to bone length respectively to body surface area). Univariate analyses of MFS revealed a high prognostic significance of all absolute measures except the maximum extension of the soft tissue component. Relative measures at best showed comparable predictive values. Cox regression analysis on 84 patients indicated a high prognostic significance of the absolute tumor volume (ATV) and the histologic response, whereas age, sex and site did not show an independent prognostic influence. None of the patients with an

ATV $\leq 70cm^3$ and only 4/53 with an ATV $\leq 150cm^3$ relapsed while in patients with an ATV $> 150cm^3$ the relapse rate was 40–60% irrespective of further increase in volume. Initial tumor size is an important and easily obtainable prognostic factor in osteosarcoma and may serve as a basis for risk adapted therapy. It is best represented by the absolute three-dimensional measure (ATV).

Chordoma of the mobile spine—review of 21 cases

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We analyzed retrospectively 21 cases of chordoma arising in the mobile spine. 10 patients died because of tumor (1–135 months after treatment), 4 patients are alive with disease and only 7 patients are free from tumor at the final follow-up

(24–96 months after treatment). Conventional radiation therapy combined with palliative or debulking surgery in 15 cases lead to 12 recurrences. Intralesional surgery alone had no effect (2 recurrences in 2 cases after 18–41 months). Resection of the lesion, sometimes combined with radiation therapy as an adjuvant, gave the best results (4 patients disease-free at 24–96 months) and is the treatment of choice, even if late recurrence may occur.

Reconstruction of the upper femur with a vascularised cervico-cephalic segment

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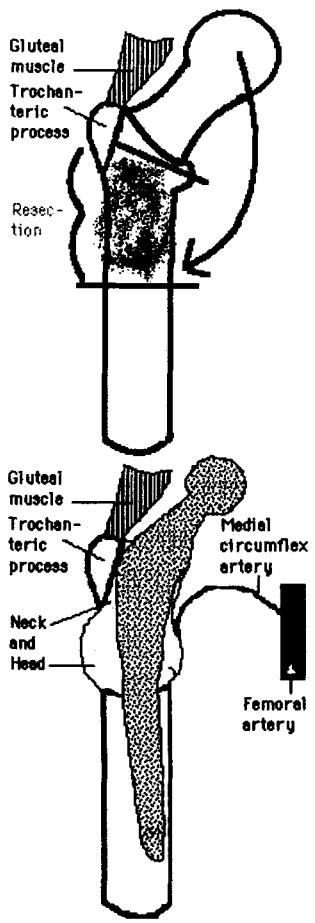
After resection of a femoral upper shaft bone tumor, located below the trochanteric area, we have preserved the cervicocephalic portion and used it as a vascularized bone graft in 3 patients with encouraging results after mean 14 months.



The graft can easily measure 10–12 cm. Its connection to the medial circumflex artery is preserved. The vascular pedicle is long enough to allow the graft to rotate 180°. The purpose of this technique is to facilitate union of the trochanter with its gluteal muscles insertions to improve the stability of a total hip replacement. The consolidation takes the same time as in a classic trochanterotomy.

Quality of life in children after treatment of osteosarcoma and Ewing sarcoma

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We used a modified reintegration to normal life (RNL) test to examine three areas important for reintegration after treatment of bone sarcomas: mobility, coping with the activities of daily living, and psychosocial factors (self-image). 16 girls and 13 boys were examined; their average age at control examination was 16 years. Treatment was completed in 21 patients, while the remaining 8 patients were still under therapy. The average follow-up was 7 years.

Our findings indicated that the degree of reintegration is highly dependent upon the stage of the disease, i.e., the children who have completed their therapy were reintegrated to a much greater extent. A high correlation was found between the 3 reintegration areas. A lower degree of reintegration was accompanied by higher degree of depression and greater emotional disturbances following the onset of the disease. Also, a great number of introverted children were found in the group of poorly reintegrated ones. The total RNL score, especially that referring to the social and psychological self index, showed a relatively satisfactory assessment of life quality. Completion of orthopedic treatment, no matter how radical, may even in objectively extremely severe conditions result in good quality of life.

Is limb salvage surgery cost effective?

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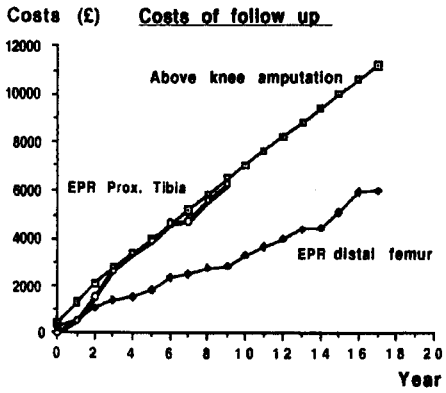
Most studies to date comparing limb salvage surgery for primary bone tumours with amputation have shown that limb salvage does not compromise the patient's survival and that there is surprisingly little difference in measurable quality of life between the two. If this is the case then cost effectiveness may dictate which is preferable!

Method. The costs of providing and servicing an artificial limb have been compared over a 20 year period with the costs of limb salvage surgery using an endoprosthesis. The survival and failure rates of both techniques have been taken into account and the additional costs of failure have been included.

Conclusion. Limb salvage surgery of the distal femur is cheaper than amputation, but there is no appreciable difference between the costs of amputation and replacement of the proximal tibia. The high failure rate of proximal tibial replacement increases the costs compared with replacement of the distal femur. The lower the rate of failure of limb salvage the more cost effective the method is in comparison with amputation.



Quality of life after Van Nes rotationplasty after tumor resection—a preliminary report

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For this study a questionnaire was developed using a number of international standardized questionnaires measuring quality of life. New items developed for this particular orthopedic subject were also included. 29 patients operated on by tumor resection and reconstruction with a rotationplasty were included. There were 16 men and 13 women with an average age of 24 (17–50) years and a mean follow-up of 6 (1–11) years.

Results. All but one patient wear their prosthesis continuously. 7 also need one or two crutches. All but 2 patients are satisfied by the fit of their prosthesis. 8 patients are more or less unsatisfied by the appearance of their prosthesis. Kneeling and bending is a problem for almost all the patients. 24 patients can ride a bike, 12 needs a shorted cranck. Two thirds are active in different kinds of sport.

Only 4 patients feel unattractive because of their rotationplasty. In starting new intimate relationships, 6 patients feel rather hampered. Of the 18 patients who were sexually active in the four weeks prior to completion of the questionnaire, 10 patients reported that the rotationplasty affected their sex life adversely. In all areas of quality of life men and women were equally affected. The overall quality of life was rated as rather good to excellent by 27 patients.

Phase II study of carboplatin (CB) and etoposide (V P16) in pretreated disseminated osteosarcoma (OS)

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Carboplatin and etoposide are known as effective agents of minor toxicity in many malignancies. Their efficacy against osteosarcoma (OS) however remains to be defined. From 5/88 through 5/93, 22 OS patients with measurable pulmonary metastatic disease were treated with CB and VP16 each at a dose of 300 mg/m2 on two successive days as an infusion over one hour. Further courses were repeated after 3 weeks. 2 patients had extrapulmonary dissemination in addition. Complete resection was possible in 12 patients, 6 had incomplete resection of metastatic disease and another 4 presented with multiple inoperable pulmonary metastases. All were preatreated with regimens of the cooperative osteosarcoma study group (COSS) including doxorubicin, methotrexate, ifosfamid and cisplatin. 16 patients received CB/ VP16 at first, 3 at second, 1 at third an 2 at the forth relapse. Treatment results were evaluated by follow-up radiographs, CT scans and histologic examination of resected specimens.

Results. 8 patients had complete/ partial/ objective response (CR/PR: >50% tumor reduction; OR: >90% tumor cell necrosis), 7 had stable disease and 7 had progressive disease. The median relapse free interval after CB/VP16 with or without thoracotomy was 10+ month (7–26+) in good responders (CR,PR,OR), 11 months (4–27+) in patients with stable disease, and 0 month (0–17) in poor responders.

The 3-year survival rate from initial pulmonary relapse in 18 patients treated with CB/VPl6 and thoracotomy is 0.6 (12/18) compared to 0.24 in a control group of 57 patients treated with different schedules and thoracotomy after relapse (COSS-80 through -86 studies). Carboplatin and etoposide appear to be a promising two-drug combination for treatment of OS.

Osteosarcoma recurrences in children previously treated with intensive chemotherapy

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Between January 1981 and June 1993, 137 children and adolescents were treated for an initially non-metastatic osteosarcoma of the extremities according to a slightly modified T10 protocol. 42 cases had tumor relapse after median 21 months. The site of the first relapse was limited to the lung in 20 patients, the skeleton in 7 patients, confined to soft tissue in 1 patient, and was a local recurrence in 6 patients. In 8 patients the first recurrence affected multiple sites. Subsequent recurrences often involved unusual or multiple sites. Management of relapses included surgery and/or various regimen of second line chemotherapy and in 1 case, high-dose chemotherapy followed by autologous bone marrow transplantation. Overall survival and event- free survival are respectively 36% and 27% at 3 years. At present, 13 patients are alive without evidence of disease.

Neither response of the primary tumor to the preoperative chemotherapy, nor the time between the diagnosis and the first recurrence, nor the number of metastatic lesions correlated with survival. Survival is better in patients with a local or a pulmonary first recurrence. The most important prognostic indicator seems to be the possibility of complete resection of all sites of recurrence. A limited number of patients achieved a durable remission after 2 or more recurrences. The potential benefit of more aggressive treatments should be investigated in this high risk population.

Local recurrence in soft tissue sarcomas. 5-year experience of the Helsinki University Soft Tissue Sarcoma Group

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We established a soft tissue sarcoma group in 1987. Adequate therapy was defined as wide or compartmental surgery alone or marginal surgery plus postoperative radiotherapy (RT).

Patients and methods. 143 patients with primary non-cutaneous soft tissue sarcomas of the trunk wall (30) or extremities (113) have been referred for consultation (18) or therapy (125). 38 were referred virgin or after fine needle aspiration biopsy. 56 tumors were subcutaneous, 7 intramuscular, and 79 either deep, extramuscular or subcutaneous with involvement of the deep fascia. 11 had metastases at diagnosis. 91 tumors were of malignancy grades 3 or 4. 52 tumors were < 5 cm, 29 > 10 cm.131 patients were primary referred, stage MO, and were treated. The median follow-up is > 2 years.

Results. 9 amputations were performed.

Surgical margin	Local recurrence/ no. patients	Local recurrence/ no. receiving RT
Intralesional	3/9	3/9
Marginal	10/58	4/31
Wide or compartmental	5/54	1/2

Thus 9 local recurrences developed in 85 patients with either adequate surgery alone or marginal surgery plus RT. 11 of the 26 local recurrences were salvaged and had no evidence of local disease at last follow-up.

Conclusions. Our results are better than those previously published from Finland with local recurrences in 32–44% of the patients.

Local recurrence (LR) in high grade osteosarcoma (OS) of the extremities treated with neoadjuvant chemotherapy and resection

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We analyzed the incidence of local recurrences in patients with osteosarcoma of the extremities treated with neoadjuvant chemotherapy and limb salvage (LS) especially to assess if the type of chemotherapy has an influence on the rate of LR.

Material and methods. 3 neoadjuvant chemotherapy protocols for OS successively activated at the Rizzoli Institute from 1983 to 1991 were studied. Of 369 patients, 311 had LS; 69 were excluded (4 died of toxicity, 9 were secondarily amputated for infection, 56 died of metastatic disease within 36 months without evidence of LR).

Results. 15 of the 242 patients had LR. 2 patients were alive with no evidence of disease and 3 patients were alive with disease. At univariate analysis LR was not related to sex, age, site, grade of tumor, histologic subtype, pathologic fracture, or tumor volume but was related to surgical margins, histologic response, and protocol of chemotherapy.

Cox regression analysis showed that only surgical margins and the protocol of chemotherapy had an independent influence on the rate of LR.

Prognosis after locally recurrent soft tissue sarcoma

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Allogeneic grafts for bone tumors—radiologic evaluation of 8 patients after 16–23 years

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The extent of creeping substitution with replacement of a bone graft matrix by a new revascularized trabecular network is not well known. We performed plain films, quantitative computed tomography (QCT) and low-field (0.1 T) magnetic resonance imaging (MRI) with contrast enhancement to assess the viability of allogeneic bone grafts 16-23 years after surgery. 6 patients had massive osteoarticular grafts of the distal femur, 1 of the proximal tibia and 1 had an intercalary graft of the tibia because of aggressive and malignant bone tumors. At the follow-up the mean age of the patients was 48 (35–59) years.

Results. In all patients plain films showed an excellent fusion with both periosteal and primary bone formation. QCT showed that the cortical bone mineral density (BMD) of the grafts was lower (p 0.05) than in the hosts. There was no significant difference in BMD between graft and host. 5 patients underwent MRI. The proximal parts (39% of graft length) of the 4 femoral grafts showed homogenous signal intensity (SI), which was isointense to that of the host. The tibial intercalary graft had also homogenous SI at both ends (40% of graft length). The tibial interaction and one distal femoral graft showed slight uniform contrast enhancement throughout the graft. In another distal femoral graft with a total knee prosthesis there was contrast enchancement from the femoral component 4.5 cm proximally. In 2 distal femoral grafts there was no contrast enhancement.

Conclusion. Our findings indicate that revascularization varies considerably and may be complete.