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CHEMOTHERAPY OF BONE TUMORS

Osteosarcoma in the first decade of life

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Osteosarcoma is typically a disease of adolescents and young adults. Only few reports have specifically dealt with younger children. We therefore report the experience of the Cooperative Osteosarcoma Study Group COSS with patients less than 10 years of age at diagnosis.

Patients and methods: Inclusion criteria: participant of a completed neoadjuvant COSS-study 1980–1996. Histologically confirmed osteosarcoma. Age at diagnosis > 10 years. *Scheduled treatment:* (neo)adjuvant chemotherapy (high-dose-methotrexate ± doxorubicin ± cisplatin ± ifosfamide ± BCD) plus surgery.

Results: Overall, 192 patients (102 males, 90 females) were identified, the youngest being 2 years 7 months at diagnosis. 190 patients presented with high-grade central osteosarcoma and 2 with periosteal variants. Primary metastases were detected in 35 (29 distant, 6 skip). Bones involved by the primary were the femur (110), tibia (35), humerus (30), fibula (5), and other extremity sites (7). The axial skeleton (3) or cranium (2) were rarely affected. Tumors measured > 1/3 of the involved bone in 80 of 178 evaluable cases. As for surgery, limb-salvage was only performed in a minority of patients (67), while the majority (110) were treated by ablative surgery including amputation, disarticulation, or rotation plasty (6 no surgery, 10 type not recorded). 91 of 142 tumors analyzed responded well to preoperative chemotherapy. With a median follow-up of 7 years for survivors, actuarial overall and event-free survival at 5 years were 66% and 58% in the group of all 192 patients. Among those 120 who presented with a primary, previously untreated, localized, high-grade central extremity osteosarcoma and started chemotherapy within 3 weeks from biopsy, the corresponding values were 73% and 65%. Here, tumor response to preoperative chemotherapy was the most important prognostic factor.

Conclusion: Tumor distribution, prognostic factors and outcome of very young patients with osteosarcom are similar to those reported for the typical adolescent patient. A higher proportion, however, will have to cope with the loss of a limb.

An analysis of correlation of mtx seric intensity and long term disease free survival in osteosarcoma (OS) in fuction of the infusion length

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In 1986, we described the crucial rôle of the MTX seric peak at the end of the infusion to improve treatment of osteosarcoma. To optimize the response rate, we observed that the MTX seric peak at the end of 6 hour-infusion should be attained 1000 mmol/L, combined with a good "hand on" clinical response. Later, to take into account the intercourse delay and timing, we defined the notion of "seric intensity" (SI) as the sum of seric peaks by time unit in mmol/week.

Material: The accuracy of SI is becoming evident by analyzing the histological response of the tumor and DFS. In our series, in DD1 and DD11 protocols (90 patients, average age 10 (4–45) years, 1986–1995) the tumor response is correlated with MTX SI. Higher SI given, higher response rate. With a short preoperative monodrug induction (4 weekly HD MTX), SI < 25%. If SI > 1000 mmol/L/week GR > 66%. The prognostic value of SI on disease free survival is also evident. Increasing the SI from 425 mmol/L/week to 570 mmol/L/week increases the 10 years overall survival from 69% to 91%. All differences are statistically significant.

Discussion: We must insist on the value of the seric peak established for a 6 hour infusion. When authors use a 4 hours infusion, they must study the corresponding seric peak correlated with the AUC of MTX. In COSS protocols (as in Rosen's protocols), the infusion of MTX is done over 4 hours and a 1000 peak for 4 hours infusion should be between 1400–1600 mmol/L. At the IGR in Villejuif, the methodological bias testing the 1000 mmol/L values for a 4 hour-infusion without considering the intercourse dealy and including a too small number of patients explains the failure to find a statistical correlation between seric peak and DFS. On the opposite, in the Rizzoli Institute, data available on 382 patients, showed than when the MTX peak at the end of the 6

hour-infusion was below 700 mmol/L the DFS was 56% compared to 77% for higher levels (p>0.001). The difference remains significant also using the limit of 1000 mmol/L (67% versus 80%) (p=0.02 (Picci and al., Oslo 1998). These data confirm the high necessity to adjust individually the dose of MTX, to analyze not only the seric peak but the area under the concentration time curve and the seric intensity to take into account the length of the infusion (4 versus 6 hours) and the delay between the courses of MTX (seric intensity).

Conclusion: HDMTX remains the best drug correlated with DFS pharmacokinetics guidance helps to choose the optimal dose for a particular patient. Nevertheless, no one must forget that even with a pharmacokinetic guidance, the tumoral and patient variability compels doctors to examine the patient and tumor before every infusion and increase the dose if the response is uncertain, following the old Rosen's advise.

Nonmetastatic Ewing's sarcoma/PNET (ES/PNET)—preliminary results of a protocol with ifosfamide since the induction phase added to vincristine, doxorubicin, actinomycin d, cyclophosphamide and etoposide

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From October 1991 to December 1997, 148 patients (median age 17 (3–36) years) with nonmetastatic ES/PNET were treated according to a chemotherapy protocol (IOR-REN 3/AIEOP-SE91) with an induction phase consisting of 2 courses of vincristine (VC), doxorubicin (AD) and cyclophosphamide (CP), alternating with one course of VC, actinomycin D (AC), and ifosfamide (IF). Tumor was locally treated with surgery (S); hyperfractionated radiation therapy (RT) was added to S in case of inadequate surgical margins. When surgical resection was not feasible, RT alone was used for the local control of disease. In the maintenance phase, patients were given 3 cours of VC, AD, CP alternating with 2 coures of VC, AC, IF, followed by 3 cours of IF, etoposide (ET) alternating with 2 courses of VC, AC, CP. Primary sites were: extremity in 93 (63%), pelvis in 26 (17%), other in 29 (20%) 113 (76%) patients were treated with RT alone. In 106 of the 113 patients who underwent surgery, the histologic response to induction chemotherapy was evaluated: a good histologic response (no viable tumor cells or only small foci of tumor cells) was observed in 70 (66%) patients, a poor histologic response was registered in 36 (34%) patients. With a median follow-up of 53 (12–86) months, 111 (75%) patients were continuously free of disease, 35 (24%) patients relapsed. Two patients died of chemotherapy related toxicity. The 5-year EFS and OS are 73% and 80.5%, respectively. A the univariate analysis site of the tumor, type of local treatment, age, serum level of LDH did not significantly affect prognosis. Patients with good histologic response had 5-year EFS 87%, those with poor response 45% ($p < 0.0001$). Patients with PNET had a worse prognosis (5-year EFS 44%) than those with ES (5-year EFS 83%; $p < 0.0006$). Patients with tumors < 100 mL had a better prognosis thant those ≥ 100 mL (5-year EFS 85% vs 65%; $p < 0.03$). In the small group of 13 patients with fever at diagnosis the outcome was very poor: 5-year EFS 31%. At the multivariate analysis the histologic response was the main prognostic factor ($p < 0.0002$) followed by PNET differentiation ($p < 0.002$). The follow-up is relatively short, however, this study seems to confirm the crucial role of the chemotherapy-induced necrosis on the prognosis of ES/PNET and suggests the importance of an early use of VC, CP, AC, AD and IF given since the induction phase, with ET added in the maintenance phase: with this regimen a 5-year EFS more than 70% was achieved and patients with tumor with central location reached the same prognosis of those with extremity location. The poor prognosis achieved in patients with poor histologic response and with PNETs suggests the adoption of more aggressive strategies of treatment in these high risk patients.

Treatment of Ewing tumours (ET)—preliminary report of EICESS 92—concepts of EURO-E.W.I.N.G. 99

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Between July 1992 and April 1998, 631 Ewing tumours patients (pts) were registered in the German office of the European Intergroup Cooperative Ewing's Sarcoma Study (EICESS). 369/631 pts were protocol patients, 275/369 pts (75%) with localised and 88/369 pts (24%) with primary metastatic disease (in 6 pts metastatic status was not available). According to tumour volume and existence of primary metastases pts were divided into two risk groups: SR-pts (localised tumours < 100 mL, n=85) were randomised between VACA (vincristine, adriamycin, cyclophosphamide and d-actinomycin) and VAIA (ifosfamide substituted for cyclophosphamide). Patients with primary metastases or tumour volume ≥ 100 mL (HR-arm, n=284) received either VAIA or EVAIA (VAIA plus additional etoposide). Local therapy consisted of surgery and/or irradiation.

After a median time under study of 37 months (04./998), 258 patients (70%) are in remission. 111 patients (39%) had adverse events: 98 patients had relapse or progress, 10 patients died of disease without relapse and 2 patients died of complications (in 1 patient cause of death was not available). Three-years EFS was 0.65 for localised tumours: 0.72 for

SR-patients and 0.62 for HR-patients. For patients with primary metastases three-years EFS was 0.33.

Based on analyses of EICESS 92 and on other European trial groups, a new treatment protocol for localised and primary metastatic ET-patients was discussed in a European cooperation, consisting of the French, Scandinavian and Swiss bone sarcoma groups and the EORTC in addition to the previous cooperation between the Austrian, British, Dutch and German groups.

EURO-E.W.I.N.G. 99 assigns a common intensified induction therapy for all patients, independent of primary metastases or other risk factors: vincristine 1.5 mg/m^2/d x 1 day, ifosfamide 3.0 g/m^2/d x 3 days, doxorubicin 20 mg/m^2/d x 3 days and etoposide 150/m^2/d x 3 days (VIDE). After 6 courses VIDE patients are divided into 3 risk arms according to histological response and existence of primary spread: patients in R1 (localised tumours, good response (< 10% viable tumour cells after chemotherapy, and previously irradiated patients with tumours < 200 mL, respectively)) are randomised between 8 courses VAC (vincristine 1.5 mg/m^2/d x 1 day, d-actinomycin 0.75 mg/m^2/d x 2 days, cyclophosphamide 1.5 g/m^2/d x 1 day) and VAI (ifosfamide substituted for cyclophosphamide, 3.0 g/m^2/d x 2 days). Patients with primary lung metastases and pts with poor response (> 10% viable tumour cells after chemotherapy, and previously irradiated pts with tumours ≥ 200 mL, respectively) are treated in R2, randomised between 8 courses VAI and 1 course VAI plus additional high dose busulfan (150 mg/m^2/d x 4 days) and melphalan (140 mg/m^2/d x 1 day). In R3 patients with disseminated osseous metastases receive high dose busulfan/melphalan and are open for experimental phase II trials. By participating of several European countries the anticipated number of patients amounts at least 220 per year.

Report of the EMSOS study—osteosarcoma over the age of 40

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Since the 1997 meeting of EMSOS, members have been invited to contribute details about patients with osteosarcoma over the age of 40 to a central registry.

Material: Thus far 298 patients have been contributed from 9 centres between 1968 and 1997. The ages ranged from 40–89 with a mean of 54. 174 were male and 122 female. The most common sites were femur followed by pelvis and tibia and 50 had a secondary osteosarcoma—28 related to Paget's disease and 22 secondary to radiation. 20 patients had "low grade" osteosarcoma, the remainder having high grade tumours of which 54 had metastases at presentation. 149 patients were documented to have received chemotherapy but only 58 were noted to have completed the full course. Surgery consisted of amputation in 68 and limb salvage surgery in 145 with 63 having endoprostheses and 9 having allografts. 123 were felt to have had adequate surgical margins and 59 had close or inadeqaute margins. 55 patients had radiotherapy of which 41 were palliative.

Results: The overall survival rates were 37% at 5 years falling to 27% at 10 years. The 5 and 10 year survival rates for stages 1, 2 and 3 tumours were respectively: 78% and 62%; 41% and 28%; 9% and 9%. Patients over the age of 60 and patients who did not have adequate treatment not surprisingly fared worse, as did all patients with secondary osteosarcoma. The median survival time for patients with Paget's osteosarcoma was 7 months and for radiation sarcoma was 12 months. For patients with stage 2 tumours the eefect of age was such that the 5 year survival rates were 45% for those less than 60 and 28% for those over 60. There was little information about effectiveness of chemotherpy but there was a trend for those with a good response to fare better than those without.

Local recurrence arose in 10% of those having amputations and 27% of those having limb salvage surgery. It was closely related to margins of excision with 34% of those having inadequate margins developing local recurrence compared to 13% of those with adequate margins.

Conclusion: Osteosarcoma over the age of 40 requires just as much care and multidisciplinary working as osteosarcoma in the younger age group. Patients with secondary osteosarcoma have a dismal outlook.

Non-Hodgkin-lymphomas of bone: a long term follow-up

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We present a retrospective study of 18 patients with primary non-Hodgkin-Lymphomas of bone (NHL-B) treated and followed for 6–188 months. 18 patients with NHL-B were identified, histologically reviewed and treated by our institutions from 1982–1998. The NHL-B was located in the thigh 9x, in the pelvis 6x, others included spine, clavicula and humerus. The initial symptoms were pain and palpable tumors, but rarely B-symptoms or hypercalcemia. Osteolytic bone changes were mostly seen, one patient presented with sclerotic changes only, a mixed pattern was identified as well. 11 patients presented solitary lesions confined to one bone, the others had several bony lesions. According to Ann Arbor Classification 10 patients were I E (one extra nodal manifestation) and 8 stage IV disease, 2 were IWF-F, 11IWF-G and 5 IWF-H. After diagnostic biopsy, 17/18 underwent a CHOP-like chemotherapy, followed by involved bone radiation in 13 patients. 2 patients underwent high dose chemotherapy and bone marrow retransfusion due to unfavourable risk factors. Treatment responses included one CR (histologically confirmed) and PR in 9/10 patients assessable because of soft tissue masses adjacent to the bone involved. 2 patients had progressive disease, underwent salvage treatment and died of progressive lung and CNS disease respectively

after 5 and 6 months. 16/18 patients (89%) are alive and free of disease after a median observation time of 82 (33–188) months.

Response assessment is difficult, one patient had a biopsy proven complete remission, 14 patients had remaining bone changes after completion of multimodal treatment that included diminishing osteolytic areas and increasing sclerotic changes. Bone remodelling was observed in sacral, humeral and pelvic NHL-B, it was a slow process and occurred gradually over 4–7 years. In summary we confirm the experience of others, that standard therapy of NHL-B includes chemotherapy and local radiation.

NEOADJUVANT TREATMENTS IN SOFT TISSUE TUMORS

Meta-analysis of adjuvant chemotherapy for localised resectable soft-tissue sarcoma in adults—meta-analysis of updated individual patient data

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Randomised trials of adjuvant chemotherapy for soft tissue sarcoma in adults have been too small (typically including less than 400 randomised patients) to have a realistic expectation of showing, beyond reasonable doubt, a difference in survival. Meta-analyses, based on published trials, have suggested that there may be an advantage for adjuvant chemotherapy. However, this method is unreliable, since it does not include the totality of all patients who have been entered into trials, whether published or not, and does not use updated individual patient data.

The Sarcoma Meta-Analysis Collaboration* has carried out a meta-analysis of all patients (N=1568) appropriately randomised into trials addressing this question and has updated the individual patient data with strictly defined criteria of randomisation, and lack of confounding of the therapeutic question. The hazard ratio for overall recurrence-free survival was 0.75 (95% C.I. 0.64–0.87, p=0.0001), for distant recurrence-free interval 0.70 (0.57–0.85, p=0.0003) and for local recurrence-free interval 0.73 (0.56–0.94, p=0.016).

For overall survival the hazard ratio was 0.89 (0.76-1.03) which was not significant (p=0.12). The meta-analysis provides good evidence that recurrence-free survival is prolonged by doxorubicin based chemotherapy, but inconclusive evidence as to the value of adjuvant chemotherapy on survival. The methodological basis and details of this analysis will be discussed.

Reference: The Lancet 1997) 350, pp 1647-54.

Benefit of adjuvant therapy in soft tissue sarcomas?

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Despite of adequate surgical therapy, adjuvant radiation and/or chemotherapy are widely accepted in the concept of soft tissue sarcomas treatment. For evaluation of a possible benefit of adjuvant therapy 231 patients (97 female, 134 male) with a mean age of 47.2 (1–94) years were analyzed. The diagnosis in 37 patients were MFH, synovial sarcoma in 33, liposarcoma in 31, leiomyosarcoma in 28, fibrosarcoma in 20, spindle-cell-sarcoma in 19, rhabdomyosarcoma in 13, malignant schwannoma in 9, pleomorph soft tissue sarcoma in 19, and others in 22 patients. The histological grading according Coindre was G I in 13%, G II in 24% and G III in 63%. Surgical treatment consisted of limb salvage tumour resection in 185 patients, amputation or exarticulation had to be performed in 34 patients, hind quater resection in 9 patients and resection-replantation in 3 patients.

In 104 patients radiation therapy was administered pre and/or postoperatively, 113 patients received chemotherapy pre and/or postoperatively according to several soft tissue sarcoma protocols.

After a mean follow-up of 5 years (1–360 months) and a minimum follow-up of 2 years for survivors the overall survival was 51%. In 7% death occurred unrelated to the disease, 42% of the patients died of the tumour. For statistical analysis a log-rank-test and Kaplan-Meier-estimation for patient groups according to radiation or chemotherapy was performed.

Chemotherapy did not improve the overall survival significantly. Moreover, there was a negative statistical trend in patients who received chemotherapy. Postoperative radiation therapy showed a significant benefit in patient's survival when only one operation was performed (p=0.01). In patients with repeated tumour resections a negative trend could be observed despite of radiation therapy (p=0.071).

The presented results could not prove a significant benefit of chemotherapy, so far; radiation revealed some improvement of patient's survival. However, a possible bias of patient selection in respect of tumour size and grading has to be taken into account.

Adjuvant chemotherapy for high grade soft tissue sarcomas of the extremities in adult patients: results of the italian randomized trial

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From June 92 to November 96, 104 patients affected with high risk soft tissue sarcomas of the extremity were randomized to adjuvant treatment or control after definitive local treatment. Eligibility criteria were: age 18–65, histology grade III–IV spindle cell sarcomas, site extremity and girdles, primary diameter ≥ 5 cm or any size in case of recurrent tumors. Local treatment was radical surgery or wide resection and pre- or post-operative radiation therapy. After surgery, patients were randomized between control or adjuvant chemotherapy. Stratification criteria were primary versus recurrent tumors and diameter of the primary ≥ 10 cm versus < 10 cm. Adjuvant chemotherapy consisted of : 4'-epidoxorubicin 60 mg/m^2 , day 1 and 2 and ifosfamide 1.8 g/m^2/day for 5 consecutive days; mesna was given at 20% of the ifosfamide dose. Granulocyte colony stimulating factor was administered from day 8 to day 15 after chemotherapy. The same treatment program was repeated for 5 consecutive cycles at a 21-day interval. 53 and 51 patients were randomized to treatment or control arm, respectively. According to the statistical rules, an interim analysis was performed after half of the estimated patients were accrued. Since this analysis revealed a statistically significant difference of p=0.001 for disease-free survival, patient accrual was discontinued for ethical reasons. After a median follow-up of 36 months and a minimum observation time from the last randomized patients of 24 months, 59 patients relapsed and 39 died (27 and 15 in the treatment and 32 and 24 in control arm, respectively). Median local disease-free, metastasis free and overall disease-free survival was: not reached 51 months (p=0.04), 49 versus 27 (p=0.05), 46 versus 18 (p=0.02) for the treatment and control arm respectively. Median overall survival was not reached versus 44 months (p=0.01), again in favor of the chemotherapy group.

In conclusion, our mature results confirm the interim analysis data and in accordance with the recently reported meta-analysis, strongly support the usefulness of the intensified adjuvant chemotherapy in this selected group of patients. In the Italian collaborating institutions, adjuvant chemotherapy is now routinely offered to every new patient presenting the same eligibility criteria.

Consequences of local recurrence after surgery for soft tissue sarcoma—the Scandinavian Sarcoma Group experience

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From the Scandinavian Sarcoma Group Register, information on 1224 surgically treated patients with soft tissue sarcoma (STS) of the extremity or trunk wall diagnosed between 1987 and 1995 was collected. 205 patients, one third of whom were referred to a center with a local recurrence, had a total of 284 local recurrences; these patients were analysed to (1) describe the treatment of these local recurrences, and (2) estimate the costs to both patient and society.

169 patients were surgically treated for their first local recurrence. 54 had a second local recurrence. The second local recurrence rate was 0.50 if the first local recurrence was treated with only surgery with a marginal margin, compared to 0.28 if treated with surgery with a marginal margin with adjuvant radiotherapy or with a wide margin (p = 0.0008). In extremity STS, the total amputation rate for local recurrences was 0.22 (31 of 142), higher than for primary tumours 0.09 (96 of 1065) (P < 0.0001). The average cost of treating a patient with a local recurrence was ~ USD 11.000 for surgical treatment, and an additional ~ USD 12.000 for those hospitalised for oncological treatment, bringing the average sum in excess of ~ USD 20.000.

In Scandinavia, only patients with marginal or intralesional margins are given radiotherapy. To evaluate this treatment regime, we examined the local recurrence rate in 458 patients with primary, deep-seated, high malignant tumors reported to the Scandinavian Sarcoma Group Register 1986–1993.

Among 180 patients with intralesional/marginal margins, 65% received postoperative radiotherapy. Among 189 patients with myectomy/wide margins, 10% received postoperative radiotherapy. Median follow-up was 6.5 (0.5–11) years. 215 patients are alive. Only 12 of these patients were followed for less than 3 years. Comparisons were based on observed local recurrences.

The over all local recurrence rate was 25%. There were 34% local recurrences among patients with intralesional/marginal margin and no radiotherapy compared to 24% among patients with a wide margin and no radiotherapy (p=0.01). Adding radiotherapy to the treatment regimen of patients with inadequate margins reduced the local recurrence rate to 25%. Following criterias strictly, 60 resections could be classified as myectomies. The local recurrence rate was 27% among these patients and no advantage could be demonstrated for myectomies compared to other wide margins.

Localized tenosynovial sarcoma of the foot and ankle

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Tenosynovial sarcoma is a rare tumor but, nevertheless, the most frequent soft tissue sarcoma of the foot. Its slowly painless growing can be misleading for the primary treatment (including the biopsy). In this area, conservative treatment is difficult: the disease is frequently extracompartmen-

tal, making en bloc extratumoral wide resection a gajeure. Radiotherapy gives frequently heavy sequellaes without safe local control. Moreover, contrasting with its often quiet appearance, it remains a severe illness, with less than 25% patients surviving more than 10 years. This monocentric study tries to define the optimal therapeutic approach.

Methods: From 1980 to 1997, 14 patients (mean age 30 years, 7 men, 7 women) with tenosynovial sarcoma of the foot and ankle have been treated by our team. Only 3 were seen on first hand. First local treatment included en bloc resection in 12 and amputation in 2. 12 were treated with postoperative radiotherapy (45–50 Gy). 13 patients received chemotherapy (6 of them in preoperative phase). All patients were followed up by physical examination, anteroposterior and lateral X-rays, CT scan of the foot and the lungs and bone scintigraphy every 3 months for 2 years, then every 6 months for 2 years, then every year.

Results: With a median follow-up of 7 years, 3 patients are dead of disease and one of a second tumor (leukemia). The first relapse was a lung metastasis for one of the amputate and a local recurrence for two patients treated by limb salvage who secondarly died with lung metastases. 10 years overall survival reaches 70%. The most important prognostic factors of disease free survival appeared to be chemotherapy with high dose Ifosfamide and primary local control. For safe limb salvage, the analyze pointed out the crucial importance of primary approach (including biopsy) and comprehensive treatment by experimented team.

Discussions: Comparison to other published series plae for systematic use of adjuvant or neoadjuvant chemotherapy.

Conclusion: Tenosynovial sarcoma is a severe disease requiring a strict comprehensive approach for optimal results: 1) Biopsy mus be direct through small longitudinal incision. Excisional biopsy should be avoided because it is never wide enough. 2) En bloc resection must be wide. 3) For small tumors, resections followed by chemotherapy seems appropriate. For big tumors, short preoperative high dose ifosfamide (6 weeks) seems more reliable. Good responders can benefit of safer conservative surgery. For bad responders, amputation must be considered when wide margins cannot be obtained. 4) Very long follow up is necessary: many recurrence appeared after 5 years. For that reason comparison of results of different therapeutic approach needs 10 years DFS.

Anoxic hyperthermic pelvic perfusion with low dose TNFα

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Isolated pelvic perfusion (PP) has been in use since 1959. We report our experience in phase I study of extended Hyperthermic Anoxic PP with antineoplastic drugs and low dose TNFa. Between December 1996 and June 1998, 17 patients, were treated in our department of surgical Oncology at Sheba Medical Center, University of Tel-Aviv, Israel, for a variety of pelvic malignancies unsuitable for surgical resection. The tumors were 6 mal. Melanoma, 7 sarcomas, 3 rec. colorectal carcinomas and 1 rec. carcinoma of the ovary. Only 5 of 17 patients were chemotherapy, RTX or immunotherapy naive. The rest were failures of multiple and combination adjuvant therapies. The indications for performing the AHPP were: 1 failure of previous treatment—and progression of local disease—in 10 patients. 2) Severe pain in the pelvis and perineum in 4 patients. We used Aigner's technique adding mild hyperthermia of 38 °C to the anoxia and extending gradually the time of the hyperthermix anoxia, thus enabling the synergism between anoxia and hyperthermia to potentiate the antineoplastic effect of the drugs used. In addition, in 10 patients we added 15–25 minutes of oxygenated perfusion—at moderate hyperthermia of 39.5–40.5 °C—thus allowing for 60 minutes perfusion. In the last 3 patients we added to the above mentioned treatment a small dose of 100 microgr. of TNFα—Interferon Lab. Denmark— with hydrocortisone 100 mg.

The chemotherapeutic drugs used were according to the primary origin of the tumors. There was one mortality probably related to the procedure and rew complications that would be discussed. Patients were evaluated clinically, by their response to pain, by the level of the markers, and by computed tomography and MRI. In 7 of the patients the tumor did not respond (NR). 2 had stable disease (SD) and are alive. 1 patient had partial response (PR). 4 patients showed either complete, or near to complete response (CR). Release of endogenous TNFα may play a role in the necrosis of tumors following anoxic hyperthermic perfusion. We found an increase in endogenous TNFα levels in the pelvis (and systemic blood) at the time of the anoxic hyperthermic perfusion. As for the effect of anoxic hyperthermic perfusion on pain: 1 patient had a CR, 2 PR, and 1 NR, these results of 60–80% response on pain were reported already. No sphincters malfunction or other muscular, neurological, bony or vascular damage was detected in any of the patients undergoing anoxic hyperthermic pelvic perfusion with our without TNFα over 2 years of follow-up.

Conclusions: the results of our phase I study of 14 patients undergoing anoxic hyperthermic pelvic perfusion demonstrate the feasibility of long therm hyperthermic anoxia to the pelvic organs. An added synergistic effect on tumors is suggested by combining chemotherapy with long term anoxic hyperthermic perfusion. The addition of low dose TNFα to the perfusate may have some additional value with no systemic side effects.

Overview of neoadjuvant treatment of high grade soft tissue IIB tumour

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Neoadjuvant chemotherapy and radiation therapy were applied to improve the long term survival and decrease the rate of local recurrence. Monocentric comparative results of two groups of patients who were treated by neoadjuvant chemotherapy and preoperative radiation therapy or conventional postoperative radiation following wide excision of II B soft tissue tumours were presented.

Patients and method: Between October 1989 and June 1998, 53 patients with II B soft tissue malignant tumour treated in two different groups. First group received neoadjuvant treatment with preoperative radiation therapy and second group received conventional postoperative radiation therapy following wide resection. All patients were operated by the same surgeon to standardise the surgical approach and margins were defined as wide resections without contaminated margins by independent pathologist. First group consisted of 26 patients (19 male and 7 female) with a mean age of 40.4 (17–65). Histological diagnosis of these patients were 18 synovial sarcoma, 4 MFH, 2 liposarcomas, 2 malignant mensenchymal tumours. Localisations were 13 proximal thigh, 3 poplitea, 3 cruris, 2 upper extremity, 1 pelvis, 4 intermetatarsal. Epirubicin 100 mg/sqm and Iphosphamide 4 gm/sqm with Mesna were applied to patients at 3 cycles with 3 weeks intervals together with 5000 cGy radiation therapy. The tumour volume in that group was 30 per cent more than the other group and tumour shrinkage of at least 1 cm at diameter was obtained in the end of preoperative arm of the protocol. Wide resection was applied after the third cycle of chemotherapy and the same chemotherapy regimen was continued regardless of necrosis rate of the tumour. Mean follow-up was 24.9 (6–81) months. The other group consisted of 27 patients (18 male, 9 female) with mean age of 40.7 (17–70) years. Histological diagnosis of these patients were 6 synovial sarcoma, 7 MFH, 10 liposarcoma, 1 rhabdomyosarcoma, 2 fibrosarcomas, 1 malignant schwannoma. Localisations were 15 proximal thigh, 2 poplitea, 5 upper extremity, 3 cruris, 1 paravertebral, 1 intercapsular. These patients were treated by wide excision after biopsy and following 5000 cGy conventional radiation therapy with shrinking field technique using Co 60 accelerator. Mean follow-up was 23.9 (8–96) months. 13 NED, 9 AWD, 4 DOD in the first group and 14 NED, 7 AWD, 6 DOD in the second group. Local recurrence was 3/26 and 7/27 respectively in both groups. There was not any significant difference between 2 groups regarding infection and late fibrosis. 3/26 and 4/27 delayed wound healing was present in both groups respectively.

Conclusion: although the number of the patients included in the series were small to obtain statistically significant results, regarding disease free survival systemic and local control neoadjuvant treatment of II B soft tissue malignant tumor did not provide any striking superior effect than the conventional treatment with wide surgical margins and postoperative radiation therapy. Nevertheless, neoadjuvant protocol enabled the surgeon to perform limb salvage surgery in relatively larger tumors instead of ablative surgery by maturation of the pseudocapsule and shrinking of the tumor with relative ease of surgical manipulation.

Possible role for gemcitabine in sarcoma of bone and soft tissue resistant to standard chemotherapy

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Gemcitabine has a documented activity in relatively chemoresistant diseases such as cancer of the pancreas, and palliative role in other malignancies. Gemcitabine was found to be active on xenograft of soft tissue sarcoma growing in nude mice. Recently (ASCO 1998) gemcitabine was reported to yield several responses in patients with soft tissue sarcoma. We report our limited, but promising, experience with gemcitabine in patients with sarcoma of soft tissue or bone.

Patient: Gemzar was given to 14 patients with recurrent sarcoma of bone or soft tissue that was resistant to any previous therapy and beyond any further surgery or radiotherapy. There were 4 patients with osteosarcoma, 2 with chondrosarcoma, 1 with Ewing's sarcoma, 7 with visceral or extremity soft tissue sarcoma (angiosarcoma – 2, leiomyosarcoma – 2, alveolar soft part sarcoma – 1, liposarcoma – 2). Of the 14 patients, only one was asymptomatic. All underwent systemic workup and signed an informed consent prior to therapy.

Protocol: After getting an approval from the local ethic committee, weekly gemcitabine 1000 mg/m^2 for 7 consecutive weeks followed by one week rest, followed by 3-weekly every month until lack of effect.

Results: Three objective responses were observed: one partial response in lung metastases of leiomyosarcoma of the uterus, one minimal response in case of osteosarcoma of the pubis, and one minimal response in case of angiosarcoma of the face. Clinical benefit responses were observed in 80% of the symptomatic patients, manifested by reduction in narcotic consumption, improvement of performance status and well being. Toxic events included anemia, leukopenia, thrombocytopenia, rash, and limb edema, but none were serious nor required hospitalization.

Conclusions: Gemcitabine was found to be effective in achieving some responses and stabilization of sarcomas refractory to standard-chemotherapy. Although disease stabilization is generally accepted as failure of chemotherapy, in these rare cases it should be regarded as success in view of failure of other drugs. Gemcitabine administration also resulted in a clear clinical benefit response. The toxicity profile was low. It is clear that no treatment recommendations can be made on the basis of single cases. However, it may be warranted to investigate the activity of gemcitabine in other patients with refractory sarcoma.

Brachytherapy and external beam irradiation as adjuvant treatment of soft tissue sarcomas

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Radiation has proven to be effective in improving local control after surgical excision of soft tissue sarcomas with both inadequate or adequate margins. Brachytherapy has been successfully employed for management of soft tissue sarcomas but, when it was used alone, a high incidence of relapse at the margins of the field of treatment was observed due to the rapid fall off of the dose at this level.

From 1992 to 1997, 96 patients affected by a soft tissue sarcoma were treated with limb sparing surgery, brachytherapy and external beam irradiation. There were 50 men and 46 women with an average age of 50 (8–75) years. The histology showed a low grade STS in 26 cases and a high grade in 70 cases. The tumor was a primitive lesion in 28 cases, a local recurrence in 30 cases and a radical excision of a previous inadequate surgery was performed in 38 cases. The margins were considered adequate in 85 cases (radical or wide) and inadequate in 11 cases (marginal or intralesional). With brachytherapy was delivered an average dose of 33 (15–55) Gy after one week from surgery. About one months after surgery external beam irradiation was administered with an average of 40 (30–60)Gy.

All patients have a minimum follow-up of one year. At an average follow-up of 34 months a local recurrence was observed in 3% of patients and 22% developed metastatic disease. At control, 73% of patients are free of disease, 10.5% are alive with disease (metastatic lesion), 8.5% are free of disease after recurrence or metastasis excision and 8% of patients are dead (5 of disease and 3 of other cause).

Complications were observed in 29% of cases requiring surgical revison in 2/3 of cases. Radiotherapy was the cause of complication in 20% of cases determining 12 wound sloughts, 6 fractures on irradiated bone and 1 severe neuritis of the sciatic nerve.

In conclusion, brachytherapy and external beam irradiation used as adjuvants of limb sparing surgery showed to be effective in allowing an extremely low local recurrence rate (3%). Nevertheless one out of five cases required surgical revision due to radioinduced complications.

Surgery and postoperative radiotherapy for soft tissue sarcoma of the trunk and extremity, survival, local control, limb salvage

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Previous reports of treatment with surgery alone for soft tissue sarcomas indicated that the probability of local control was dependent on the adequacy of surgical margins. With inadequate margins, the failure rates were substantial. To improve rates of local control, postoperative radiotherapy was added to the treatment regimen in selected cases. We assessed indications, local control, survival and radiotherapy for this regimen.

Methods: Between 1970 and 1991, 114 adults with soft tissue sarcoma of the trunk or extremities (excluding rhabdomyosarcoma) were treated with curative intent with surgery and postoperative radiotherapy in cases that are referred after excisional biopsy or when adequate margins (wide for low grade, radical for high grade) are not obtainable in limb salvage. 91 patients had previously untreated lesions, and 23 patients had recurrent primary disease after initial treatment by surgical resection alone. Minimum follow-up was two years. 72% of the tumors were high grade and 69% were extracompartmental. 6 were stage IA, 26 stage IB, 29 stage IIA and 53 IIB. Only postoperative external beam radiotherapy was employed ; the mean tumor dose was 65 Gy.

Results: The actuarial probability of local control at 5 years was 86% (92% for low-grade and 85% for high-grade tumors). The probability of local control at 10 years for 91 previously untreated tumors was 92% and for 23 recurrent tumors was 55% (p=002). 26 patients developed metastatic disease, 32% for high-grade and 0% for low-grade tumors. Two patients required an amputation as a result of complications. The affected limb was preserved in 85% of the patients with extremity or limb girdle lesions. The local control rates were similar for wide versus marginal margins but were only 38% in low grade and 46% in high grade lesions when intralesional.

Conclusions: Postoperative radiotherapy after limb-conserving surgery resulted in local control rates that are equal to those obtained by radical surgery alone. Limb function was preserved in 85% of patients. Failure to eliminate distant metastasis was the main impediment to cure. Local control rates were lower for recurrent primary tumors than for previously untreated tumors.

The patterns of relapse of extremity non-osteogenic sarcomas following neoadjuvant hyperthermic isolated limb perfusion with tumor necrosis factor-a and melphalan

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Recombinant tumor necrosis factor alpha (rTNF-α) has been recently introduced as a treatment approach towards locally advanced soft tissue sarcomas (STS) of the extremities. TNF-a delivery in high doses together with melphalan via

hyperthermic isolated limb perfusion (HILP) enabled to achieve response and limb salvage rates reported to exceed 85%.

Patients: 25 chemo-naive patients with biopsy-proven primary intermediate or high grade soft tissue sarcoma of the lower limb underwent ILP with TNF-α and melphalan in hyperthermic conditions. 3 patients were lost for follow-up shortly after the perfusion. 22 were clinically evaluable (9 females, 13 males). Their age ranged from 18 to 73 (median 46) years.

Histologic subtypes of STS included liposarcoma (8 cases), malignant fibrous histiocytoma (MFH 5 cases), synovial sarcoma (2 cases monophasic; 2 cases biphasic), malignant schwannoma (2 cases), pleomorphic unclassified soft tissue sarcoma (1 case), extra-skeletal myxoid chondrosarcoma (1 case), clear cell sarcoma (1 case).

Methods: Neoadjuvant HILP was carried out in the patients with localized primary non-osteogenic sarcoma of the lower limb, using 4 mg rTNF-α and 1.5 mg/kg body weight melphalan, in hyperthermic conditions. Limb sparing surgery was carried out 6–8 weeks after the procedure. The surgical specimen was studies for adequacy of resection and the percentage of induced necrosis. Radiation therapy up to 63–70 Gy was delivered in patients in whom the resulted necrosis was less than 90%, and the resection was marginal.

Results: Within follow up time of 9–55 months, 3 patients were lost for follow-up. Of the remaining 22 patients, 13 (59%) are disease-free, 7 had systemic spread (lung only in 6/7; lung + bone 1/7), and one had combined local recurrence and pulmonary involvement. There was no isolated local recurrence. However, three of the 25 patients (12%) developed the first and solitary recurrence within the perfused limb volume but out of the primary surgical bed and the irradiation target within 9–19 months. Histologically, all the recurrent tumors were identical to the original primary sarcoma. The three patients had undergone marginal resection of the residual tumors after the HILP, and showed suboptimal response to TNF-α and melphalan.

Conclusions: HILP with TNF-α and melphalan might have changed the pattern of relapse of extremity STS. Isolated local recurrence was not observed, hence the local control of the disease was excellent. Pulmonary metastases occurred as expected for sarcomas. The unique pattern of relapse within the perfused volume but out of the surgical and irradiation bed might result from the development of solitary intransit metastases in the absence of distant spread. The mechanism responsible for this phenomenon remained to be elucidated.

SURGERY

Tridimensional computed guidance in oncologic surgery for pelvic bone sarcomas

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Nowadays 80% of patients with bone sarcomas can benefit of limb salvage. Their disease free life expectancy is not jeopardized by conservative surgery as long as safe margins are obtained. For this reason, the oncologic result relies on the adequacy between preoperative and peroperative surgical measurements. Preoperative evaluation of tumor is now very accurate with digital medical imaging. But till now, surgeons still use cm or conventional radiographs for peroperative evaluation. This results in an average in 25% contaminated margins and 30% local recurrence after surgery of pelvic bone sarcomas. A more accurate technique is needed.

Material: The system is composed of 3 components:

- A color graphic computer workstation with software to calculate and present the location of the surgical instrument on the 3 dimensional reconstructed bone image.
- A complete set of hand held instruments containing infrared emitters.
- An infrared receiver linked to work station.

This material allows the determination of position and incidence of surgical instrument in real time during surgery with an accuracy of less than 1 mm.

Methods: The use of the system needs 4 steps :

- Recording data from CT, NMR or digitalized angiography.
- Creation of three dimensional image and displaying it on computer screen for preoperative simulation. Performing a virtual operation on screen permits to record the very important anatomic points of the patient and the optimal incidences of surgical instruments.
- Preoperative fixation of an infrared become on the safe part of the tumoral bone and linkage of it position to the 3 dimensional virtual image on the screen.
- Preoperative localization of surgical instruments and control of their incidence on bone.

Results: This system is very useful for resection of bone tumors when conventional location is uncertain (innominate bone) or when very sharp accuracy is needed (to preserve the acetabulum). The stereotactic device is also very accurate in the reconstructive phase of limb salvage when nothing remains of the acetabulum (resections of the 3 zones of innominate bones). After internal hemipelvectomy, it permits to localize the acetabular prosthesis in the exact location of the acetabulum before resection. In our practice, the accuracy of the video guiding system is always inferior to 2 mm compared to conventional measurements usually between 1 or 2 cm for long bones and tridimensional computed 3–5 cm for innominate bone.

Conclusion: Limb salvage surgery for pelvic bone tumors can now benefit of the accuracy of guidance. More cases and longer follow-up are needed to confirm that this new tech-

nique of peroperative imaging will decrease the risk of contaminated margins and local recurrence.

Chondrosarcoma of the pelvis and extremities. risk factors for survival

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The purpose of our study was to analyze risk factors for local control and survival in patients with chondrosarcoma treated over the past 25 years.

Material: 194 patients with chondrosarcoma were treated at our centre between 1970 and 1993. 154 patients had adequate follow up and documentation to allow analysis. The median age was 47 (14–80) years. There were slightly more men than women and there was a minimum followup of 5 years. 52 patients had pelvic/spinal tumours and the other two thirds were in the limbs. The mean duration of symptoms prior to diagnosis was 56 months. 52% were grade I, 37% were grade II and 11% were grade III. All patients had surgical management, 25 having amputation, 45 a local resection and 84 resection and reconstruction with an endoprosthesis. The margins of excision were judged adequate (wide or radical) in 66 and inadequate in 72 (marginal or intralesional) whilst 16 gave no information about margins.

Results: The long term survival of these patients was related to several factors. The 5, 10 and 15 year survival was respectively 78%, 70% and 63%. Survival was related to the following factors ($p > 0.001$ on univariate analysis): grade, adequacy of surgery, local recurrence, tumour size and whether the tumour was contained within the bone or was extracompartmental. On multivariate analysis the most important factor was local recurrence (HR 5.8, confidence interval 2.7–12.6) followed by size (greater than 10 cm doing worse). Local recurrence itself arose in 40 patients (26%) after a mean of 25 months and was related to adequacy of excision, size of tumour and whether the tumour was intracompartmental or not. On multivariate analysis adequacy of excision was the sole significant factor. Whilst both survival and local recurrence were higher for patients with pelvic tumours than limb tumours this did not reach statistical significance.

Conclusion: Adequacy of surgical excision remains the single most important factor both in obtaining local control and in curing patients with chondrosarcoma. This begs the question of whether more aggressive surgery by amputation should be considered more frequently.

Surgical treatment in Ewing sarcoma of the pelvis, about 27 patients of the french society of pediatric oncology (SFOP)

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It is now widely admitted that treatment in Ewing sarcoma of limbs is an association of multiple-agent chemotherapy and surgical resection. In pelvic Ewing sarcoma, the rôle of surgical treatment versus radiation-therapy is still debated. In most studies, the prognosis of pelvic Ewing sarcoma remains poor. The results of surgical resection associated with chemotherapy in 27 patients were analysed.

Patients and methods: 27 patients, with non metastatic pelvic Ewing sarcoma were followed-up, since April 1984 to 1993. There were 15 males and 12 females, aged 6 to 28 years (mean 13). All patients received pre- and post-operative chemotherapy : 4 had the SFOP's Ewing 84 protocol, 14 had the SFOP's Ewing 88 protocol, 7 had the Ewing 93 protocol, and 2 were initially treated elsewhere. Radiotherapy was associated in 9 cases. All patients, but one had intended en bloc resection. Resections were 9 type I (iliac wing), 2 type I=II (iliac-wing and peri-acetabular), 2 type I=II + sacro-iliac joint, 5 type II + III (peri-acetabular and around the obturator foramen), 3 type III (obturator foramen) and 2 partial sacral resections. Differents types of reconstruction were achieved.

Results: Resection was complete in 24 cases, intralesional in 2 and uncertain in one. According to Huvos, microscopic response to chemotherapy was complete in 13 cases, good in 7 cases and poor in 7 cases. Four patients had local recurrence, at mean 2.4 years after surgery (11m to 4.3y). None of them had received radiationtherapy after surgery in spite of incomplete response to chemotherapy. Nine patients had distant metastases, in which 4 were not associated with local recurrence. Mean delay for the first metastasis was 24.5 months (7 to 74). There was no radio-induced sarcoma. At mean 4.9 years (4 mo. to 11 y) follow-up, 18 patients had no evidence of disease, one had an evolutive disease, and 8 were deceased. Overall survival was 69.7 ± 9% at five years FU. Mean functional score, according to the MSTS was 22.3 points (74%).

Conclusion: There was a significant improvement in Ewing's sarcoma outcome, with modern chemotherapy, and systematic surgical treatment, even in pelvic locations. Radiation-therapy should be avoided, but remains mandatory, in case of incomplete resection or incomplete response to chemotherapy.

The effect of local recurrence on prognosis in osteosarcoma

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Local recurrence (LR) is generally held to be a very poor indicator of survival in most sarcomas. We have looked at the significance of LR on prognosis using a variety of statistical methods.

Material: We have used data obtained from two previously completed trials run by the European Osteosarcoma Intergroup. 559 patients with non metastatic osteosarcoma had chemotherapy and surgery between 1983 and 1991. The LR rate was 8%.

Analysis: We have looked at the data obtained using multivariate analysis with Cox's proportional hazard method with variables being chosen by a forward conditional stepwise approach. In Method 1, LR was considered as a simple prognostic factor and utilised as a fixed covariate. The disadvantage of this method is that patients with recurrence must live long enough for recurrence to be detected – ie. some patients who may otherwise get LR will have died before they get it. In the Method 2 LR patients are considered non recurrent until they develop LR when their status changes, ie. LR becomes a time-dependent covariate. Finally, the landmark method (3) has been used in which a time is chosen and all patients alive at that time are designated as having had LR or not and their survival is computed from that point.

Results: On univariate analysis both local recurrence and type of surgery (amputation worse than limb salvage) were highly significant. On multivariate analysis using Method 1, LR is highly significant (HR 3.3, 95% CI 2.2–4.8) but it becomes even more significant using Method 2 (HR 5.1, 95% CI 3.5–7.4). Using landmark analysis with a time interval of 18 months it is found that 440 patients remain eligible for analysis of whom 5% have suffered LR. Again, LR remains highly significant (HR 4.6, 95% CI 2.8–7.6). All these figures suggest that local recurrence carries with it an increased risk of death compared with those not having had LR of between 3.3 to 5.1 at the time of last measurement.

The data available for this study did not contain other important parameters such as % necrosis, tumour size and alkaline phosphatase levels. On a subset of 165 patients with these previously identified risk factors, LR becomes slightly less significant as a risk factor for survival with HR 1.7 compared to % necrosis (HR 3.0) and amputation (HR 1.9) using Method 1. Using landmark analysis however LR becomes the most significant factor with HR 3.5, (95% CI 1.4–8.4) compared with 90% necrosis (HR 2.6) and amputation (HR 1.2).

Conclusion: Local recurrence remains a very poor prognostic factor. Every effort to decrease the incidence of local recurrence must be made in treating osteosarcoma.

Sacral chordoma—a retrospective study of 11 cases treated surgically

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Chordoma is an uncommon neoplasm which is believed to arise from notochord remnants. This malignant tumor accounts approximately for 3 to 4% of primary bone tumors and is localized along the axial skeleton, 50% being sacrococcygeal. Clinical presentation, radiographic and histological findings are well-known since first description by Ribbert in 1894. However, sacrococcygeal chordomas are difficult to manage and remain a challenge to both surgeon and radiotherapist. The purpose of this study is to evaluate the long term results of surgical treatment and the patterns of failure for patients with chordoma of the sacrum.

Material and method: This is a retrospective study of 11 cases of sacral chordomas from 1973 to 1998. The age ranged from 36 to 77 years. Six patients were female and five were male. The initial treatment was surgery in all cases including intralesional removal in four cases, marginal resection in four cases and complete en bloc resection in three cases.

Results: The median follow-up was 6 years ranging from 1 month to 14 years. Tumoral recurrences were observed in nine cases 5 months to 8 years after treatment (mean 30 months). In two cases, these recurrences occurred 18 months and 8 years after radical sacrectomy. The treatment consisted of partial surgical removal associated with radiation therapy (40 to 70 Grays). Four patients died 6 years to 11 years postoperatively, three of them with metastatic disease. Only four patients were alive with tumoral progression at the final follow-up. The 5-year overall survival was 64%, but only 18% of the patients survived 10 years. The average disease-free survival was 18% at 5 years and 0% at 10 years.

Discussion: Chordoma is a slow-growing malignant tumor allowing survival for several years with recurrent disease. However, only 10 to 20% of the patients survive free of disease at 5 years. Recurrences occure frequently (45 to 80% of cases) and in many cases several times. Chordoma inevitably recurs and eventually leads to death after intralesional removal or marginal resection. Although complete resections in last years have produced long survival and may result in cure, recurrences have been observed, sometimes more than 10 years postoperatively. Chordomas usually metastasize late with an incidence ranging from 10 to 43%. The most common site is lung, followed by the liver and the lymphatic nodes.

Conclusion: Radical surgery should be attempted whenever it is technically feasible. When performed early, particularly for smaller lesions, it offers the best chance for cure. However, tumoral recurrences can occure postoperatively despite a macroscopically complete resection. Because radiation therapy seems to be more successful in controlling microscopic disease, it appears useful in combination with radical surgery. Irradiation, although not curative, offers the

possibility o significant palliation on pain and tumoral volume using radiation doses from 40 Grays and should be also considered when surgical removal is incomplete or not feasible.

Adamantinoma—the Istituto Ortopedico Rizzoli experience

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Adamantinoma is a very rare low-grade primary malignant bone tumor. Because of its rarity it has been misdiagnosed for many years and confused with other primary or metastatic bone tumors. Although its peculiar features are currently relatively well known, long term follow-up studies on large series of patients are still lacking in the literature. A retrospective study was therefore undertaken in order to review clinico-radiographic and pathologic features, diagnostic problems, management and results at the author's institution.

Methods: Between October 1939 and December 1993, 24 cases of adamantinoma were observed: 18 were admitted and treated while 6 were sent for consultation. There were 15 males and 9 females, average age was 31 (8–62), tibia was the primary site in symptoms at the time of diagnosis averaged 53 (2–216) months. Radioograhic features showed an osteolytic process with minimal or no periosteal reaction in all cases, a soft tissue mass in 9 cases and a pathologic fracture in 3 cases. Of the 18 patients admitted, 12 had previous surgical treatment other than biopsy (1 operation in 8 cases, more than 1 operation in 4 cases), usually consisting of intralesional procedures. Surgical treatment was an amputation in 6 cases and a conservative procedure in 12 cases ; surgical margin was adequate (radical or wide) in 14 cases, inadequate reconstructive techniques was emplyed including autografts and/or allografts (3 cases), Ilizarov apparatus (2 cases) and a vascularized fibula (6cases) ; no reconstruction was needed in 1 cases. In 4 cases the vascularized fibula was combined with a massive allograft. Little information was available on treatment received by consultation cases.

Results: At a minimum FU of 60 months, 12 patients have no evidence of disease (NED): 11 remained continuously disease free (CDF) while 1 is disease free 17 years after bilateral lung metastasectomy. One patient is alive with uncontrolled metastatic disease and 4 patients diedd survival averaging 87 (38–169) months: 1 patient is lost at follow-up. Distant metastases were observed in 7 cases (lung, lymphnodes and bone) and a local recurrence occured in 3 cases, all having had an inadequate margins. Correlation was observed between surgical margin and local recurrence and between duration of symptoms and distant metastasis. Of the 14 patients with adequate margin, there was no local recurrence in 13 cases, while 1 case was lost at follow-up. Nine patients, more recently treated, had a wide intercalary resection ; 8 of them remained CDF while 1 is NED 17 years after lung metastasectomy.

Conclusions: Treatment of adamantinoma is currently exclusively surgical. Chances of cure are excellent when an adequate margin is achieved with the first procedure ; in most circumstances a wide resection can be accomplished. Vascularized fibula combined with a massive allograft seems to provide the most satisfactory functional result. Inadequate margins is invariably associated with local recurrence while delay in diagnosis and local recurrence as well lead to distant metastasis.

"Hand on" prosthesis reconstruction after wide peri-acetabular resection for bone sarcomas

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After peri-acetabular resection for bone sarcoma, a reconstructive procedure is necessary to stabilize the hip, avoid limb discrepancy and permit full weight bearing. But, as resection of this area is time and blood consuming, this procedure needs to be easy to perform. This leads to an "hand on" composite prosthesis.

Methods and material: Our reconstructive procedure uses a titanium cup with long screw fixed in remaining bone (sacrum or spine). Once the cup is firmly fixed to the bone, the gap between cup and bone is filled with cement loaded with antibiotics and polyethylene component cemented on the innominate prosthesis. Then, the femoral component of an usual hip total prosthesis is implanted. Since 1990, we used such a reconstructive procedure in 27 patients with bone sarcoma involving the acetabulum (11 chondrosarcomas, 9 Ewing's sarcomas and 7 other sarcomas). 7 of these patients were arleady metastatic when operated. The average duration of the reconstructive procedure was 45 minutes. Walking started 4 to 10 days after operation but full weight bearing was usually authorized after 6 weeks.

Results: Postoperative complications were frequent : 4 deep infections occurred and 3 required ablations of the prosthesis (one could secondary benefited of a saddle prosthesis). 33% of the patients experimented postoperative dislocation of the hip prosthesis. 9 patients had to be reoperated. Only 2 loosening have been observed till now, one after deep infection and one after local recurrence in sacral bone.

Oncologic results : With a median follow-up of 5 years, 9 patients died of disease and 1 from unrelated disease. 4 others are alive with disease. 5 local recurrences were observed (4 in chondrosarcomas with contaminated resection). The difficulty to obtain wide margins explains the high rate of local recurrence (22%). For patients seen with localized disease, the 5 year overall survival is 75% and the 5 year disease free survival 60%.

The orthopaedic results grades according to Society of Musculoskeletal Oncology criteria were excellent in 4, good in 18, fair in 5, bad in 5. The mean survival score of 24

patients who had still their prostehis is 83% with usually no pain, excellent acceptance, length discrepancy < 1 cm, average flexion 100° and illimited walking without support.

Discussion: "Hand on" composite prosthesis gives similar functional result than custom made prosthesis and much better function than alternatives techniques. It is cheaper, more flexible than custom made prosthesis and can be used even when no part of iliac wing remains. The use of cement permits the adjunction of antibiotics needed for these complicated cases.

Conclusion: The rapidity and the flexibility of this procedure plae for this reconstructive technique. But, in very large peri-acetabular resection, the perfect positioning of the prosthesis remains difficult. A computed guide will be of great help to specify safe margins and prosthesis positioning. A longer follow up is needed to ensure that the rate of late loosening will not be too high.

Epiphyseal fracture-separation during high-dose methotrexate chemotherapy

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Metaphyseal fractures (not at the tumour site) are not exceptional during chemotherapy of osteosarcoma or leukemia, not only by osteoporis in non-weight-baring patients but also by the chemotherapy itself. The purpose of that study was to point-out an unusual complication of high-dose methotrexate (HDMX) in osteosarcoma, by reporting five cases of epiphyseal separation, or physeal fractures in four pediatric patients.

Cases reports: From 1995 to 1998, four children treated for osteosarcoma by HDMX, according to the OS 94 protocol, underwent an epiphyseal separation without or for a minimal trauma. There were two males and two females, aged 7 to 13.5 (mean 11.5). One boy had two epiphyseal separations. There were 2 distal-femur, one distal tibia, and one proximal fibula osteosarcomas. Epiphyseal separation occurred at the distal tibia in 2 cases, at the distal femur, distal radius and distal cubitus in the other cases. This complication always occurred lately, after surgical treatment, and eight months after beginning of chemotherapy. All patients were good responders to initial chemotherapy and had received in mean 16 cures of HDMX, representing a mean total dose of 191 mg/m^2. In one case, HDMX was associated with VP16 (1500mg/m^2) and ifosfamide (60g/m^2), and in 3 cases with adriamycine (350 mg/m^2). In the first case, a distal radius separation, there was a significant posterior displacement at time of diagnosis. No treatment was applied and successive radiographs showed an asymptomatic progression of that displacement. The second case had radiographs two months after the beginning of very moderate pain of the ankle, showing a displaced distal tibia separation. In 2 other patients treatment consisted of plaster-cast immobilization for a minimum of 2 months, allowing healing. In the last case, a distal ulna separation, no healing was seen in spite of 4 months of above-elbow plaster cast.

Discussion, conclusion: Non traumatic epiphyseal separation is a rare and often neglegted complication. It occurred in patients younger than usually in osteosarcoma, and only after HDMX in good responders. Even in case of very moderate pain radiographs should be taken, because these epiphyseal separation showed very few symptoms, and because there is a risk of progressive displacement. Prolonged treatment by cast immobilization seems necessary, because healing is much longer than usually in these lesions, due to the inhibition of osteogenesis by HDMX. 2 months of cast with radiographs to control actual healing are recommended.

Large reconstruction for malignant bone tumor in children—the alternative of vascularized fibular bone graft

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Late failures of massive allografts and megaprosthesis are often describe in children. That the reason why we used free vascularized fibular bone grafts as often as possible. This technique allows full activities unless the fibula reached mecanically well adapted width.

Material and methods: During the past 5 years, a vascularized fibular graft was indicated in 13 patients : 4 ewing sarcomas and 9 osteosarcomas. The site lesions were the proximal femur (1 case), distal femur (5 cases), proximal tibia (3 cases), distal tibial (1 case), distal fibula (1 case), iliac bone (1 case), proximal humerus (1 case). In 4 cases the remaining femoral or tibial epiphysis was less than 3 cm after resection. In one case the vascularized graft was indicated after prosthesis failure, in two cases after long term cryopreserved allograft reconstruction failure, in the remaining 10 cases the vascularized bone graft reconstruction was primary indicated.

Results: No patient showed infection or local recurrence, but one died of pulmonary metastases at 7 years follow-up. The graft fractured at 6 months in one patient with tibial reconstruction and in one patient with femoral reconstruction. In both cases consolidation with a large new bone formation was obtained in 2 months.

Discussion: Compared with other type of bone reconstruction the free vascularized bone graft garantees permanent stability and good fonctional status with no fear or breakage. The main disadvantage is the long period before total weight baring.

Conclusion: We recommend a vascularized bone graft in all cases where after bone resection a short part of the epiphyse can be preserved and after failure of massive allograft.

High grade bone sarcomas of the pelvis in children—surgical considerations—a retrospective analysis of 31 patients

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High grade pelvic sarcomas of bone in children are rare and associated with a poor prognosis and high rate of local recurrence (20%–50%). Limb-sparing surgery (internal hemipelvectomy) is advocated in these children in order to maintain quality of life and avoid major amputative surgery such as true hemipelvectomy.

Materials and methods: Between January 1988 and January 1998, 31 patients with high-grade pelvic bone sarcomas where referred to our unit. There were 20 men and 11 women. Their age ranged from 3–22 years (mean 12 years). Diagnosis: there were 28 patients with Ewing's sarcoma (ES) and 3 with other bone sarcomas. Anatomical location: in 20 patients the tumor involved the entire or part of iliac bone (in some cases with extension to sacrum). In 5 patients the tumor involved the pubis or ischium. In 6 patients the tumor involved the sacrum with some extension to the posterior iliac bone. All the patients received neoadjuvant chemotherapy. 19 ES patients received preoperative radiation therapy of 4000 rads completed to 6000–6500 rads postoperatively. 8 ES patients received postoperative radiation 6000–6500 rads.

Results: Out of the 31 patients 4 did not arrive to surgery and died from systemic disease or chemotherapy complications. 27 patients were available for follow-up (1–10 years). All the patients underwent internal hemipelvectomy: in 20 patients type I resection was performed, in 2 patients type II resection was performed, in 4 patients type III was performed and in one patient a combined resection was done. The average surgical time was 3 (2–7) hours and average blood loss was 1000 cc. Surgical margins: in 10 patients wide margins were achieved, in 17 patients marginal margins were achieved. In 18 patients some kind of reconstruction was needed, using plates screws cement and bone graft. In 9 patients no reconstruction was done. We had 4 wound infections that were managed successfully by surgical debridment, antibiotics and wound care. In one case removal of the "implant" was needed. There were 6 local recurrences (22%) and no secondary amputations. Functional status: (at last follow-up or before death), according to the AMSTS functional rating systems we achieved 6 excellent results, 17 good, 3 fair, and 1 poor result. All patients maintained their walking ability.

Conclusions: It seems that internal hemipelvectomy is achievable and justified for better quality of life in children suffering from high grade bone sarcomas of the pelvis. Further efforts are needed to improve the reconstructive options in the pelvis.

An original biological reconstruction of the hip in a 4 year-old girl

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A 4-year-old little girl presented in June 1997 with the diagnosis of Ewing's sarcoma in her left proximal femur. After preoperative chemotherapy staging studies showed the tumor involving the bone from the cervico-cephalic physis to the femur midshaft with small soft tissue involvement.

An intraarticular wide resection of the proximal femur (13 cm) including the surrounding tissues was performed while the proximal left fibula (16 cm) was harvested with its vascular supply represented by the anterior tibialis artery and vein. The smallest available femur allograft was shaped, cutting the femoral head, reducing the external cortex and reaming its medullary canal up to 13 mm, then an anterior window was prepared on the upper 3/4 of the anterior allograft surface. The fibula was inserted into the allograft through the anterior window allowing the distal fibula to merge from the allograft osteotomy for 2.5 cm. A subperiosteal osteotomy of the fibula itself was performed, 4 cm distally from the fibular head, to aligne the fibular segments to the cervico-diaphyseal angle inside the allograft. A long titanium plate was used to fix the allograft to the femur. Great care was taken to order to avoid any damage to the vascular pedicle that came out of the anterior window and was anastomosed in a termino-terminal fashion to the profunda femoris artery and vein. The fibular head was posed into the acetabulum and the hip capsule, maintained during the resection, was sutured on itself and to the neck of the allograft. All main muscles (ilio-psoas, medius and major gluteus) were reattached to the tendon insertions of the allograft.

During postoperative chemotherapy, the small patient was managed in an hip spica cast, twice renewed and maintained for 3 months. Protected weight-bearing by brace was started after 8 months. Active physical therapy was allowed from the 4th month p.o.and the active motility of the hip reached 90% of normal, 9 months after surgery. Postoperative isotope scan, serial conventional radiographies, CT and MRI performed at 9 months, confirmed the viability of the fibular head. A second CT scan was taken at 15 months demonstrating the growth in length and size of the metaepiphysis and the activeness of the transplanted fibula whose hypertrophy involves now the allograft shell. The fibular osteotomy completely healed at two months. Allograft/host femur osteotomy healed at 8 months.

At 16 months the girl is attending the first class in a public school, she walks with the brace without canes, she rides an exercise bike, swims and trains herself to walk in the pool. At home she is starting to keep the standing position without the brace and with a partial weight-bearing on the operated limb. No limb-length discrepancy is present and the postoperative transient peroneal palsy of the donor site has completely recovered.

Survival after radical surgery for the solitary renal metastasis

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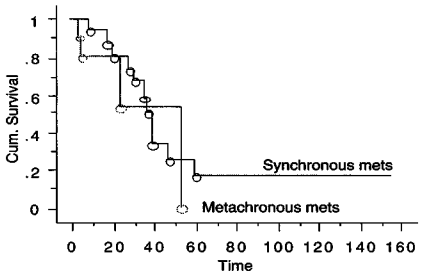
The purpose of our study was to assess the outcome of radical surgery for patients presenting with a solitary metastasis from renal carcinoma.

Materials and methods: 25 patients presented with solitary metastases from a renal cell carcinoma. In 10 (metachronous) patients the renal tumour was already known and the patients had previously undergone nephrectomy between 12 and 84 months previously (mean 42 months). In the other 15 patients the diagnosis of the metastasis and the causative tumour coincided (synchronous). The most common site for the metastases was the femur followed by the humerus, tibia and pelvis. Two patients had excisions of the lesions, five had amputations and 18 had endoprosthetic replacements.

Results: the surgical management of the metastases was successful in maintaining function and mobility in most patients. There was one local recurrence treated with a further excision. The survival of the patients from the diagnosis of the first metastatic lesion was 95% at 1 year, 59% at 3 years but only 11% at 5 years. One patient remains alive ten years after prosthetic replacement of the distal humerus and elbow. There was a slight difference in survival between patients with synchronus and metachronous metastases (Figure)

Conclusion: Aggressive surgical management of patients with solitary metastases from renal cell carcinoma is justified and can produce long term survivors.



IMAGING

Traumatic or tumoral musculoskeletal lesions— a sometimes difficult radiological diagnosis

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Three main types of lesions may give rise to clinical, radiological and histological problems concerning the differential diagnosis between traumatic lesions or tumours.

Stress fractures: In oncology, women mainly suffer from stress fractures following radiotherapy for pelvic tumours. A metastasis may be suspected due to new pain, a positive bone scan, the heterogeneous appearance of the bone on CT or a hyposignal on T1-weighted MR images. It may be very difficult to interpret a bone biopsy specimen and treatment may even have been performed. Systematically, a stress fracture should be suspected. Then a fine line will be conspicuous on plain films, a linear hot spot on the bone scan, thin CT slices can then be obtained to confirm the rupture of the cortex and the fracture, contrast can be injected for MRI so that the signal of oedema is enhanced and the fracture line discernible. If the correct diagnosis is made, all signs will disappear after 3 weeks of rest.

Periosteal bone formations: Periosteal bone tumours are located in a saucerisation. They may be sclerotic, like osteosarcoma, with perpendicular bone formations, or lytic, like Ewing's sarcoma. Bone avulsions, secondary to tendinous lesions, may also lead to perpendicular bone formations. The location and history may be very helpful. If an biopsy is performed, reactive osteogenesis may be misdiagnosed as malignancy.

Soft tissue masses: Hematomas are usually easy to diagnose. They exhibit a high signal on T1-weighted MR images especially when the muscular rupture is associated. Myositis ossificans with its typical "3-phase evolution", is sometimes far more difficult to diagnose. Inflammation, the first clinical sign of onset, normal initial radiograph, a peri-lesional edematous reaction on MRI, peripheral calcifications (mainly late-after 3 weeks) very often permit an accurate diagnosis and avoid biopsy. It is sometimes difficult to differentiate between heterogeneous, partially calcified tumours, especially after bleeding and parosteal osteosarcoma.

Conclusion: In difficult cases, the radiologist, the surgeon and the pathologist may, together, be able to solve the problem. If not, the fourth dimension (time) may be the only way to find an answer.

Imaging in local evaluation of musculo-skeletal tumors— limitations and pitfalls?

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Conventional radiographs, bone-scintigraphy, MRI and CT eventually are the standard imaging procedures. While conventional radiographs allow differentiation of the aggressiveness of tumor (Lodwick-Grading) and typing of tumor due to localisation, patient age, calcification etc, allows 3-phase-bone-scintigraphy an evualuation of the local tumor-perfusion, metabolic bone-turn over and evidence of bone-marrow metastasis.

In radiographically unclear cases the additional use of CT with contrast may outline more definitely the real tumor size (volume) with or without necrosis, relationship to neuro-

vascular structures, structure of the bony-destruction, periosteal new bone formation and fine-detail calcification. Diagnostic pitfalls could be due to nutrient vessels of the bone. But also diaphyseal skip lesions may be missed if the whole of the bone is not examined in contiguus sections. Moreover the diagnostic accuracy in the assessment of tumor-extent is decreasing in the distal regions.

The standard imaging procedure in the assessment of locoregional spread is MRI, nowadays. It allows most precisely to visualize the osteomedullary tumor spread with or without skip-lesions and eventually of the neigbouring joint. The soft-tissue extension and relationship with neuro-vascular structures can be well-documented. Pitfalls and limitations are due to absence of signal and chemical shift artefacts at the cortical border. Small calcifications may not be discernable. Due to the limited spatial resolution small lesions may be overlooked. Finally the tumor boundaries may become isointense with fatty marrow on contrast-enhanced images and on T2-w. images there is usually an overestimation of the extent of the tumor due to neighbouring inflammatory reaction or (and) aseptic necrosis.

Costly mistakes!—a review of "missed" tumours on x-rays which have resulted in costly compensation claims

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The purpose of our study was to highlight the current problems in the UK with the tendency for litigation against doctors especially in light of the effects of delays in diagnosis both on treatment and outcome.

Material: We have been referred over 7000 patients with suspected musculoskeletal tumours in the past 30 years. In 1986 we became concerned about the problems of late diagnosis of musculoskeletal tumours and we reviewed all new referrals over a one year period. We identified that 25% of patients who actually had a primary malignant bone tumour had already had an Xray taken prior to being diagnosed which had reported as being normal but which in fact showed the tumour. This misreporting led to significant delays in diagnosis and led to the need for amputation in many. A recent analysis of patients presenting has shown a similar figure of 25% underreported X-rays.

Litigation: Many patients will ask why their tumour was not detected on the initial X-ray and in some cases they will pursue this further through the courts.

We present some typical X-rays of "missed" tumours and identify the cost that this has led to in litigation.

We suggest guidelines that should be used to try and minimize this problem in the future.

Limitations of radiographs and CT in correlation with local response, tumor necrosis and patient survival in high grade osteosarcoma after chemotherapy

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The necrotic effect of chemotherapy on primary osteosarcoma has been shown to predictive of the final outcome. Little attention has been directed to the local response of the host (LHR).

Design: A four stem grading system was developed based on distinct histologic patterns of the local host response about the lesion. These responses were correlated with the chemotherapy-induced necrosis and analyzed in an attempt to ascertain their impact on the oncological outcome. In addition the ability of conventional radiographs and computed tomography to measure the LHR was studied.

Methods: The grading system was applied to the macroscopic histologic sections of the specimens obtained from 72 randomly selected patients with a Stage II B primary osteosarcoma in various limbs after wide resection and complet courses of pre- and postoperative chemotherapy treated between 1985 and 1991 with a median follow-up of 5 years and 9 months. The macrosections were blindly reviewed by four experienced musculoskeletal oncologists to assign a grade of response. The results were correlated to response features on conventional radiographs and CT images as well as with the histologic tumor response and clinical oncological outcome.

Results: Significant correlations were found between the LHR and tumor necrosis (corr=0.55), LHR and CT response features (corr=0.56). LHR did not correlate to findings on conventional radiographs. A LHR was predictive of a long term survival.

Conclusions: The local host response observed after preoperative chemotherapy reflects the tumor-host relationship, has a prognostic impact on oncological outcome, and can be predicted by computed tomography.

Pitfalls of imaging in staging assessment of children osteosarcoma

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In the years 1991–1995, 88 patients younger than 15 years, with a high-grade osteosarcoma (OS) of the knee, were treated by neoadjuvant chemotherapy and surgery. At presentation the patients were studied by conventional radiography, T^{99} bone scan, computed tomography (CT) and magneting resonance (MR) of the affected segment. All patients also

received CT of the chest. Primary lesion was in the femur in 55 patients and in the tibia in 33, always presenting an extraosseous component. All patients received chemotherapy according to 3 different protocols. After preoperative treatment, conventional radiography, MR imaging and CT of the lesion were repeated in all cases while chest CT was repeated only in the previously positive patients.

Distant metastases were suspected in 15 cases: 12 had positive chest CT while 3 presented distant bone metastases on bone scan (2 cases) or comparative lower limb CT scan (1 case). A suspect for "skips" was found on MR in 11 cases (2 with lung nodules and 1 with distant bone mets). Preoperative staging was: stage IIB: 65 cases and stage III: 23 cases (10 only lung nodules, 2 lung associated to skip nodules, 8 only skip nodules, 2 distant bone lesions, 1 both distant and skip bone mets).

Surgical removal of the primary lesion was always performed. There were 4 amputations, 11 rotation plasties and 73 limb-salvage procedures. In the 12 patients with positive chest CT, a contemporary thoracotomy was attempted in 8, 2 were considered inoperable, and in the other 2 no thoracic surgery was performed because the nodules disappeared on preoperative chest CT. Both suspected skip lesions and distant bone metastases were always removed together with the primary tumor. All patients were subsequently treated by postoperative chemotherapy according to the applied protocol. No patient was lost and the average follow-up was 56 (27–87) months.

The staging of 4 patients was changed after the pathologic evaluation of the specimens. In 3 where a contemporary thoracotomy was performed (37%), no metastatic nodule was found. In one femur case where MR demonstrated a skip nodule in the proximal tibia, an extraarticular resection was performed but no tumor tissue was found in the tibia. All other metastatic lesions were pathologically confirmed. Therefore, final staging of the series was:

⇒OS stage IIB: 69 cases,

⇒OS stage III: 19 cases; and according to the various spread of the disease:

- 7 patients with lung metastases only (GROUP 1),
- 2 patients with distant bone metastases only (GROUP 2),
- 7 patients with skip metastases only (GROUP 3),
- 2 cases with lung and skip metastases (GROUP 4),
- 1 cases with distant and skip bone metastases(GROUP 5).

Patients whose final stage was IIB, presented a DFS of 54%, while another 19% was alive and without evidence of disease after surgical treatment of a metastatic relapse. Local recurrence occurred in 7% of IIB patients.

In patients presenting with stage III OS, Group 1 behaved differently according to the treatment performed on pulmonary mets. Three out of 4 (75%) patients who had a contemporary thoracotomy were CDF 45, 49 and 50 months after surgery, while all other patients died. All patients in Group 2,3,4 and 5 died for the disease. Local recurrence occurred in 33% of the patients in these groups.

These data confirm that imaging data must always be confirmed by pathology. In suspected lung metastases, aggressive contemporary surgery is advised to define the right stage and to improve prognosis. Skip lesions must be considered as real metastases; their outcome is worse than that of pulmonary metastases and seems more similar to primary osseous metastases.

The problem of false positive lung nodules at initial staging of osteosarcoma

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In patients with lung nodules at diagnosis the common approach today is the removal of these nodules contemporarily to that of the primary bone lesion or at a different time either before or after. The histological analysis of these lung nodules very often revealed different aspects with no evidence of neoplastic disease. At diagnosis this problem can impede a correct staging of osteosarcoma. This is of particular importance when preoperative chemotherapy is differentiated according to the stage of the disease at diagnosis. Aim of this work is to present the experience of the Rizzoli Orthopaedic Institute in Bologna on this topic.

Materials and methods: Between June 1988 and April 1997, 51 patients with osteosarcoma defined as metastatic at diagnosis received lung surgery contemporarily to surgery of the primary bone lesion in 44 cases and postponed in the remaining 7. 46 patients received preoperative chemo. All patients received postoperative chemo. Experts from the Italian Sarcoma Scandinavian Sarcoma Group separately reviewed all CT scans.

Results: Imaging: at revision of the CT scans all patients were confirmed as metastatic. A total of 119 CT scans were reviewed ranging from 1 to 4 for each patient. A very good concordance was observed between the Italian and Scandinavian investigators with 247 nodules average 4.8 detected by the Italian investigators compared to 268 nodules average 5.2 detected by the Scandinavian investigators on the first CT. This difference decreased in the preoperative CT evaluation, 143 and 146 nodules respectively (average 3.1 for both).

Histology confirmed the presence of metastatic nodules in 29 cases (57%), whilst in 22 cases (43%) the histological examination failed to revealed evidence of metastatic disease.

Surgery and histology: a total number of 204 nodules were surgically excised, ranging from 1–19 per patient. 109 (53%) were histologically confirmed as metastasis. In the 22 cases without metastasis 53 negative nodules were removed (range 1–7, average 2.4). In the 29 cases confirmed to be metastatic 151 nodules were removed (range 1–19, average 5.2). 42 of these were negative. Analysing the number of nodules at surgery only 4 of the 13 patients (31%) with only one nodule were confirmed to be metastatic. The higher the number of nodules the higher is the percentage of cases that prove to be metastatic, reaching 100% for those patients

with more than 7 nodules. Regarding the size of the nodules at the 1st CT, false positive lesions tended to be smaller, 68% < 5mm, compared to true metastatic nodules 35% < 5mm (p=0.035). In the 46 cases with more than one preoperative CT available we analysed the variations in terms of number of nodules. Of the 19 cases which turned out to be false positive, 12 (63%) showed no variation compared to only 22% for those 27 patients who had real metastatic nodules (p=0.01). In the same 46 cases we analysed the variation in dimension of the nodules which showed no difference between false and true metastatic nodules. The histological review of false positive nodules is still ongoing, but so far revealed subatelectesia areas in about 1/3 of the nodules, inflammatory or lymphoide tissue in about 20%, interstitial fibrosis in another 20%, and different lesions in the remaining nodules.

Conclusion: Reliable diagnostic criteria are necessary to solve this important problem. Further investigations are also necessary to confirm the prognostic value of the number, dimension, and/or the evolution of nodules during preoperative treatment.

Benefits, pitfalls and limitations of multiple imaging techniques in monitoring neoadjuvant chemotherapy in patients with high-grade bone sarcoma

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Monitoring preoperative chemotherapy in patients with high grade bone sarcoma may have critical consequences for the strategy and timing of surgery and :or radiation therapy. In particular, early, noninvasive identification of patients with a high probability of a poor histologic response following completion of the full course of chemotherapy is a clinically relevant issue. Furthermore, accurate preoperative prediction of response to chemotherapy may have an impact on modification of neoadjuvant chemotherapy regiments and selections on postoperative chemotherapy schedules.

To assess the capabilities, expected benefits and limitations of conventional radiography and various other (perfusion-sensitive) techniques in monitoring the effects of chemotherapy, studies were performed in our institute during the past 5 years comprising 90 patients with a high-grade osteogenic sarcoma (n=52) or Ewing's sarcoma (n=58). All patients underwent 2–6 courses of neoadjuvant chemotherapy prior to surgery. The resected specimens always served as the gold standard for the ultimate histologic response to chemotherapy. Fifty-seven patients (63%) showed a poor histologic response and 33 patients (37%) showed a good response. Conventional radiographs and morphologic MRI parameters (tumor demarcation, changes in signal intensity, homogeneity) were not reliable in monitoring the effect of chemotherapy in patients with high-grade bone sarcoma.

Increase in tumor volume, assessed on MR images during chemotherapy indicated poor response in osteogenic and Ewing's sarcoma. Only substantial decrease in tumor volume (>75%) in Ewing's sarcoma suggested good response.

Three-phase bone scintigraphy was hampered by low specificity and poor spatial resolution.

Static contrast-enhanced T1-weighted spin-echo images were not useful because of overlap between viable tumor, vascularized granulation tissue, edema and reactive hyperemia.

Tumor neovascularization and perfusion were principal targets in monitoring chemotherapy, in particular fast dynamic contrast-enhance MRI, as part of a routine musculoskeletal MR protocol, which allowed identification of even small remnants of viable tumor (early enhancing foci within 6 sec after arterial enhancement). Limitation of this method comprises sampling errors due to limited number of slices examined in large heterogeneous tumors which may result in underestimations of the mount of residual viable tumor.

The use of ultrafast sequences, covering an entire tumor volume, may defeat the problem of sampling errors. Moreover, functional, so-called parametric images can now be acquired, reflecting the contrast enhancement kinetics (wash-in-rate, maximum enhancement, and washout rate) of different tissues on a pixel-by-pixel base. Color Doppler ultrasonography may be a suitable and cost-effective method of monitoring chemotherapy, unless the tumor is small and purely intraosseous.

Fast dynamic constrast-enhance subtraction MR imaging in the characterization of musculoskeletal tumors

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In various MR imaging studies, designed to differentiate between malignant and benign musculoskeletal tumors, morphologic parameters as well as enhancement features after administration of Gd-DTPA have been evaluated, yielding controversial results. In a prospective study, we analyzed the value of fast dynamic contrast-enhance subtraction MR imaging in the characterization of both bone and soft tissue tumors. A T1-weighted turbo gradient echo sequence temporal resolution, (1–3 sec) after administration of Gd-DTPA (0.1 mmol/kg of body weight i.v.), as part of a routine MR imaging protocol was performed in more than 200 consecutive patients with a musculoskeletal mass. All dynamic contrast-enhanced images were subtracted and time-signal intensity curves were obtained. The interval between arterial and early tumoral enhancement, progression of tumoral enhancement and pattern of enhancement (peripheral vs diffuse) were used as discriminating factors. Differentiation of benign from malignant soft tissue tumors was possible with a

sensitivity of 91% and specificity of 72% based on start of enhancement, a sensitivity of 73% and specificity of 97% bases on pattern of enhancement, and a sensitivity of 86% and specificity of 81% bases on progression of enhancement. In particular, initial enhancement at the periphery of a soft tissue mass indicated malignancy, whereas absence or late and diffuse enhancement indicated benign soft tissue masses.

These parameters were not accurate in the differentiation between benign and malignant bone tumors (sensitivity, 63–76%, specificity, 50–76%), due to high overlap between high-grade malignant and active, well vascularized benign bone tumors (e.g. giant cell tumor). Differentiation between benign and low-grade malignant tumors is clinically relevant but unfortunately not possible based on dynamic imaging parameters.

In conclusion, early enhancement characteristics, assessed with dynamic MR imaging, reflect biologic activity rather than the malignant potential of bone tumors. This readily available technique may be used in the differentiation between benign and malignant soft tissue masses.

Detection of lesions in the cortical bone around tumour prostheses by extended field CT scans

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Diagnosing tumour recurrence in the bone and soft tissue around tumour prostheses has faced tremendous problems because of metallic artefacts in both CT-scans and MR imaging. Detailed information about the character and size of the lesion are often necessary to decide wheter surgical intervention is needed.

Methods: We implanted titanium and cobalt-chrom distal femur MUTARS tumor prostheses in 10 human femurs. Drill hole lesions of 1 mm, 2 mm, 3 mm, 5 mm and 8 mm diameter were placed in the bone around the hexagonal stem of the tumor prosthesis, another 1 mm and 2 mm drill hole at the round end of the stem and 4 additional 1 mm and 2 mm drills further up the femoral diaphysis. Each specimen was examined in an extended field Siemens Somatom Plus 4 CT using the AB 91 high resolution filter (140 kV, 146 mAs, slice thickness: 3 mm). The scans were evaluated by a radiologist and two orthopaedic surgeons.

Results: The AB 91 high resolution filter produced nearly artefact free CT-scans except for a regular artefact pattern arond the hexagonal part of the prosthesis stem. In all scans we saw a smooth line arising from each hexagonal plane continuing into the adjacent bone making it difficult to detect 1 mm drills within the artefact. This pattern was not seen in scans of the round stem. We identified all 2 mm, 3 mm, 5 mm, and 8 mm dril holes as well as the 1 mm drill holes along the artefact free round stem of the prosthesis. The 1 mm drills around the hexagonal stem were partly covered by artefacts, still we identified 8 out of 10 dril holes. It was possible to detect all 10 using an 1 mm slice thickness for scanning.

Clinical relevance: Using an extended field CT it is possible to detect lesion as small as 1 mm around a tumor prosthesis. Because of these results we recommend using the high resolution CT scans for evalutating all suspicious lesions around tumor prostheses.

Does direct magnification radiography (DIMA) improve the diagnostics of bone tumours?

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The purpose of this study was to assess the diagnostic performance of magnification radiography in diagnosing bone tumours as compared to conventional radiography. 130 patients with primary bone tumours and tumour-like lesions were radiographed with both conventional and magnification technique. All radiographs were analysed by one orthopaedic surgeon and two radiologists and the findings were correlated with histo-pathology. Two microfocal x-rays units were used for magnification radiography with a focal spot size of 20–130 mm. Using magnification versus conventional radiography the diagnosis of benign and malignant lesions as well as the individual tumour diagnosis was determined with higher accuracy (85% versus 71% and 69% versus 51%, $p<0.01$). Margins of destruction, periosteal reactions and matrix patterns were evaluated with higher certainty by all observers ($p<0.01$). We conclude, that magnification radiography may improve evaluation and diagnosis of bone tumours.

Role of TC-MIBI in musculoskeleetal tumors of the limbs

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Technetium-99m-hexakis-2-methoxyisobutylisonitrile (^{99m}TC-MIBI) is a lipophylic and cationic radiopharmaceutical, proposed as Thallium-201 substitute for myocardial perfusion imaging, because of the favourable imaging characteristics of ^{99m}TC. Recently it has also been used as a tumor imaging agent in various benign and malignant lesions, including lung, breast, thyroid and brain tumors, because it accumulates in viable tumor cells being dependent on motochondrial and plasma membrane potentials.

Twenty patients affected with various bone and soft-tissue pathologies (12 malignant and 8 benign lesions), were studied with ^{99m}TC-MIBI.

The study demonstrated that ^{99m}TC-MIBI is able to detect bone and soft tissue lesions, but could not delineate benign from malignant lesions. Moreover ^{99m}TC-MIBI proved to be a particularly useful method in distinguishing recurrence within scar tissue.

Ultrasound guided needle biopsy of primary bone tumours

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Needle biopsy is an established technique for histological diagnosis of bone tumours, traditionally guided by fluoroscopy or computed tomography. However, aggressive tumours that have extended through the cortex and surface lesions are amenable to imaging with ultrasound (US). The purpose of this study is to assess the diagnostic accuracy of US guided Trucut needle biopsy in a consecutive series of patients referred to a Bone Tumour Unit with suspected primary bone tumours. Of 144 patients referred over a period of 2 years (83 men, 61 women; mean age 34.7 (2–81) years), 63 were considered suitable for US guided biopsy based on the presence of a relatively large extraosseous component, as shown by pre-biopsy magnetic resonance imaging (MRI). The diagnostic accuracy was 98.5%, with only a single failed biopsy.

Therefore, in a selected group of patients, US is a very reliable guidance technique for percutaneous needle biopsy of bone tumours.

"Tumourculosis-like lesions"

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Our aim was to evaluate a series of patients who came to our Department due to a suspected musculoskeletal tumour, and were diagnosed to have an extra-pulmonary tuberculosis (TBC).

Patients and methods: From 1971 to 1996, 106 patients affected by musculoskeletal TBC were treated in our Department. 64 were sequelae of previous TBC (ankylosis, pain) and 42 were diagnosed at our institution. 7 out of these 42 patients came to our centre after detection by image methods of a suspected musculoskeletal tumour. 1 Ewing's sarcoma, 1 soft tissue sarcoma, 1 giant cell tumour, 1 chondroblastoma and 3 metastases.

Results: 19/42 patients diagnosed of TBC in our centre had not clinical data suggesting an infection (no fever, no leuko- or lymphocytosis, etc). None of these 42 patients had any image in the chest x-ray suggesting a pulmonary TBC. Three cases had renal TBC. Only in 5/42 patients previous contact with TBC (Combe) was verified. Seven cases were previously diagnosed by image methods of musculoskeletal tumour.

Diagnosis was made in 7 cases by culture, in 19 cases by biopsy, and in 16 cases by both culture and biopsy. Treatment was performed with three tuberculostatic drugs in all cases, during a mena time f twelve months. Thirty-four cases required also a surgical debridment.

Conclusion: Since the incidence of TBC is increasing, and its diagnosis is difficult, we conclude that we should bear in mind this possibility when a musculoskeletal tumour is suspected, and we recommend the specific culture of the bacillus when biopsing those lesions.

Percutaneous computed tomography-guided thermocoagulation for osteoid osteomas

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Osteoid-osteomas are small benign tumours of bone (< 1 cm), usually painful that occur in patients in the first three decades of life. Treatment predominantly consists of surgical excision of the nidus. Surgery on lesions located in hard to reach areas (femoral neck, pelvis, or joint) often requires extensive surgery and may lead to complications. Presented is a minimal invasive technique (percutaneous thermocoagulation under CT-guidance).

Material and methods: Since 1994, 95 patients (age 4–52 years, median 21.9) with clinical and radiological suspect oseoid osteoma and one with recurrent osteoblastoma were treated by percutaneous thermocoagulation of the nidus under CT-guidance: femur (37), tibia/fibula (21), pelvis (8), hand (7), humerus (6), spine/sacrum (6), foot (5), ulna (4), patella (1). Symptoms of pain were often present for many years. The procedure requires CT-scan, orthopaedic surgeon, interventional radiologist and anaesthesiologist. General anaesthesia or regional anaesthesia is used. The nidus is localised with 1–2 mm CT-sections and a « Boneopty » needle system is entered into the centre through a small skin incision (0.5 cm). After control-CT-images a biopsy-needle is advanced through the « Boneopty-needle » to access the nidus for sampling is necessary (histology, cultures). Next the probe and electrode tip is entered and heated to 90 °C for 4 minutes (Radiofrequency-generator Radionics). Removal of the needle, skin closure. Patients are discharged the same day or next morning and encouraged to resume normal activity immediately. Procedure time ranged from 45 min to 2 hours.

Results: In 81 patients a single procedure was sufficient resulting in complete pain relief. In 14 patients a second thermocoagulation was necessary. This second procedure was indicated because of recurrent complaints immediately because of procedural reasons in 8 cases (apparatus or inappropriate localisation of the needle) or after pain free inter-

val when discomfort slowly increased. The second thermocoagulation relieved the symptoms totally in 11 patients, 2 needed a third thermocoagulation, both successfull. Only 1 patient still has discomfort (fibula). Final results showed 93 patients pain free during follow-up at 0–12 months – 23, 12–24 months – 23, 24–36 months – 21, 48–60 months – 12. No complications were encountered during the thermocoagulation procedure or later, except one small fistula due to fat necrosis in a tibial lesion which healed after excision.

Conclusion: Percutaneous thermocoagulation is a minimal invasive effective treatment for osteoid osteomas with excellent results.

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PATHOLOGY

pRB and p16 analysis in high grade osteosarcoma and influence on prognosis

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Cell cycle regulation depends on a fine balance between cyclin-cyclin dependent kinase (cdk) complexes and a family of cdk inhibitors (CKIs) that bind cyclin-cdk complexes and block their kinase activity (1).

p16 protein associated with cyclin D/cdk4 complex prevents phosphorylation of the Rb gene (pRB) product of and consequently cell entry into S-phase. The gene encoding p16 protein, CDKN2, is localized on chromosome 9p21 where a higher frequency of alterations, like homozygous deletion or mutations were found. Recently, it has been discovered that the CpG island methylation can inhibit trascription of structurally inaltered CDK2 gene (2).

To investigate the role of mechanisms regulating cell cycle progression in human osteosarcomas, we analyzed the alterations of the components involved in G1 phase progression and their possible influence on prognosis.

Materials and methods: 39 high grade osteosarcomas (OS) were studied: 19 of these developed metastasis (relapsed group) and 20 had no evident signs disease (NED group).

Immunohistochemical studies (IHC), on RB, cdk4, p16 and cyclin D1 protein expression, were performed on formalin-fixed and paraffin-embedded samples.

All tumor tissues were also frozen for immunoblotting analysis (IB), on RB, cyclin D1, and cdk4 protein and for methylation-specific PCR (MSP) of CDKN2 gene. Co-immunoprecipitations of Cdk4 protein with anti-D1 and anti-p16 were performed.

Results: IHC positive reaction for functional pRB was found in 18/39 (46%) OS, while 21/39 (54%) OS were negative. IB analysis revealed that the different pRB expression reflected a different pRB phosphorylation status. No correlation was found between pRB and p16 expression in IHC. A positive correlation was found between pRB and D1 expression ($r=0.739$, $p<0.001$). In 74% of OS a moderate to strong of cdk4 protein expression, confirmed by IB, was found. In p16-positive tumors higher levels of cdk4 were seen and a positive correlation was found ($r=0.44$, $p=0.0045$). Methylation status of the CDKN2 gene was evaluated on the 15 p16 negative tumors showing 8 samples with 5' CpG island methylation; 4/8 had a complete methylation status, while in the remaining 4 the gene was only partially methylated.

Studying clinical follow-up, the statistical analysis confirmed a higher probability of metastasis in patients without active pRB (chi-square=4.41, $p=0.035$).

Conclusions: Our results on 39 high grade OS confirm that patients with pRB-positive tumors have a better prognosis than the pRB-negative ones (3), while p16 functionality does not seem to affect the relapsed neither in pRB-positive nor pRB-negative OS. Alterations of CDKN2 gene, like methylation of 5' CpG islands which was found in 8/15 OS, can contribute to explain the unbalance in the control of R check-point in G1 phase, a possible mechanism involved in the pathogenesis of OS.

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Presence of telomerase activity in different sarcomas histotypes and correlation with tumor aggressiveness and grade

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Telomerase is a ribonucleoprotein complex that is implicated with cellular immortalization. The presence of telomerase activity has been observed in different neoplasms and it has been related to tumour aggressiveness and grade. In this study we investigate 55 samples of bone and soft tissues sar-

comas coming from our tissue bank to evaluate the presence of telomerase activity and the possible correlation with aggressiveness and tumor grade. These samples included high grade tumors (7 osteosarcomas, 7 Ewing sarcomas, 5 chondrosarcomas, 11 malignant fibrous histiocytomas, 7 synovial sarcomas and 1 fibrosarcoma), tumor with intermediate or low malignancy (7 giant cell tumors, 1 chondroblastoma, 1 benign fibrous histiocytoma) and locally aggressive but benign lesions (2 aneurismatic bone cysts). We also examined 6 liposarcomas (1 low-grade, 3 mixoid, 1 round celles and 1 pleomorphic) to study if a different level of telomerase activity was present in different histotypes of the same tumor. To perform this study a non-radioactive polymerase chain reaction-bases Elisa assy was used (Telomerase PCR Elisa; Boehringer Mannheim Gmbh, Mannheim, Germany). All the tumors investigated were positive for telomerase activity and its intensity was dependent on the tumor grade. We also found telomerase activity in benign (but locally very aggressive) lesions such as aneurismatic bone cysts (ABC). However, the intensity of telomerase activity in ABCs was low compared to the presence of telomerase activity and its intensity seems to be correlated with aggressiveness. In high-grade bone tumors, the results showed tha the majority of the istotypes investigated presented a very high telomerase. Soft tissue tumors also presented telomerase activity, which may also be related with the presence of pulmonary metastases. In particular, analysis of the liposarcoma specimen showed a progressive increase of telomerase activity in relation to tumor aggressiveness and grade. These results support the hypothesis that, for each histotypes investigated, telomerase activity might be considered an important factor for tumor aggressiveness. Moreover, some results suggest a possible correlation between the intensity of telomerase activity and the patient's outcome. Our purpose is to investigate telomerase activity in bone and soft tissue tumors in a higher number of patients with a homogeneous and longer follow-up to highlight the possible correlation between intensity of telomerase activity and tumor aggressiveness and the presence of metastases or local recurrences.

Morphological diagnosis of unknown skeletal lesions— analysis based on cytology in 110 cancer patients

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We have previously shown that cytologic diagnosis based on fine needle aspiration biopsy (FNAB) is a safe and efficient method for the discrimination between benign, primary malignant and metastatic bone lesions. In this study, we address metastatic lesions specifically to assess the diagnostic accuracy and to ascertain whether FNAB permits identification of the primary lesion.

Patients and methods: Between 1990 and 1997, 444 patients were referred to the Department of Orthopedics, Karolinska Hospital for diagnosis of skeletal lesions of unknown type. Patients who had undergone prior biopsies or had been operated were not included. 116 of these patients proved to have metastatic disease or myeloma/lymphoma. In 6 patients the medical records could not be retrieved leaving 110 consecutive patients with metastatic carcinoma (80), myeloma (16) or lymphoma (14). All were investigated with FNAB and none had a previous history of malignancy.

Results: A correct diagnosis of metastatic carcinoma, lymphoma or myeloma was achieved by FNAB in 101 of the 110 patients (92%), it was misleading in 4 and inconclusive in 5. The four misleading diagnoses were of no clinical consequences. In 5 patients the FNAB was inconclusive. In all these patients the final diagnosis was made on histological material from surgical biopsy specimens. FNAB correctly diagnosed 15 of 16 patients with myeloma, 12 of 14 with lymphoma, and in 75 of 80 patients with metastatic carcinoma. Furthermor, the site and type of malignancy was correctly suggested in 2/3 of the patients with metastatic carcinoma.

Conclusion: FNAB is a safe and reliable method for the diagnosis of metastatic carcinoma, lymphoma and myeloma. Time consuming and costly investigations can be limited by choosing FNAB as the initial diagnostic method in the search for the primary tumor. Hence, the choice of radiological examinations, laboratory tests and biopsies can be efficiently guided by the result of FNAB of the skeletal lesion.

Osteofibrous dysplasia—clinico-pathologic features and risk of association with adamantinoma

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Osteofibrous dysplasia is a rare lesion usually observed during childhood, most commonly before age 10. Hidden for many years by the most frequent fibrous dysplasia, it has been recognized hand described as a separate entity in the early 70's. Since then several reports in the literature have confirmed its own peculiar features.

It is painless, self limiting benigne process almost invariably located in the tibial diaphysis and occasionally involving the ipsilateral fibula too, clinically associated with bone expansion and anterior bowing. Although pathologic fractures may occur significant deformity is uncommon and pseudoarthrosis is exceptional.

By far, the most interesting and intriguing aspect of this entity is its relationship with adamantinoma. Undoubtedly, they share clinical features : age range may overlap, location is essentially the same, radiographic features may be very similar, histologic aspects consisting of fibro-osseaous stroma and epithelial cells may be found in both the lesions. There is well documented evidence that some cases of adamantinoma have histologic features of osteofibrous dyspla-

sia. Despite scattered isolated reports, the "progression" of osteofibrous dysplasia into adamantinoma is less convincting.

Long term follow-up studies documenting the risk of adamantinoma development in patients with a well established and pre-existing diagnosis of osteofibrous dysplasia are lacking in the literature. Therefore, the relationship between these 2 entities remains controversial.

A study was undertaken in order to obtain clinico-radiographic long term follow-up on patients with histologically proven diagnosis of osteofibrous dysplasia, search for the possible occurrence of adamantinoma and eventually quantify this risk.

Methods: Between June 1943 and December 1997, 49 cases of histologically proven osteofibrous dysplasia were recorded at the author's institution. Of these, 24 cases were admitted and treated while 25 were sent for consultation.

All the patients with a potential minimum follow-up of 20 years have been contacted in order to obtain current physical examination and radiographs. Data are currently in the process of collection and elaboration but preliminary results are already available on 11 cases.

Results: Preliminary results obtained on 11 patients do not show any clinico-radiographic feature possibly suggesting the development of adamantinoma. Pain is essentially absent and the deformity, when present, is usually well tolerated. Unsatisfactory functional results and severe deformity are associated with inappropriate surgical treatment and complications.

Conclusions: Relationship between osteofibrous dysplasia and adamantinoma is unclear. Preliminary results seem to suggest that osteofibrous dysplasia-like areas may be encountered in adamantinoma more frequently that a clear development of adamantinoma on a pre-existing osteofibrous dysplasia can be currently proven. Data collection completion and its elaboration will hopefully help to clarify this debated topic.

Prognostic value of PCNA, Ki-67 (mibi) and p53 expression—results of a clinicohistopathologic correlation in a series of 36 cases of synovial sarcoma

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The aim of our study was to investigate about the prognostic significance of PCNA, Ki-67 and p53 expression in a series of 36 patients with synovial sarcoma (Ss) and evaluate the interrelations with other established clinicopathologic parameters (histotypes, nuclear grade, mitotic score, tumor necrosis, glandularity, tumor size and depth, chemotherapy and follow-up). Paraffin embedded tissue specimens of 36 patients who received definitive surgery for Ss of extremities were examined to detec nuclear immunoreactivity for PCNA, Ki-67 and p53 protein and each index was correlated with clinicopathologic features. Our study involved 23 men and 13 women, mean age 39 (5–64) years; median follow-up for entire group was 30 (1–168) months. 14 patients received chemotherapy (CT) in the last four years. Survival curves were generated using the Kaplan-Meier method. The overall survival rate for the group was 45% at 5 years, 30% at 10 years. Histologic subtype (monophasic versus biphasic), glandularity, age at diagnosis did not significantly affect survival rates.

All tumours contained cells with nuclear immunoreactivity for PCNA, Ki-67 (MIB1), just 8 cases were positive for p53 protein immunostain. The relationship between all parameters investigated were evaluated using univariate statistical analysis. A significant correlation between PCNA and Ki-67 scores was found. PCNA and Ki-67 indices were a more sensitive parameter for proliferative activity of tumor than nuclear atypia and histotype and were positively correlated with mitotic ratio. Our data suggest that large tumor size, mitotic ratio and high PCNA/Ki67 indices were a more sensitive parameter for proliferative activity of tumor than nuclear atypia and histotype and were positively correlated with mototic ratio. Our data suggest that large tumor size, mitotic ratio and high PCNA/Ki67 scores were adverse prognostic factors in Ss. The small number of cases (14) and the short follow-up does not allow us to evaluate a possible correlation with CT treatment.

Ki-67 is strongly prognostic in synovial sarcoma—analysis based on 86 patients from the Scandinavian Sarcoma Group Register

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The study was bases on 86 patients treated for primary synovial sarcoma 1986–1995 and reported to the Scandinavian Sarcoma Group Register of musculoskeletal tumors. All tumors were located in the extremities or on the trunk wall. MIB-1 and p53 was assessed in formalin-fixed paraffin-embedded tumor tissue. The prognostic importance of MIB-1 index, p53-expression as well as tumour size was analysed. Multivariate analysis identified 2 metastatic risk factors: increasing tumour size and MIB-1 > 9%. P 53 was not prognostic. The 5-year metastasis-free survival-rate for patients with small tumors (≤ 5 cm) and low MIB-1 (<10%) was 0.83 (95% confidence interval 0.64–0.92) but only 0.31 (95% CI 0.11–0.53) among patients with large tumors and high MIB-1.

Our study shows that metastatic disease in synovial sarcome is closely related to MIB-1 index. Using our model based on tumour size and MIB-1 index, cases with good and poor prognosis can easily be discriminated. Therefore our model can be used to identifiy patients who should be considered for adjuvant chemotherapy.

Metastais-free survival with respect to MIB-1 index and tumour size according to Cox's proportional hazard model.

Criteria	Hazard ratio	95% C.I.	p-value
Tumour size 1–3 cm	(Reference)	–	–
Tumour size 4–5 cm	3.9	0.86–18	0.08
Tumour size 6–20 cm	7.1	1.6–31	0.009
MIB-1 >=10%	2.2	1.0 –4.6	0.04

Osteosarcoma and the growth plate—imaging, pathology and outcome

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Prior to the use of preoperative chemotherapy, the growth plate was defined as a poor barrier to epiphyseal invasion of osteosarcoma (OS). Since those studies, the advent of more accurate staging techniques and the effect of preoperative intense chemotherapy have been changing this concept allowing the surgeon to expand limb-salvage indications. The authors analysed a homogeneous series of 40 children (age range: 7–14 years) affected by central high-grade OS and surgically treated after preoperative chemotherapy between January 1994 and December 1996. The tumors were all located in the knee area, 27 cases in the distal femur and 13 in the proximal tibia.

After surgery the specimen were histologically studied by macrosections. The growth plate was evaluated in all its patterns and the relationship between the OS and the physis was described according to a newly developed anatomical grading system in five groups:

- Grade 1: metaphyseal OS at more than 2.5 cm from an unaffected plate (7 patients).
- Grade 2: OS from 2.5 cm upto an otherwise unaffected physis where thin vascular channels were frequently seen (7 patients).
- Grade 3: OS abutting to a growth plate with unexpected maturative patterns, large vascular channels and transphyseal bone bridges. The range display of interposed tissue justified the definition of three subgroups (3a – 4, 3b – 3, 3c – 4; total 11 patients).
- Grade 4: gross epiphyseal invasion of OS tissue (11 patients).
- Grade 5: OS massively invading the epiphysis (4 patients).

The various grades were analyzed correlating the pathologic data with the preoperative imaging studies and with the outcome at a mean follow-up of 32 (17–50) months. In 21 cases (52%), the epiphyses were completely free of OS.

Standard radiography, isotope scan and CT did not always correlate with the pathologic evaluation. On the contrary, MR imaging, and particularly the coronal fast STIR sequence proved to be 100% accurate in evaluating the epiphyseal extent of OS tissue. No technique however was able either to differentiate the various features displayed in grade 3 or evidentiate the small intraphyseal channels seen in grade 2.

The anatomical grading system developed in this study would seem to correlate with prognosis. In grade 1, 2 and 3, IIB patients displayed an overall CDF survival of 83% while grades 4 and 5 showed an overall CDF survival of 55%.

The maturative patterns of the physes and particularly the presence of vascular channels and transphyseal bone bridges seen in grade 3 patients suggested a mechanism involving tumor-produced growth factors. Chemotherapy could arrest this mechanism in different phases, allowing the growth plate to react according to its residual viability.

These data suggest how the role of growth plate in facing the spread of OS cells must be reviewed and confirm the feasibility of intraepiphyseal osteotomies in selected OS cases.

Evaluation of prognostic significance of C-MYC and MDM2 expression in synovial sarcoma of the extremities

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Synovial sarcoma (SS) accounts for 5–10% of soft tissue tumors of the extremities and is characterized by a poor outcome, the overall survival rate of patients with localized disease being less than 30–40% at 10 years. Although primary tumor size, surgical margins, histologic variants (monophasic *vs* biphasic), and mean mitotic activity have been reported as prognostic markers of SS, their actual predictive value for clinical outcome is still controversial. Therefore, the identification of new reliable prognostic markers, is needed to improve the outcome of this tumor.

In a previous study (ref), we have found that the most common genetic aberrations in SS are gains at 8q and 12q, the chromosomal regions to which *C-MYC* and *MDM2* genes have been assigned. In the present study, in order to investigate whether these oncogenes may be important for tumor progression in SS, we evaluated by immunohistochemistry the overexpression of *C-MYC* and *MDM2* in a series of 32 primary SS.

Immunohistochemical analysis revealed nuclear accumulation of *C-MYC* in 9/32 cases (28%), whereas a positive nuclear immunostaining for *MDM2* was detected in 6/30 cases (20%). Since *C-MYC* appears to play a key role in the control of cell proliferation, on the same cases we also evaluated the proliferation rate with the MIB-1 MoAb, which specifically stains proliferating cells only. A high proliferation rate was found in 8/31 tumors (26%) and it was not significantly associated either with *C-MYC* or *MDM2* nuclear accumulation or with the histologic subtype.

The relationship with clinical outcome was analyzed in a subgroup of 27 patients with a minimum follow-up of 24 months. Among the parameters here considered, only *C-MYC* expression resulted significantly associated with a

worse clinical outcome, *C-MYC*-positive tumors showing a significantly higher incidence of relapse compared to *C-MYC*-negative lesions ($p<0.05$, Fisher's exact test).

These data suggest that, in SS, chromosomal aberrations which lead to an increased expression of *C-MYC* are associated with a higher incidence of relapse and may define high-risk groups of SS patients.

Reference: Szymanska et al., Genes Chromosomes & Cancer 23:213–219, 1998.

High incidence of probable non-Hodgkin's lymphoma in retrieved femoral-head specimen during routine hip arthroplasty (six cases out of 216 femoral-heads)

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In the bone bank of our hospital, histopathological screening has been performed as a screening test besides the recommended standards by the American Association of Tissue Banks (AATB) and the European Association of Musculo Skeletal Transplanting (EAMST).

We found 6 cases of probable non-Hodgkin's lymphoma out of 216 femoral-head grafts retrieved from 193 patients who underwent total hip arthroplasty, due to osteoarthritis of the hip. The donors included 42 males and 151 females (age: 42–90 years , mean: 69.1 years). The incidence was 2.8%.

According to the AATB and the EAMST criteria, three ptients would have been eligigle for donation while all screening tests were negative. Three other cases were excluded while they did not meet the criteria set by these organizations (one case had history of tuberculosis, one had prednisolone medication, the other had multiple sclerosis). Pre-operative radiographs of the hip joints showed all features of conventional osteoarthritis; there was no evidence of malignancy.

The incidence of NHL is rising in Europe, howewer, the reason for this increase is uncertain. Donors of femoral-head bone banking who undergo total hip arthroplasty are usually elderly people and malignancies such as lymphoma are more common amongst the elderly. Long latency periods prior to development of NHL has bee described on the patients with benign lymphoid aggregates. Therefore, the results in our bone banking cannot be ignored.

Few articles on histological examination of retrieved femoral-head grafts in total hip replacement have shown low incidence of similar cases suspicious of malignancy, especially lymphoma. The increased risk of NHL by donation, e.g. blood transfusion, has been discussed and the possibility can not be denied at present. This implies that bone allografts also migh increase the risk of NHL, which necessitates exclusion of all histopathologically suspicious materials. Further investigation seems to be necessary.

QUALITY OF LIFE

What is the price of cure in patients with a bone tumour located in the distal femur?— rotationplasty versus endoprosthesis

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Objective and methods: the distal femur is the most common primary site of malignant bone tumours in children and young adults. With the availability of different modalities of local therapy (limb salvage versus amputation) late functional results and quality of life measurements have become essential. In a prospective study the functional evaluation score of Enneking and quality of life (EORTC-QLQ C30) were determinded in a cohort of 713 patients. To date data of 133 patients with a musculoskeletal tumour in the distal femur were complete and evaluable.

Results: the median age at diagnosis was 15.5 (5.6–62.5) years. The median time of follow-up was 48 months. The surgical procedures included tumour resection and endoprosthetic replacement in 52 patients and A 1 rotation plasty in 53 patients. In patients with rotation plasty the functional results were better: the mean functional status scored 23.3/30 compared to 22.5/30 in pts with endoprosthesis. In the analysis of walking distance and fait these differences were significant. (walking distance $p=0.009$, gait $p=0.016$). In the quality of life analysis pts with rotation plasty had significant better results in physical functioning (PF) (mean 89.3 compared to pts. with rotation plasty faired better (mean 85.1) compared to pts with endoprosthetic replacement (mean 67.4) ($p=0.025$). Asking for limitation in hobbies work or other daily activites (RF2) pts. with rotation plasty had significant better results ($P=0.0001$) (mean rotation plasty 81.2, mean endoprosthesis 57.0). No or only mild pain related restriction in daily activities reported by pts. with rotation plasty (mean 9.3) whereas in the group with endoprosthetic replacement plain related restrictions were reported more often (mean 29.1) ($p=0.0001$).

Conclusion: The rotationplasty states a convincing surgical procedure and is characterised by practically unrestricted work activities. Significant better results in social, role and physical functioning show that there is no psychological outcome disadvantage of rotationplasty despite ist mutilation in pts. with distal femur tumours. The procedure have to be considered instead of amputation.

Functional outcome and quality of life after wide resection of pelvic Ewing tumors (ET)

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Local therapy of pelvic ET has remained a challenge due to its central localization and the usually large tumor volumes. Surgery has improved overall survival but may associated with considerable mutilation. The aim of the study was to analyze late outcome of surgical procedures.

Method: 15 patients were evaluated prospectively after wide resection of pelvic ET. All patients underwent surgery in a single institution, chemotherapy was administered according to the appropriate EI/CESS protocols, radiotherapy was added in all patients. Complications necessitating operative revision were analysed and functional results were scored using the functional evaluation system of Enneking. Quality of life and psychosocial functioning was assessed by the EORTC-score: QLQ-C 30. The mean follow-up was 5.8 (2.1–10.4) years. These results were compared to a référence group of 44 ET patients, surgically treated in the same institution with non pelvic primary tumor site, chemotherapy was administered in all cases, 38 patients underwent radiotherapy pre- or postoperatively. Both groups were comparable regarding age, gender, therapy modalities and follow-up.

Results: Mean incidence of surgical revision was 1.6 (0–6) times per pelvic patient, the reference group had a mean incidence of 1.1 (0–7) times per patient. Functional evaluation reached 68 (37–90)% in the pelvis group, the reference group got equal results (mean 75%, range 37% to 93%). Quality of life, function scales and symptom scales showed comparable results.

Conclusion: Wide tumor resection is recommended for pelvic ET. The functional result and quality of life parameters are comparable to other primary tumor sites and surgery adds to the safety of local control and overall survival.

Comparison between ondasetron vs granisetron vs tropisetron in the prevention of emesis induced by cisplatinum, adriamycin, and ifosfamide (delivered for prolonged continuous infusion) in patients with osteosarcoma—results of a randomized study

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The antimetic efficacy of ondasetron, granisetron and tropisetron was evaluated during the first two cycles o preoperative treatment in 90 patients with osteosarcoma of the extremity treated with neoadjuvant chemotherapy. The first cycle of chemotherapy consisted of 120 mg/m^2 of cisplatinum (CDP) for a 48-hour continuous infusion followed by 75 mg/m^2 of adriamycin (ADM) for a 24-hour continuous infusion. In the second cycle, delivered 3 weeks later, patients received 15 g/m^2 of ifosfamide (IFO) for a 120-hour continuous infusion. As prophylaxis of chemotherapy-induced emesis, pts were randomized to receive ondasetron (5.3 mg/m^2), granisetron (2 mg/m^2) or tropisetron (3.3 mg/m^2) in addition to 8 mg :m2 Dexamethasone. The cycles of chemotherapy always started at 8.00 a.m., and the antiemetic drugs were intravenously administered at 7.30 a.m. of each day of treatment.

A complete protection of emesis, defined as total absence of vomiting, was obtained in 512 of the 807 days of treatment (63%), without significant differences for the 3 drugs considered (67% of complete protection with ondasetron, 61% with granisetron, and 62% with tropisetron). Only 9 patients (10%), 3 for each group of the antiemetic drugs evaluated, had a complete protection for all the days of treatment.

The rate of complet protection was significantly higher for the cycles of IFO that for DCP/ADM (68.7% vs 56.9%, $p < 0.002$). For both CDP/ADM and IFO cycles, the rate of complete protection progressively decreased from the first to the last day of treatment (95.5% on day one vs 41.1 on day four, $P < 0.0001$).

In spite of the different half-life of the 3 antiemetic drugs, no differences in terms of complete protection were observed during the various hours of the day (complete protection=79%) in the morning hours; 83% in the afternoon, and 82% during the night).

We conclude that ondasetron, granisetron, and tropisetron show the same antiemetic efficacy with the regimens of chemotherapy used in the present study, and that in case of protracted infusion, cisplatinum, adriamycin and ifosfamide are highly emetizing and the antiemetic protection achieved is not adequate at all.