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Genomic changes in bone and soft tissue tumors

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In all extensively studied tumor types acquired chromosomal aberrations have been demonstrated. Some of these are characteristic for certain tumor types and may be of importance in diagnosis and prognostication. More than 70% of 150 solitary lipomas investigated have chromosome abnormalities. Three cytogenetic subgroups may be distinguished: changes involving chromosome segment 12q13-15, supernumerary ring chromosomes, and other structural changes. Rings are primarily found in atypical lipomas/well differentiated liposarcomas. The aberration t(12;16)(q13;p11) is a consistent change in myxoid liposarcomas. Malignant fibrous histiocytomas (MFH) of low malignancy grade may have ring chromosomes as the sole anomaly, whereas high malignant MFH often have multiple chromosome changes, with chromosome bands 11p11 and 19p13 most frequently involved. Other consistent aberrations are t(2;13) (q35-37;q14) in alveolar rhabdomyosarcoma and t (X;18) (p11;q11) in synovial sarcoma. More than 100 Ewing's sarcomas have been investigated, and t(11;22) (q24;q12) is a consistent aberration, which is also found in Askin tumor, peripheral neuroepithelioma, and esthesioneuroblastoma. Osteosarcomas frequently have extremely complex changes with no particular recurring aberration identified. Chondrosarcomas seem to be cytogenetically heterogeneous; recurring changes, seen in 2–4 tumors have been del (5) (q13), t(9;22), and loss of chromosomes 6 and 22. A comparative cytogenetic and DNA flow cytometric study of 118 benign and malignant bone and soft tissue sarcomas showed a good correspondence between the two methods concerning quantitative genomic changes. Highly malignant synovial sarcomas and Ewing's sarcomas have in some cases t(X;18) and t(11;22) as the sole anomaly, resulting in tumor cells with a diploid chromosome number, which can easily be detected by cytogenetic but not by cytometric analysis. Using both methods genomic changes could be demonstrated in 50% of the benign and in 86% of the malignant tumors. Cytogenetic studies may also provide a biological explanation for the findings of skewed and bimodal DNA histograms with peaks close to each other.

Evaluation of osteonectin as a marker of the osteoblastic lineage in bone tumors

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Osteonectin, a bone matrix non-collagenous 32 Kd glycoprotein, has been indicated as a marker of the osteoblastic lineage. We have investigated the in vitro expression of osteonectin in bone tumors to evaluate its possible diagnostic and prognostic use. The intracellular expression of osteonectin was evaluated by immuno-fluorescence and immunocytochemistry in primary cell cultures from bone tumors (6 osteosarcomas, 3 osteoblastomas, 3 giant cell tumors, 1 chondrosarcoma, and 1 chondroblastoma), as well as in 2 established cell lines of osteosarcomas (U2-OS and Saos-2), 1 cell line of Ewing's sarcoma (LAP-35), and 2 cell lines of normal human fibroblasts (HSF and SCF). A rabbit anti-bovine osteonectin polyclonal antibody (BON-II), kindly supplied by Dr. L. W. Fisher from the Bone Research Branch, N. I. H., Bethesda MD, was used. Osteonectin was variably expressed in all the specimens without a clear relation with the cell type. A typical perinuclear punctate pattern was constantly present. Electron microscopy showed that osteonectin was diffusely present in the cytoplasm without any binding to the fibrillar component. Osteonectin expression was also investigated by Northern blot using the 800 bp Hind III - Bam HI insert of p2-4 containing cDNA osteonectin sequences probe. Primary cultures from 2 osteosarcomas, 1 osteoblastoma, and 1 giant cell tumor as well as the LAP-35 and the SCF cell lines were analyzed. Osteonectin transcripts were variably present in all the samples, showing no relation with the cell type. Our results indicate that osteonectin may be expressed in vitro by cells with different phenotypes. The positivity found by immunostaining cannot

be attributed to a non-specific binding of the antibody; in fact, the mRNA coded by the osteonectin gene was detected in all the cell types. Osteonectin does not appear to be a good differentiation marker of the osteoblastic lineage.

In vivo localization of HBA 71 monoclonal antibody in Ewing's sarcoma

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The human cell surface antigen defined by the monoclonal antibody (mAb) HBA 71 is a marker of Ewing's sarcoma that distinguishes this tumor antigen from other small round cell tumors of childhood and adolescence. Immunohistochemical studies in over 40 normal human frozen tissues have shown that the HBA 71 antigen expression is sufficiently restricted to investigate the HBA 71 antibody as a candidate for in vivo radioimmunolocalization in Ewing's sarcoma. Most importantly, the HBA 71 antigen is not expressed on epithelial components of important organs such as lung, kidney or liver. The targeting potentials of mAb HBA 71 were tested in balb/c athymic nude mice xenografted with the human Ewing's sarcoma cell line 6647. After radiolabelling with iodine using the chloramine T method mAb HBA 71 retained its immunoreactivity. An irrelevant radiolabelled IgG antibody was used as negative control. The human colon cancer cell line SW1116 served as HBA 71 antigen negative xenograft. External gamma camera imaging as well as organ distribution and autoradiography studies were performed. The HBA 71 antibody showed selective tumor uptake in Ewing's sarcoma xenografts. Tumor to non-tumor ratios of 2.5–20: 1 (normalized for tissue weight) were obtained. In comparison to other tissues and SW1116 xenografts up to 10% of the injected dose of mAb HBA 71/g/tissue localized in the Ewing's sarcoma xenografts. These data suggest the HBA 71 antigen as a useful target antigen for imaging and adoptive immunotherapy in Ewing's sarcoma.

Relationship between DNA content and histology of musculoskeletal tumors

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All 177 benign bone and soft tissue tumors so far analyzed have been found to be diploid. Among 334 malignant tumors diploidy has been demonstrated in 31% and aneuploidy in 69%. The most important conclusion from these observations is that aneuploidy precludes benignity.

In malignant tumors we have found a clear relationship between ploidy and histologic grade. The vast majority of low grade lesions are diploid. With increasing histologic malignancy grade, the proportion of aneuploid tumors becomes higher. Hence, only 10% of Grade I lesions were aneuploid as compared to 91% of Grade IV lesions.

There is also a relationship between histologic type and DNA content. For example, in chondrosarcoma we found that 62% were diploid. The high incidence of diploidy in this entity may explain why the majority are low grade. In contrast to chondrosarcoma, the vast majority of osteosarcomas appear to be aneuploid. Among the 111 classical osteosarcomas that we have analyzed 96% were aneuploid. Therefore, we consider aneuploidy a typical feature of osteosarcoma which we utilize in the differential diagnosis. Analogously, there is a high incidence of aneuploidy in malignant fibrous histiocytoma, which mostly are high grade. However, there are exceptions to the rule that high grade tumors are aneuploid. In Ewing sarcoma and synovial sarcoma, both highly malignant entities, the lesions are commonly diploid. Hence, it is important to analyze each tumor entity separately to assess the relationship between histology and DNA content.

Oncogene structural changes are unfrequent in malignant bone tumors

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The genomic organization of four oncogenes—i. e., c-myc, c-myb, c-Ha-ras and V-fms—was investigated in fresh surgical specimens from 22 patients with malignant bone tumors; 9 chondrosarcomas, 9 osteosarcomas, 2 Ewing's sarcomas, 1 chordoma and 1 lymphoma. 18 were primary lesions and 4 local recurrencies. 4 to 6-fold amplification without rearrangement of the c-myc proto-oncogene was the sole abnormality in 5 tumors (2 chondrosarcomas, 2 osteosarcomas and 1 lymphoma). All myc-amplified tumors were primary lesions. DNA hybridizations with c-myb, c-Ha-ras and v-fms probes showed no gene structural abnormalities. Point mutations at the 12th codon of the H-ras gene was investigated by PCR and no alterations were detected. Two of the myc-amplified tumors were diploid and the remaining 3 aneuploid, according to flow DNA cytometry. In this limited series, there was no relationship between c-myc amplification and histologic subtype, malignancy grade, surgical stage or ploidy level. Our study shows that amplification of the c-myc presumed to be involved in the development of malignancy in a variety of solid tumors, is encountered in occasional malignant bone tumors without any relationship to other well known histopathological features. However, it appears that new subtypes of bone tumors can be identified by oncogene characterization, the clinical significance of which remains to be established.

Characterisation of cartilagenous tumours using monoclonal antibodies to proteoglycan epitopes

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Cartilage tumours encompass a spectrum of behaviour from benign to high grade malignancy. Attempts to predict clinical behaviour have employed conventional histological grading and flow cytometry to estimate nuclear DNA. Little attention has been given to qualitative changes in the extracellular matrix as a further possible indicator of biological behaviour.

Proteoglycans are a major component of all connective tissues, but are particularly abundant in cartilage where they occur intracellularily, on cell surfaces and at very high concentrations within extracellular matrices. They consist of a central protein core to which carbohydrate (chondroitin sulphate and keratan sulphate) chains are covalently attached. Consequently they show enormous diversity with respect of composition and structure.

Polyclonal and monoclonal antibodies have been used to localise substructures of these macromolecules within a range of tumours, including chondrosarcoma (CS), dedifferentiated CS, periosteal CS, chordoid CS and chordoma. Antibodies to various protein epitopes and to keratan sulphate showed a significant correlation with the grade of chondrosarcoma. Cartilage related epitopes were also present in the extracellular matrix of tumours that had no histological evidence of cartilage matrix. Monoclonal antibodies that recognise novel epitopes (sulphation patterns) on native chondroitin sulphate chains, gave particularly interesting results. These epitopes have recently been shown to be uniquely expressed during normal tissue development and in tissue responses associated with pathology (eg. arthrosis). It has also been postulated that they may bind metabolic growth factors and thus regulate growth and development, and tissue remodelling. Their distribution in cartilage tumours illustrates the diversity of structure and molecular organisation of proteoglycans (i) at the different sites within any one specimen (ii) between tumours of the same class and (iii) between different tumours.

Morphometric analysis of cartilagenous tumors

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Histologically verified chondromas, "proliferating chondromas" and chondrosarcomas of long and short tubular bones were investigated with quantitative histopathologic methods. We measured the most important morphologic characteristics for the grading of these tumors: the relative volume density of nuclei, the number of binucleated and multinucleated cells per 50 fields and the nuclear area. The morphometric measurements were performed with a coherent quadratic test grid at a magnification of 400 times and an interactive image analysis system ASM Leitz Wetzlar. Our findings lead us to the following conclusions: Separation of histopathologic classes of cartilagenous tumors is not possible by the number of binucleated cells alone. Volume density measurements of nuclei enable a more precise grading of chondromas and chondrosarcomas with regard to localisation. The relative volume density of nuclei of long tubular bone and trunk chondrosarcomas and the relative volume density of nuclei of short bone chondromas overlap considerably.

Distinction between enchondromas and well differentiated chondrosarcomas on the base of quantitatives measurements

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57 conventional chondrosarcomas and 124 enchondromas were reviewed to check the significance of different morphologic features including the cellular DNA-content for the diagnosis. We used undecalcified sections for the morphological examination and Feulgen-staining for DNA-measurement using an automatic image analysing system. All enchondromas were diploid but all well-differentiated chondrosarcomas showed a small number of hypertetraploid cells. Other morphologic features were uninformative.

Nuclear DNA-content, nuclear features, and growth behavior are suitable for grading of conventional chondrosarcomas. Using morphologic features 49% of all investigated chondrosarcomas were classified as grade 1, 47% as grade 2 ,and 4% as grade 3. There was a correlation between the number of hypertetraploid cells and morphologic grading.

Our study demonstrates the significance of morphologic features and DNA-measurements to distinguish between enchondromas and distinct differentiated conventional chondrosarcomas.

Light and electron-microscopic examination of fine-needle aspirates in the preoperative diagnosis of cartilaginous tumors

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30 patients with chondrogenic tumors—2 chondroblastomas, 4 chondromas, 20 chondrosarcomas, 1 clear-cell chondrosarcoma, and 3 mesenchymal chondrosarcomas—underwent preoperative fine-needle aspiration biopsy (FNAB). The cytologic features in smears were compared with the histopathologic findings in the surgical specimens and in 16 cases also with the light and electron-microscopic findings in resin embedded fine-needle aspirates. The smears of the vast majority of the classical chondrosarcomas presented features which enabled the FNAB diagnosis of a chondrogenic tumor to be made. In low-grade chondrosarcomas, which were poorly or moderately cellular in smears and showed chondroblastic cells often in lacunary structures of hyaline matrix, consideration of the clinical presentation, size, location and radiographic appearance was essential for the diagnosis of a chondrosarcoma. The high-grade chondrosarcomas presented cytologic features which clearly indicated their malignancy and they usually had a myxoid matrix. The resin-embedding technique for the light- and electron-microscopic examination of FNAB, and the histochemical analysis for the demonstration of sulphated glucosaminoglycans and the immunocytochemistry applied to smears were found to be of value in the definite diagnosis and especially in the distinction of chondrogenic tumors from chordoma and metastatic mucous-producing carcinoma which may at times be considered in the differential diagnosis.

Dedifferentiated chondrosarcoma—evaluation of 20 cases

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Dedifferentiated chondrosarcoma (DCS) is characterized by the combination of a common chondrosarcoma, mostly of high or moderate differentiation and a highly malignant dedifferentiated tumor tissue with other forms of differentiation, as osteosarcomatous, fibrosarcomatous, rhabdomyosarcomatous, or as a malignant fibrous histiocytoma.

We reviewed the 22 cases of DCS found in the files of the Swiss Bone Tumor Registry. The sex distribution was even, the mean age was 54(14–90) years. With two exceptions, the rib and first metacarpal, all tumors were located in the femur and the pelvis. In 9 cases, a two step "dedifferentiation" was observed, with calcified enchondroma, chondrosarcoma and anaplastic tumor parts side by side. In 13 cases a chondrosarcoma of high or moderate differentation was found, with dedifferentiated parts. In 14 cases there was dedifferentiation to osteosarcoma, in 9 to malignant fibrous histiocytoma, and in 3 cases to fibrosarcoma. In 6 cases, autopsy showed metastases in several organs, with a distribution pattern resembling carcinoma. In particular, in 4 cases lymph node metastases were found. Treatment—surgery, chemotherapy or radiotherapy—had no influence on the poor outcoume with a mean survival of 11 months.

In agreement with the literature, we think that the development of a chondrosarcoma from an enchondroma is caused by activation of a new cell clone, and that dedifferentiation is caused by activation of a primitive multipotent malignant stem-cell.

Growth patterns in chondrosarcoma

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We evaluated the growth patterns in central chondrosarcoma and their relationship to local recurrences and distant metastases. Three types of growth were distinguished: "pushing", "multinodular", and "infiltrative". The first one (usually observed in low grade tumors) is histologically seen as a compact front pushing against the trabecular or the cortical bone forcing it "to retreat from the tumor". In the second (usually observed in high grade tumors involving the medullary canal) the tumor seeps through the bony trabeculae along the medullary canal or in the epiphysis, forming typical "satellite nodules". In the third, the tumor, which is generally of a higher histologic grade, seldom allows a cortical reaction; it infiltrates Havers' canals destroying the bone, and rapidly reaches the periosteum. According to these findings we have redefined the MSTS anatomical classification of the tumor extension:

Stage 0: The tumor is confined by the cortex or by a rim of reactive bone. It may penetrate into the haversian system, but does not touch the periosteum; no natural barrier is overcrossed by the tumor.

Stage 1: The tumor penetrates into the periosteum without bypassing it; the tumor overcrosses one barrier, the cortex.

Stage 2: The tumor extends into a defined structure or compartment: muscle, ligament, periarticular (tumor covered by synovium), intraarticular (tumor within joint and not covered by synovium), adjacent bone, or space (e. g. popliteal fossa); the tumor overcrosses two barriers, the cortex and the periosteum.

Stage 3: The tumor extends into 2 or more structures or spaces.

According to these criteria, 34 cases of chondrosarcoma (22 cases not previously treated and 12 presenting as local

recurrences) were evaluated. The follow-up was median 20 (1–65) months. Four local recurrences and 3 metastases were seen. The four local recurrences appeared only in Stage 3 cases and with an "infiltrative" growth pattern. Histology was grade 2 in three cases (with a marginal but contaminated margin in 2 cases and wide in the third; in one case the patient came to observation with a local recurrence). The fourth recurrence appeared in a Stage 3 previously untreated case after wide but contaminated surgery. The three cases with metastases were also Stage 3 with an "infiltrative" growth pattern. They were all previously untreated cases, surgery had been wide in 2 and radical in the third. Histology was grade 2 in the first two and grade 3 in the third. For this type of slow growing neoplasia, our follow-up is not sufficient, and therefore the oncologic results must be considerated preliminary.

Malignant transformation of osteochondromas in MCE probably is a continuous process from the primarily benign lesions into low grade malignancies with local proliferative potential and a rather low potential for distant metastases. Since most patients with chondrosarcomas in MCE are young adult, repeated bone surveys and scans at fixed intervals can hardly be recommended throughout life. In a patient with MCE who develop a chondrosarcoma it is difficult to recommend radical surgery when other lesions must have the same potential to develop into malignancy. In the patient with "quiet" lesions we recommend a bone scan when growth is finished as base line documentation and clinical examinations at 1 to 3- year intervals. If symptoms develop (increase in size, pain etc.) bone scans are repeated and then additional imaging is chosen as appropriate (radiography, CT, MRI). To define the extent of surgery needed seems to us most difficult.

Giant chondromas

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Giant chondromas are observed not only within the pelvis but sometimes in such bones as ribs or fingers. Their insidious growth allows unusual enlargement, since functional loss ensues slowly and pain may be absent. I have observed 6 such tumors approaching a size between 18 cm in a thumb tumor and 50 cm in a thigh tumor. The tumors grew up to 40 years, without metastasizing.

Malignant transformation in hereditary multiple cartilaginous exostoses

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The reported incidences of malignant change in inherited (autosomal dominant) multiple cartilaginous exostoses (MCE) vary between 10 and 20 %. The question remains open, how to handle check-ups in patients with MCE and how to treat lesions suspected of malignant transformation.

During the last 20 years, 45 patients with MCE have been seen at our hospital many of whom have been followed until today. In 3 patients (aged 20 to 30 years) resections of proliferative lesions (2 scapula, 1 femur) have been performed, that histologically were classified as chondrosarcomas grade I–II. There has been a local recurrence of the femoral lesion shortly after the first marginal excision. Review of the literature dealing with chondrosarcomatous lesions in MCE revealed that only a few cases with proven metastases have been seen.

Enchondroma and low-grade chondrosarcoma—a clinical follow-up

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We assessed recurrence rate after surgical treatment of enchondroma and low-grade chondrosarcoma. 90 patients with a follow-up period of more than 2 years were available for analysis. There were 24 patients with enchondroma and 66 with Grade I–II chondrosarcoma. The mean age was approximately equal for the two groups, 43 and 47 years, respectively. Enchondroma was predominant in women (3:1) whereas chondrosarcoma was more common in men (2: 1). At presentation, 5 patients had a pathologic fracture, all with chondrosarcoma. The enchondromas were predominantly located to the femur and humerus and chondrosarcomas were most often found in the femur, the pelvis, and the humerus. The tumor volume was higher in chondrosarcomas compared to enchondromas, mean 380 and 20 cm^3. The surgical stage (Enneking) for the enchondromas was B1–B2 and the chondrosarcomas were uniformly distributed between IA and IB. Two patients had lung metastasis at presentation. Patients with enchondroma were subjected to open biopsy or treated with curettage with or without autograft or bone cement. No local recurrences were encountered during a follow-up period of 6 (2–14) years.

Among the 66 chondrosarcomas, 11 Grade I lesions were treated with curettage only. Among these patients, two had local recurrence, one of whom later developed lung metastasis. The remaining 55 patients with chondrosarcoma were subjected to local excision in 49 cases and amputation in 6. Intralesional or marginal margin was achieved in 34 cases and wide or radical margin in 15. During a follow-up period of 9 (2–23) years, 12 patients developed local recurrence and 8 lung metastasis, 5 having both local recurrence and metastasis. Large tumor size, histologic Grade II as

compared to Grade I, and intralesional or marginal surgical margin were correlated to local recurrence whereas only large tumor size and histologic Grade II were correlated to metastasis.

Secondary peripheral chondrosarcoma of bone-long term follow-up cases

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We evaluated the clinical, radiographic and histologic features of secondary peripheral chondrosarcoma of bone in relation to the surgical treatment and long term follow-up (more than 10 years). The tumors were rare, about 15% of usual chondrosarcoma. In a study of 56 patients, 41 patients had a single exostosis and 15 had multiple exostoses. More males (37: 19) than females were affected, ranging in age from 14 to 69 years. The tumors involved various bones but the pelvis, sacrum and proximal femur were involved in more than 50% of the cases. Radiographically malignant changes were: fuzzy and irregular margins of the cartilaginous thick cap and irregular large lucent zones. Microscopically the criteria we used were the same as in central chondrosarcoma. Grade (G) 1 was the most differentiated with slightly more cellularity than osteochondroma, few double cells, and minimal cellular atypia. G 2 showed enlarged hyperchromatic nuclei with different dimensions, frequent double nucleated cells. G 3 had pronounced cellularity, oval to spindling nuclei with marked pleomorphism. 39 tumors (70%) were G 1 and 17 G 2. Grade 3 was present in 2 cases at the time of recurrence. In 61% of G 1 tumors the first treatment was intralesional or marginal (inadequate) and local recurrence occurred in 54% of the patients: lung metastases along with progression of histologic grade occurred in 25% of these patients. In inadequately treated G 2 tumors (53%), local recurrence occurred in 78% and lung metastases in 44% of the patients. Patients with secondary peripheral chondrosarcoma remain at risk of recurrence several years after treatment; in fact 3 patients had a recurrence more than 9 years after first treatment. One important difficult problem is: histologic diagnosis of G 1 tumors may be difficult, so malignant changes in a peripheral cartilaginous lesion have to be confirmed with strict radiographic criteria. One has to avoid underestimating G 1 lesions and diagnosing them incorrectly as osteochondroma.

Chondrosarcoma—a review of patients treated by the Birmingham Bone Tumour Treatment Service

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Between 1963 and 1989, 125 patients with chondrosarcoma were treated by the Bone Tumour Treatment Service in Birmingham. The mean age was 45 (10–79) years and the sex ratio was M/ F ; 1.14/ 1. Tumour location was: femur 51 (proximal 35, distal 16), pelvis 35, humerus 20 (proximal 18, distal 2), tibia 9 (proximal 8, distal 1), scapula 7, and ulna, fibula and hand one each. Resection of the tumours with endoprosthetic replacement was carried out in 73 patients, amputation in 22, excision with or without bone grafting in 27 and curettage of the lesions in 3. Of the tumours that were histologically graded, 45% were grade I, 28% were grade II and 6% were grade III lesions. Mesenchymal, dedifferentiated and clear cell chondrosarcomas accounted for 5 %, 6 % and 2 % of the total numbers, respectively. Local recurrence occurred in 20% of patients and was related to tumour grade (occurring in 16% of grade I and 40% of grade III tumours), site (being most common with tumours of the humerus), and the adequacy of the surgical margin—9% when margins were wide or radical and 31% when marginal or intralesional.

Chondrosarcoma:The Rizzoli Institute experience

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Until 1984 we diagnosed 388 chondrosarcomas (CS): 204 central, 112 peripheral, 12 periosteal, 6 mesenchymal, 8 clear cell and 46 dedifferentiated tumors. 61% were in men. It was most common in the third and fourth decades of life. The most common sites were the pelvis (24%), the proximal femur (23%), the distal femur (12%) and the proximal humerus (12%). In 74% of the cases the tumor was stage I, in 24% stage II and in 2% stage III. 357 cases all surgically treated had a long term follow-up. 276 patients (77%) had conservative surgery, the remaining 23% had an amputation. Surgical margins were adequate (radical or wide) in 51% and inadequate (marginal or intralesional) in the remaining 49%. There were 107 local recurrences: 55 (31%) in central CS, 36 (32%) in peripheral CS, 1 (8%) in periosteal CS and 15 (36%) in dedifferentiated CS. The local recurrence rate was 12 % after adequate and 48% after inadequate surgery. 100 patients with a minimum follow-up of 36 months developed lung metastases.

Chondrosarcoma—grading, surgical staging, treatment, and prognosis

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From the files of the Netherlands Committee on Bone Tumors 230 cases of classic chondrosarcoma were analysed (1960–1975). Histologic grade was related to the prognosis: 10-year-survival was in grade I 75%, in grade II 56%, and in grade III 30%. Local recurrence after surgery influenced mortality: in the recurrence free group grade I 0%, grade II 10%, grade III 50%, in the group with recurrence, grade I 50%, grade II 70%, grade III 90%. Wide and radical operations (recurrence rates 5% and 3%, respectively) can be considered adequate procedures. Intralesional and marginal operations are inadequate (recurrence rates 63% and 54%, respectively). After adequate surgery 10-year-survival was higher (wide 89%, radical 84%) than after inadequate treatment (intralesional 44%, marginal 59%). After wide or radical surgery the prognosis is good and is dependent solely on whether metastasis occurs, which in turn is dependent on the histologic grade of the lesion.

A practical surgical staging of osteosarcoma

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Neoadjuvant chemotherapy has changed the surgical management of osteosarcoma, by shrinking the tumour allowing marginal excision to suffice in many cases. The incidence of local recurrence remains a problem however following limb salvage, at around 10%. A system of surgical staging is proposed with categorises tumours by two prognostic factors. The risk of local recurrence can then be estimated and appropriate steps taken to reduce that risk.

1) Tumour progression. In a recently completed trial of neo-adjuvant chemotherapy (MRC/EORTC 80831), the strongest predictor of survival was preoperative response to neo-adjuvant chemotherapy. Of those who progressed radiologically during their neo-adjuvant courses 73% were dead in 3 years, while of those who showed no progression, or actual regression only 28% had died. Stage or "resectability" at presentation was a poor predictor of outcome.

2) Local infiltration. Of 10 local recurrences in 128 consecutive osteosarcomata, tumour had penetrated periosteum in all cases. This was detectable on imaging.

We suggest that these are two major factors contributing to local outcome in osteosarcoma which can be used when planning treatment to optimise local control: "P", progression during chemotherapy monitored by radiographs or SPET. "L", local extraperiosteal extension shown by radiographs or CTscan. Osteosarcoma may thus be locally staged for decision of treatment:

Stage P0 L0 : Marginal excision. Stage P0 L1 : Wide excision or prophylactic DXT. Stage P1 L0 : Early surgery and prophylactic DXT. Stage P1 L1 : Early amputation.

Surgical margins in primary bone tumors

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Enneking's Surgical Staging System has been used for an analysis of 71 primary malignant bone tumors, which had been operated personally. All patients who were resected or amputated for grade II tumors, which purposely or inadvertantly turned out intralesional (2) or marginal (11), eventually died from their disease, 9 after local recurrences. 41 surgical procedures with wide margins were followed by 2 local recurrences, 1 in a malignant fibrous histiocytoma of a humerus and 1 in an osteosarcoma of the lower femur, which proved to be a skip lesion. There were no local recurrences in 17 tumors with radical margins. The study has now been updated with 50 new cases demonstrating that wide margins are essential—and sufficient—for the treatment of primary malignant bone tumors. Marginal margins should not be planned, even in combination with chemotherapy.

Complete and high sacrum amputations

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Involvement of the first sacral body has been considered a limitation for operability of primary sacral chordomas and teratomas. In a case presenting with a large chordoma of the upper third of the sacrum the involved bone was completely removed. The body of S1 was piecemeal curetted including monolateral resection of the right sacral wing and sacro-iliac articulation, the inferior plate and bilateral laminectomy of L5. The dura mater was opened at the level of L5 infiltrated by chordoma, and the cauda was resected at this level, saving the S2 root on the left and only S1 on the right. After one month of bedrest the patient could walk without canes but suffered from urinary retention and anal incontinence. Since 1948 we have performed 21 resections of the sacrum for primary sacral tumors, 16 chordomas and 5 teratomas, mostly in the recent years, 17 after 1977. The level of sacrum amputation was S3 in four cases, S2 in 9, S1 in three, L5 in one and not evaluable in four. Surgical margins have been reclassified according to the recent criteria and no operation

can be considered adequate. For chordoma 9 were marginal (6 recurred) and 7 intralesional (all recurred). The latency of local relapse was often long; the actuarial overall recurrence free rate at three years was 82% and 73% at five years. The five operations for teratomas were performed after 1984, four marginal (one recurred) and one intralesional, four patients are living free of disease. In these young patients prognosis depends also on chemotherapy. The technique of recent sacrum resection is the posterior approach, the abdomino posterior combination was employed two times.

Pelvic resection—the Rizzoli Institute experience

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Between 1970 and 1989, 106 pelvic resections for bone tumors were done at the Rizzoli Institute. There were 59 chondrosarcoma, 13 osteosarcoma, 17 Ewing's sarcoma, 5 malignant fibrous histiocytoma, 3 fibrosarcoma, 1 angiosarcoma, 2 GCT, 3 osteoblastoma, and 3 ABC. The surgical stage was: stage 3, 8 cases; IA, 2 cases; IB, 37 cases, IIA, 5 cases; IIB, 54 cases. 39 patients had resection of the iliac wing; 47 patients periacetabular resection, while 20 patients had resection of the anterior arch. No reconstruction was performed after resection of the anterior arch and in 30 patients with resection of the iliac wing. 9 patients, after iliac wing resection, had a graft to restore the pelvic ring continuity. After periacetabular resections, 19 patients had ileofemoral coaptation with metallic wires, 6 patients had an ischiofemoral arthrodesis with screws, 19 patients an ileofemoral arthrodesis (10 of which with an intercalary allograft), while 3 had prosthetic replacement. The resection was judged wide in 49, wide but contaminated in 21, marginal in 27, and intralesional in 9. Twenty six local recurrences were found: 6 after adequate (wide) surgery (12%), 20 after inadequate (contaminated, marginal or intralesional) surgery (35%). The local recurrence rate was 15% in low grade tumors, 33% in high grade tumors (23% in osteosarcoma, 35% in Ewing's sarcoma, 40% in chondrosarcoma). 25 patients developed metastasis. At follow up 62% of patients were disease free. The disease free rate was 100% in patients operated for benign tumor, 82% operated for low grade tumor, and 41% for high grade tumor (60% chondrosarcoma, 39% osteosarcoma, 30% Ewing's sarcoma). Wound healing problems were observed in 20 patients, infection in 12 patients while mechanical complications ocurred in 15.

Wide resections of the sacroiliac joint

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Primary bone tumors may directly involve the sacroiliac joint or secondarily from the iliac or from the sacral bone. Adjuvant treatment is rarely effective, so surgery remains the main therapy. Wide resection of the sacroiliac joint is difficult due to its location and the proximity of vessels and nerves. Preoperative planning by CT and MRI is necessary.

Since 1982 through 1988, we operated on 12 patients with primary bone tumors involving the sacroiliac joint The average age was 25 (14–50) years, 6 were men. The tumors were principally chondrosarcoma (3), osteosarcoma (3), Ewing sarcoma (2) and giant cells tumor (2). The mean follow-up is 3 (2–6) years. In all cases, the joint was removed, the bone sections on the iliac or the sacral side were depending on the extension of the tumour. The margins were wide in 5 cases, marginal in 3 cases, wide but contaminated in 2 cases, and intralesional in 2 cases. Post-operative complications were frequent: primarily infection with posterior skin necrosis, secondarily impaired bone healing and neurologic problems. Three patients had local recurrence and 2 of these died. Two other patients died, 1 of metastatic disease (Ewing sarcoma), and 1 of intercurrent problem without relation to the tumour (chondrosarcoma).

Local resections of the pelvic ring for malignant bone tumours

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Historically the treatment of bulk malignant disease of the bony pelvis has been by either hindquarter amputation or radiotherapy. The function of the former is extremely poor and the success ratio of the latter is small. The development of CT scanning and MRI has allowed techniques of local resection and reconstruction within the pelvic ring with good function and a low local recurrence rate. Our results with surgery performed since 1978 are reported.

Hindquarter amputation or radiotherapy are reserved for tumours which have a large soft tissue component, or involve the sciatic nerve or iliac vessels. Generally, lesions arising in the pubis and ischium are treated by

local resection alone without major reconstruction. The extent of the resection can be up to the inferior third of the acetabulum without compromise to the stability of the hip. Secondary arthrodesis of the sacro-iliac joint may be required if pain persists. Where the acetabulum is resected, three basic methods of reconstruction have been used. Firstly a hanging hip procedure was used which achieved excellent cosmesis but poor gait. At best the patient required a stick to ambulate. More recently either a saddle prothesis has been placed in the greater sciatic notch or one stage pel-

vic replacement has been performed anchoring the pelvis only into the residual ilium.

Resection of the ilium has been used increasingly in the management of Ewings sarcoma, often following failure of primary radiotherapy to control the disease. Reconstruction following resection using strut fibular grafts has been the method of choice providing there is a residual roof to the acetabulum. Where the acetabulum has been resected, there has been no alternative but to perform a hanging hip procedure.

Sacral resections which do not involve the body of S1 have required no form of bony reconstruction, although patients may suffer a sphincter disturbance by ablation of the S2/3 and 4 nerve roots. Although the body of S1 has been removed, reconstruction has been acheived using both autogenous graft and allograft which is initially protected by spinal instrumentation anchored into the lower lumbar pedicles and the blades of the ilium.

Hip joint transposition after complete resection of the ilium

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One possible reconstruction after complete resection of the iliac bone is a pubo-femoral arthrodesis. Without reconstruction of the pelvic ring the lower pelvis rotates under strain into the symphysis and tilts in front of the sacrum. To achieve a standing position extreme tilting of the pelvis and sacrum is necessary with subsequent development of a severe scoliosis. The development of scoliosis is further reinforced by muscle imbalance. Following a total resection of the iliac bone the femoral head should be placed as closed as possible to the sacrum. When the osteotomy is done through the middle part of the acetabulum—in the growing child directly under the triradiate cartilage, half of the acetabulum can be preserved. After osteotomy of the pubic ramus and the ischium the rest of the acetabulum with the hip joint can be transposed and fused to the lateral sacrum. A mobile hip joint remains which supports itself directly on the sacrum and the back and stomach muscles can be reattached to the cranially placed soft tissue. We now have experience with this new surgical procedure in ten patients, eight have had an Ewing's sarcoma and two have had an osteosarcoma of the iliac bone. Four patients have a follow-up time of more than two years. Full weight bearing is possible about six months after the operation. The range of motion in the transposed hip joint is 90 degrees flexion, full extension, 20 degrees ab- and adduction, 30 degrees rotation. In standing position with compensated leg length discrepancy the spine is perpendicular with no scoliosis. Up until now, there are no signs of early degenerative changes in the transposed hip joint.

Closure of the pelvic ring by rotation of the proximal femur

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Tumor resections of the ileum leave the pelvic ring open. Closure by means of metallic implants and hip endoprotheses has a high risk of late loosening, after extensive resections it is difficult to fix implants to the remaining parts of pelvis and sacrum. Free transferred autogenous bone undergoes resorption. An alternative is rotation of the proximal femur as a local musculoosseus flap, vascularised by the pectineus muscle. A 40-year-old woman had undergone internal pelvic resection (total resection of the ileum, subtotal acetabulum, lateral mass of the sacrum with the hip abductors and gluteal muscles disrupted) for osteosarcoma two years ago. She had no evidence of disease at the time of operation. A computed three dimensional model of the remaining bone stock was created. The pelvic ring was closed by 180 degree rotation of the proximal femur about the pectineus muscle. Proximally the vascularised femur was fixed to the first sacral vertebral body, distally to the remaining acetabular rim. A specially designed cementless hip endoprothesis was interposed between both parts of the femoral shaft.

Subcutaneous soft tissue sarcoma—a population-based epidemiologic and prognostic study of 129 patients

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All 129 patients with a subcutaneous sarcoma diagnosed from 1964 through 1985 were culled from a population-based sarcoma series in southern Sweden. They constituted one third of all soft tissue sarcomas of the extremities and trunk wall. The annual incidence was 0.4 / 100 000. The median age was 57 years and men predominated (1.3/1). The median tumor size was 4.3 centimeters. The lower extremity was the most common location and malignant fibrous histiocytoma was the most common histotype. None of the low-grade and 7% of the high-grade tumors recurred locally after local surgery with a wide margin without radiotherapy. The cumulative 5-year survival rate was 0.8. Multivariate analysis identified only high malignancy grade and tumor size larger than 5 centimeters as independent prognostic factors. Localization, histotype, type of surgical margin, and local recurrence did not independently influence survival. One third of the patients had large and high-grade tumors and had a five-year survival rate of 0.7, compared to 0.9 in the other patients. Adjuvant therapy is generally not indicated for subcutaneous sarcoma because of the

good prognosis after wide excision, both as regards local recurrence and distant metastases. This characteristic motivates that subcutaneous sarcomas should be separately classified in reports on treatment results of soft tissue sarcoma.

Malignant fibrous histiocytoma of soft tissue—a population-based epidemiologic and prognostic study of 137 patients

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Epidemiology and prognosis were analyzed in a consecutive, population-based series of 137 patients with malignant fibrous histiocytoma of soft tissue in the extremities and trunk wall, with a complete follow-up of minimum three years. All but one patient were treated by surgery, in 28 cases combined with adjuvant radio- or chemotherapy. The annual incidence was 0.42/100 000. The ratio men to women was 1.1/1. The median age was 64 (22–87) years. The thigh was the most common location. The median size was 6 (1–20) centimeters. Superficial tumors constituted 43%, and were smaller than deep-seated tumors 83 tumors were storiform-pleomorphic, 53 were myxoid, and one was of inflammatory type. The myxoid tumors were smaller and more often superficial. The cumulative 5-year survival rate for all patients was 0.7, but differed markedly between the histologic types; it was 1.0 in patients with myxoid tumors, and 0.5 in patients with storiform-pleomorphic tumors. In the 77 patients with storiform-pleomorphic tumors without metastases at presentation, the following factors were multivariately analyzed for influence on survival: age, sex, location, size, depth, compartmentalization, histologic malignancy grade, tumor necrosis, intravascular invasion, type of surgery, and local recurrence. Only tumor size larger than 10 centimeters and tumor necrosis independently impaired survival. The 23 patients who had none of these risk factors had a 5-year survival rate of 0.8.

Prognosis in high-grade soft tissue sarcomas—the Scandinavian Sarcoma Group Experience

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From 1981 to 1986, 240 patients with primary, malignancy grade III or IV soft-tissue sarcomas were entered into a randomized adjuvant chemotherapy multicenter trial, conducted by the Scandinavian Sarcoma Group. Chemotherapy (single drug doxorubicin) did not improve the metastasis-free survival. After a median follow-up time of 46 (2–97) months, a multivariate analysis of risk factors for metastases was performed in 148 radically operated on patients with tumors of the extremities and trunk. Histologic malignancy grade IV, DNA aneuploidy, vascular invasion, tumor size >10 cm, and male sex were identified as independent prognostic risk factors. Patients with no or one risk factor had a 5-year metastasis-free survival (MFS) of 79%, with two risk factors 65%, with three risk factors 43%, and with four and five risk factors 0%. One half (78/148) of the patients had 3 factors or less and had a MFS over 60%. The combination of different risk factors seems to give a useful prognostic model for soft tissue sarcomas, which could be of value to select high risk patients for further trials with adjunctive therapy.

Prognostic factors in adult soft tissue sarcoma—a multivariate analysis in 140 patients

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We conducted a retrospective prognostic analysis of soft tissue sarcoma patients with surgery as first line treatment. From 1975 to 1988, 380 patients have were referred: 41 with metastatic disease, 123 with local recurrence, and 217 with a nonmetastatic and previously untreated primary tumour. In the latter group, 77 patients received chemotherapy. The 140 remaining patients were selected for this study. Their mean age was 50 years. Tumor location was: extremities(80), trunk (24), retroperitoneum or pelvis (22), head and neck (14). 40 tumours were superficial and 99 deep-seated. The mean tumour size was 8.2 cm. The most fre quent histologic types were MFH (34), liposarcoma (22), leiomyosarcoma (19), undifferentiated sarcoma (16) and synovial sarcoma (13). Two grading systems were used: French system (G1: 30, G2: 67, G3: 43) and EORTC system (G1: 24, G2: 96, G3: 20). Patients were staged using a classification close to the AJC/UICC and the Hajdu's system.

Surgical treatment was local excision in 66 patients, a wide local resection in 69, and amputation in 5. The resection was inadequate in 18 patients. Post operative radiotherapy was given to 112 patients. The median follow-up was 5 years.

A multivariate analysis revealed that grade and tumour depth were significant predictors of metastasis free survival. Grade, tumor depth, and invasion of neurovascular structures or bone were significant factors for survival.

These results allowed classification of patients into 3 prognostic groups: a group with a favourable prognosis including patients with grade 1 tumours or superficial grade 2 tumours (5-year survival rate: 98 %), a group with an

intermediate prognosis including patients with deep grade 2 tumours or superficial grade 3 tumours (5-year survival rate: 62%) and a group with the worst prognosis including deep grade 3 tumours and tumours with invasion of neurovascular structures or bone (5-year survival rate: 33%).

Local recurrence is of minor importance for metastases in soft tissue sarcoma

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We analyzed whether local recurrence of soft tissue sarcoma causes metastases in a population-based series of 375 patients. Of the 128 patients who developed metastases, 63 had local recurrence and 65 had not. At presentation, these two subgroups of patients with metastases had a similar distribution of clinicopathologic factors—age, sex, tumour size, localization, depth, histologic type, and malignancy-grade. Furthermore, the time course for development of metastases was the same in both groups. These similarities between the groups indicate that local recurrence was of minor importance for development of metastases. However, local recurrence occurred in half of the patients that developed metastases compared to one fifth in those who did not, whereas operations with a marginal margin were only 1.4 times more common in patients with metastases. This 2.5-fold difference in local recurrence rate was thus mainly another expression of the aggressiveness of the primary tumour: highly malignant tumours combine a potential both for local and distant spread.

Flow DNA cytometry of fine needle aspirates of soft tissue tumours

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We investigated the representativeness of fine needle biopsy in soft tissue neoplasia. The DNA content of multiple aspirates from each lesion was determined for comparison and then related to the DNA content of the surgical specimen. The series included 26 cases with soft tissue tumours treated surgically. Histopathologic analysis and flow DNA cytometry were based on specimens obtained at definitive surgery. 5 tumours were benign and 21 malignant. All malignant lesions, except one liposarcoma, were high grade (III–IV). Cell material for flow DNA analysis was procured from both the surgical specimen and the fine needle aspirates of each tumours. Tumours with a tetraploid (DI 2.0) peak comprising more than 15 % of the analyzed cells were considered tetraploid. The modal DNA value of the aneuploid tumours was defined by the most prominent aneuploid peak.

One tumour had to be excluded because of insufficient cellular yield. DNA analysis of the surgical specimens disclosed that the 4 benign tumours and the singe low grade tumour were diploid. Among the high grade lesions 7 were diploid, 5 tetraploid, and 8 aneuploid. Out of a total of 113 aspirates conclusive DNA histograms were obtained in 112. According to the classification of the histograms as diploid, tetraploid, or aneuploid there was complete agreement, i.e., homogeneity in 22 cases. However, in 2 of these cases, in spite of all 10 aspirates being aneuploid the modal DNA values differed within the same lesion. In another 2 cases, consistently displaying a diploid-tetraploid distribution, there was a discrepancy in the sense that 4 aspirates were diploid and 6 were tetraploid. In only one case was there a significant inconsistency: 2 aspirates were diploid and 3 aneuploid.

Comparison of DNA data from the surgical specimen and the fine needle aspirates of each tumour disclosed complete agreement in 19 cases. Apart from the five cases described above, there was an additional case, where the surgical specimen was diploid and the 3 aspirates aneuploid.

Conclusions:

1. Fine needle aspiration biopsies in general provide adequate cell material for flow DNA analysis

2. The representativeness of a single diploid aspirate can not be relied upon. However, a single aspirate displaying aneuploidy invalidates other aspirates from the same tumour showing diploidy.

3. A combined approach employing cytologic assessment and DNA analysis of fine needle aspirates can expect to obviate the need of surgical biopsy in most cases of soft tissue tumours.

DNA content in the prognostication of soft tissue sarcomas

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In a prospective study of soft tissue sarcoma the prognostic significance of DNA content and clinicopathologic features was analyzed. The study was based on 99 patients treated by surgery. Postoperatively 25 patients received local radiation and 9 adjuvant Adriamycin. There were 21 low (I–II) Grade and 78 (III–IV) Grade tumors. Based on DNA flow cytometry 36 lesions were diploid (normal DNA content) and 63 aneuploid (abnormal DNA content).

The 3-year metasasis free survival rate for all 99 patients was 0.60. The survival rate was 0.75 for low grade tumors and 0.56 for high grade. However, ploidy level was prog-

nostically more discriminative; the survival rate was 0.80 for patients with diploid tumors and 0.47 for those with aneuploid. Multivariate Cox regression analysis identified three independent risk factors for metastasis: increasing tumor size, aneuploid DNA content, and male sex. Unexpectedly, high malignancy grade (III–IV) was not found to be an independent risk factor for metastasis in the multivariate analysis.

Our study shows that metastatic disease in soft tissue sarcoma is closely related to aneuploidy. A prognostication model based on DNA content, tumor size, and patient sex was found to discriminate between patients with a good and poor prognosis after surgical treatment only. The approach proposed may prove to be useful for identifying patients, who should be excluded from adjuvant chemotherapy.

Dedifferentiated chondrosarcoma—high value of neoadjuvant chemotherapy

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Dedifferentiation is an infrequent, often misdiagnosed, and serious complication of chondrosarcoma. Most authors consider radical surgery the best treatment.The aim of this study is to precise the place of adjuvant therapy.

From 1979 through1989 we followed or treated 19 dedifferentiated chondrosarcomas in ilium (8), femur (9), tibia (1), and calcaneus (1). There were 10 females and 9 males. Average age was 56 (28–82) years. Two patients were seen before biopsy, 2 immediately after biopsy, 5 after inadequate surgery, 3 with local relapse, 5 with metastases. The interval between the first clinical symptom and histologic diagnosis was long, average 19 months as primarily false diagnoses were common: metastatic disease (3), exostosis (2). or enchondroma (2). This lead to inadequate surgery in 7 patients. In 3 cases metastasis were initially recognized (2 lung metastases, 1 bone metastasis). In the 15 other patients, first treatment was only surgery in 3, surgery followed by chemotherapy in 9 (plus local radiotherapy in cases of conservative surgery), short neoadjuvant chemotherapy (1 month) by high dose methotrexate followed by conservative surgery without radiotherapy in 4. Average follow-up was 3.5 years.

Three amputated patients died from metastases. Following conservative surgery, local relapse appeared each time that local treatment was not perfect (with or without radiotherapy) . The patients with metastases at the first examination died on average after one month . The patients treated by surgery alone died from metastases after average 2 months. 7/9 patients treated by radical surgery or conservative surgery and adjuvant chemotherapy died in 8 months. The 4 patients treated by neoadjuvant chemotherapy are alive and free of disease after an average follow-up of 20 months.

We conclude that neoadjuvant chemotherapy for dedifferentiated chondrosarcoma increases survival and permits local conservative surgery.

Malignant fibrous histiocytoma of bone: Combined chemotherapy and surgery

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Since January 1986, we have treated 7 patients with MFH of bone, all women; average age 28 (17–64) years. The patients had not received any previous therapy; they had no metastases; the tumors were located to long bones with extension to soft tissue except in one case. Preoperative chemotherapy included high or low-dose methotrexate (HDMTX or LDMTX), intraarterial or intravenous cisplatinum (CDDP) + vincristine, for 2 cycles. Postoperative chemotherapy including adriamycin (ADM) alternated with MTX + CDDP for 7 cycles was employed in cases with 90% tumor necrosis; in cases with less necrosis, ADM was alternated with BCD (bleomycin + cyclophosphamide + actinomicin D) for 7 cycles.

Limb-sparing surgery with wide surgical margins was done in all cases.

5 patients had 90 % tumor necrosis, 2 had100 %. Function (Enneking) is excellent in 2 cases, good in 4, and fair in 1 case. All 7 patients are disease-free at average follow-up of 26 (10–46) months. Toxicity was low, without major complications from HDMTX or from intraarterial chemotherapy.

Chemotherapy with drugs effective in osteosarcoma and conservative surgery seems justified in MFH of bone.

Assessment of chemosensitivity in osteosarcoma

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Current treatment of osteosarcoma includes multiple agent chemotherapy as an adjunct to surgery. The histologic response to preoperative chemotherapy is considered a reliable indicator of tumor sensitivity. Accurate prediction of drug sensitivity at the time of histologic diagnosis may improve the treatment of osteosarcoma.

Several methods have been developed in vitro to evaluate drug effects on tumor cells. In nonclonogenic assays cell viability following exposure to the drugs is assessed by

Trypan-blue (dead cells) staining. Short-term antimetabolic assays are also available to evaluate the interference of drugs on nucleic acid metabolism. Stem cell assays in semi-solid media have been developed to evaluate drug influence on plating efficiency of a tumor cell population. The reliability of these assays to predict drug sensitivity is about 65%, whereas their ability to predict resistance is over 90%.

More recently, a method has been developed to detect cell capability to bind Adriamycin as an index of drug sensitivity. Tumor cells obtained are incubated with Adriamycin (ADR) and stained with fluorescein diacetate. Fluorescence intensity of ADR binding may be measured by a photo multiplier connected to the microscope, and three categories of cells may be differentiated: viable cells with intense nuclear ADR fluorescence (sensitive); viable cells with ADR equally weakly fluorescent both in the nucleus and the cytoplasm (resistant); dead cells, with intense ADR fluorescence both in the nucleus and the cytoplasm. The occurrence of drug resistance is related to a cell membrane protein (P-glycoprotein), acting to decrease the intracellular levels of drugs as a drug-efflux pump. Monoclonal antibodies have been developed to glycoprotein and the expression of this protein is evaluable by immunocytochemistry or immunofluorescence as a useful control for chemosensititivy tests.

Dose-intensity and prognosis in neoadjuvant chemotherapy for osteosarcoma—a retrospective analysis

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The relationship between dose-intensity and outcome was retrospectively analyzed in 125 patients with osteosarcoma of the extremities treated at our institution with neoadjuvant chemotherapy between 1986 and 1988. Before surgery, chemotherapy was performed with high dose methotrexate (HDMTX) i.v. followed by cisplatinum i.a. and Adriamycin (ADM) i.v., while postoperative chemotherapy was tailored according to the necrosis achieved by preoperative treatment. The good responders (90% or more necrosis) had 21 weeks treatment with the same drugs used preoperatively, while the poor responders (< 90% necrosis) received a longer treatment (30 weeks) in which, in addition to the HDMTX, CDP and ADM also Ifosfamide and VP-16 were used. At a median follow up of 2.5(1.5–3.5) years , 100 patients (80%) remained continuously disease-free and 25 patients relapsed (24 with lung metastases and 1 with local recurrence). According to the dose-intensity received, calculated as percentage of the dose-intensity projected by the protocol, the percentage of continuously disease-free survival was 87% in the 82 patients who received 80% or more of the scheduled dose-intensity and only 65% for the 43 patients who received less than 80% of the projected dose-intensity ($P < 0.001$).

These preliminary results suggest that in neoadjuvant chemotherapy of osteosarcoma dose-intensity is a determinant of treatment outcome.Therefore, all efforts should be taken to avoid dose-reductions and delays of cycles of chemotherapy.

Neoadjuvant treatment of osteosarcoma: Prognostic factors

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From April 1982 to December 1989, 43 patients with pathology proven, previously untreated osteosarcoma, were treated preoperatively with intraarterial CDDP 40 mg/m^2, and adriamycin 20 mg/m^2 iv, q o d times 3, every 3 weeks for 3 cycles. Resection of the involved and adjacent healthy bone was performed subsequently and a prosthesis was implanted. Treatment was continued thereafter for 12 months with a modified T-10 proto col (Rosen G. Cancer Treat Rep 1982;66:1687). There were 16 males and 27 females, mean age 16 years. Tumor location was femur 30, tibia 9, humerus 2, fibula 1, and scapula 1. 35 patients had localized disease and 8 had pulmonary metastases at the time of diagnosis. Karnofsky index (KI) was <70 % in 38 patients and > 70% in 5 patients. 27 tumors were osteoblastic, 9 chondroblastic, 5 fibroblastic, and 2 telangiectatic. At the time of this report 35 patients are alive and free of disease for a mean follow-up of 29 months. Four patients had local progression, 3 have been amputated. Eight patients died, 6 with metastatic lung disease, and 2 from toxicity and sepsis without evidence of disease. The worst prognostic factor was chondroblastic subtype ($P < 0.001$). Other negative prognostic factors were: KI < 70%, ($P < 0.01$), metastases at the time of diagnosis ($P < 0.05$), tumor necrosis < 90% ($P < 0.03$).

Efficacy of two-route chemotherapy using cisplatin and its antidote, sodium thiosulfate for regionally confined malignancy

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Although local administration of anticancer drugs for regionally confined malignancy is often superior to systemic administration, the amount of dose given is limited as there are side effects once the drug enters the systemic circulation. We designed a combination chemotherapy

termed " two-route chemotherapy (TRC) " in which a large amount of an anticancer drug is injected locally at the tumor site in combination with the antidote given systemically, the objective being to diminish the side effects caused by the anticancer drug. We mainly used Cisplatin and Sodium Thiosulfate (STS) as antidote. In most of the cases, STS had to be given simultaneously with Cisplatin to offer protection against Cisplatin toxicity. Other investigators reported that Angiotensin II (AT-II) induced-hypertension chemotherapy selectively enhances delivery of an anticancer drug to the tumor site and transiently decreases renal blood flow as a result of an increase in the renal vascular resistance. We improved TRC—using Cisplatin and STS—by combining it with the AT-II induced-hypertension method. Here STS is systemically given over a 5-min period immediately after the local intra-arterial infusion of a mixture of Cisplatin and AT-II. Consequently, an enhanced therapeutic effect was obtained.

Heart function in survivors after chemotherapy for osteosarcoma

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With modern treatment leading to long term freedom from tumor in up to 70% of osteosarcoma patients, late effects of chemotherapy are of increasing importance. Doxorubicin (DOX) cardiomyopathy (CMY)—a potentially life threatening disease—is of major concern. However, while many papers address the assessment of cardiac function during doxorubicin treatment, data after therapy remains scanty. Therefore, we studied cardiac function in patients who had been treated with different DOX containing regimens according to the Cooperative Osteosarcoma Study (COSS) protocols.

First, we reviewed the study charts of 785 patients from 63 parti cipating institutions and, at a mean cumulative dose of 300 ±111 mg/m^2, found clinically apparent congestive heart failure (CHF) in 17 (2.2%, five fatal). Second, the extent of late subclinical heart damage was studied in detail in 29 tumor-free survivors more than one year after osteosarcoma treatment. A detailed history and physical examination for signs of overt heart disease were obtained. M-mode echocardiography (ECHO, 29 cases) with evaluation of the fractional shortening rate (FS) as well as diastolic parameters and radionuclide ventriculography (RNV, 18 cases) with determination of the systolic ejection fraction (EF) were used to screen for subclinical cardiac disease. We found impaired cardiac function leading to subnormal FS in 6/29 (21%), pathological EF values were found in 8/18 (44%). Abnormal function was documented in cases whith cumulative DOX doses as low as 360 mg/m^2 (ECH0)/240 mg/m^2 (RNV). However, the frequency and severity of clinical and subclinical heart damage increased with cumulative DOX: At over 300 mg/m^2, 11/355 patients (3 %) developed CHF, 6/22 FS and 7/14 EF were pathological. Time since cessation of anthracycline treatment was another risk factor.

Impaired heart function occurs in a large portion of patients after doxorubin therapy for osteosarcoma. High cumulative dose and long time since treatment are associated with pathological findings. Cases of cardiomyopathy may be missed if echocardiographic assessment of the FS rate is the only method used to describe cardiac status.

Local growth and prognosis of osteosarcomas of the distal femur and proximal tibia

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Macrosections, microsections, macrophoto's and radiographs of 217 highly malignant osteosarcomas of the distal femur (137) and the proximal tibia (80) were investigated regarding their local extension and the relation to prognosis. Six Types of local tumor extension were defined (Stage IIA Type O and Stage IIB Types I-V). Clinical, radiological, histological and surgical parameters were compared. The clinical and radiological aspect revealed no differences as compared to the local extension. Histologically, osteoblastic osteosarcomas were diagnosed in more advanced types (IV and V). For both locations there was a significant correlation between local tumor extension and prognosis. Between each type however, there was no difference in disease-free survival between femur- or tibia osteosarcomas. On the other hand, the distribution of types was significant different (tibia more types 0–III, femur more types IV–V) between both locations. This phenomen could explain the difference in disease-free survival between these two. Comparison of osteosarcoma patients without chemotherapy showed them to have significantly poorer disease-free survival rates in the types III–V. After chemotherapy, types 0–III had high disease-free survival rates (> 5 years: > 70%) independent from the kind of chemotherapy. For type IV, there was a significant difference in recurrence between patients with or without chemotherapy. In type V, there was no difference in recurrence between those who did or did not recieved chemotherapy. We also found that Stage III osteosarcomas of the distal femur or proximal tibia (additional 18 cases) occurred in patients belonging to type V, sometimes to type IV, but never in type 0–III. This is the first report about a direct correlation between local growth and prognosis of high-grade osteosarcomas.

Embolisation of aneurysmal bone cysts—indications and results

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Aneurysmal bone cysts are recorded in the Bone Tumor Register of the Semmelweis Medical School in Budapest. The surgical treatment is as a rule curettage and bone grafting or en bloc resection. In some cases, however, superselective embolisation of the cyst is indicated:

1) at certain anatomical locations which is unreachable for curettage (pelvis),
2) in cases of hypervascularized cysts to avoid dangerous bleeding,
3) to save articular function when the subchondral bone is destroyed.

In five cases (3 pelvis, 1 sacrum, and 1 vertebral body) of primary and secondary aneurysmal bone cysts we observed a regression of the vascularity and bone rebuilding of the cyst.