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Abstracts

1. Epithelioid sarcoma of the penis in 2 young men treated with radiotherapy and chemotherapy

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Background Epithelioid sarcoma most commonly occurs in the distal upper extremities. Penile epithelioid sarcoma have been described in only 14 cases. The clinical behavior of penile epithelioid sarcoma is similar to that in the extremities. The lesion is present for years before diagnosis and may be mistaken for Peyronie's disease, Radical surgery with or without adjuvant radiotherapy constitutes the mainstay treatment for the genitourinary sarcomas. We describe the management of 2 patients with epithelioid sarcoma treated at the National Cancer Institute of Milan.

Patients and methods 2 young men with high-grade penile epithelioid sarcoma were referred to our Institute. Both patients had a painful penile mass with urinary and sexual dysfunction. Considering the patients' young age and the clinical stage of disease, we decided to treat them with radiotherapy instead of a complete surgical resection.Both patients were treated with exclusive 3D dynamic-radiotherapy: Before radiation therapy the patients received Epirubicine/ Ifosphamide-based chemotherapy. A CT-simulation without contrast was performed to contur the target volumes, organs at risk and to evaluate the dose distribution. The beams arrangement consisted of 4 coplanar dynamic arcs using photons of 18 MV.

Results The treatment was well tolerated. The main early effect was dysuria and erythema of grade 1 (RTOG scale) but after therapy completion micturition function was improved. At the first control by MRI a PR was observed in one patients; the restaging study about the latter patient is actually in progress.

Discussion Since these lesions occurred in young men we decided to treat them by radiation, instead of surgery, using the conformal technique, to preserve and quality of life. We think that the new radiotherapy techniques decreasesing the side effects.

2. A rare case of indication for en bloc resection for metastatic tumor of the spine

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Introduction Surgical treatment of spine metastasis aims at: pain control, maintenance of spinal stability and preservation/restoration of neurological functions. En bloc resection for metastasis is done very rarely. The en bloc surgical technique and intralesional surgery is three times more difficult after preoperative radiotherapy.

Methods Male patient 40 yrs of age who in 2004 underwent intestinal resection for carcinoma. After 2 months the patient was diagnosed with metastatic lesions in the lumbar segment of the spine. After local radio-therapy his symptoms where still present. In January 2006 the patient came under our care with increased pain but with no neurological deficits. The patient underwent preoperative embolization, followed by en bloc resection of 2 adjacent vertebrae via posterior and anterior access. After 3 days the patient was able to walk.

Conclusion En bloc resection should be considered before other procedures only in case of solitary lesions or a favourable tumor histotype because of the aggressive nature of the procedure. Therefore, a multidisciplinary consensus should be obtained before any action is taken, because other treatment options may provide the same benefits without increasing morbidity risks.

3. Surgery and postoperative radiotherapy for simultaneous occurrence of malignant fibrous histiocytoma and olfactory neuroblastoma of paranasal sinuses

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Background One third of the few soft tissue sarcomas that occur in the head and neck (H&N) involve the sinunasal tract, in particular the maxillary sinus. Another neoplasm rarely arising in this area is the olfactory neuroblastoma (esthesioneuroblastoma), commonest in the upper nasal cavity in the region of the cribriform plate. For both kinds of malignancies the mainstay of treatment is surgery combined with radiotherapy (RT). To our knowledge, the simultaneous occurrence of a malignant fibrous histiocytoma (MFH) and an olfactory neuroblastoma in the H&N region has not been reported. We report the clinical management of such a patient.

Patient A 56-year-old man with a 4-month history of facial pain, epiphora and diplopia was referred to our Insitute. MRI showed a mass in the right maxillary sinus, extending into the nasal cavity, ethmoid sinus and the right orbit. A biopsy of the maxillary lesion revealed a sarcoma. The patient underwent anterior craniofacial resection, with dural excision, right maxillectomy and orbital exenteration. The defect was repaired with a vertical rectus abdominis free flap Microscopy showed a myxoid MFH of the maxillary sinus and an esthesioneuroblastoma of the ethmoid with bone and dural invasion.
The patient received postoperative RT. He underwent a planning computerized tomography (CT) scan with 5 mm slice thickness and spacing. Only one Clinical Target Volume (CTV) was outlined covering the surgery tumor bed with margin. Besides, organs at risk (OAR), such as optic chiasm, optic nerves, brainstem were delineated. The prescribed dose to target volume was 60 Gy with standard fractionation (2 Gy per fraction). The beams arrangement consisted of three 6 MV photon isocentric fields conformed with personalized cerrobend blocks. The target coverage and OAR sparing were satisfactory.

Results Before RT the patient presented with dysosmia and facial hypoesthesia. During RT the patient had grade 2 mucositis, dermatitis and dysgeusia. At present,

14 months after RT, there is no evidence of recurrence. Late effects include persisting dysnomia, mild fibrosis in the irradiated fields and occasional facial pain.

Conclusion The coexistence of these kinds of tumor is very rare. For both malignancies good reponses to surgical treatment and radiation therapy were recorded.

4. New cancer-specific fusion genes in endometrial stromal sarcoma

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Introduction Endometrial stromal sarcomas (ESS) represent less than 10% of all uterine sarcomas. Cytogenetic data on this tumor type are limited to 32 cases and the karyotypes are often complex, but the pattern of rearrangement is nevertheless clearly nonrandom with particularly frequent involvement of chromosome arms 6p and 7p. Recently, a specific translocation t(7;17)(p15;q21) leading to the fusion of two zinc finger genes, *JAZF1* and *JJAZ1*, was described in a subset of ESS.

Material and results We present 3 ESS whose karyotypes were without the disease-specific t(7;17) but instead showed rearrangement of chromosomal band 6p21, twice as an unbalanced t(6p;7p) and once as a three-way 6;10;10-translocation. All 3 tumors showed specific rearrangement of the *PHF1* gene, located in chromosomal band 6p21. In the 2 tumors with t(6;7), *PHF1* was recombined with the *JAZF1* gene from 7p15 leading to the formation of a *JAZF1/PHF1* fusion gene. The third tumor showed a t(6p;10q;10p) as the sole karyotypic abnormality leading to the fusion of *PHF1* with another partner, the *EPC1* gene from 10p11; *EPC1* has hitherto not been associated with neoplasia.

Conclusion The *PHF1* gene encodes a protein with 2 zinc finger motifs whose involvement in tumorigenesis and/or tumor progression has not been reported before, but its rearrangement clearly defines a new pathogenetic subgroup of ESS.

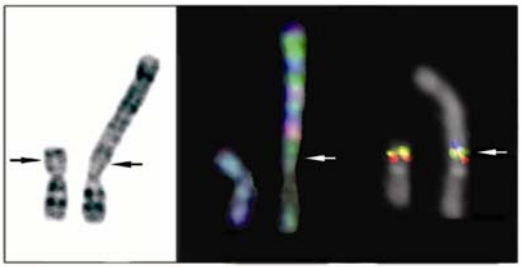

Figure Legend: G-banding (left), M-FISH (centre), and FISH cohybridization on the derivative chromosome 7 of clones RP11-81H15 (red signal) and RP4-781A18 (green signal) for the *JAZF1* gene, and clone CTD2307H19 (blue signal) for the *PHF1* gene (right).

5. Inhibitor effect of osteosarcoma cell lines on dendritic cells Types 1 (DC1) and 2 (DC2)

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Introduction Immune surveillance against tumours is inefficient, with a reduction of number and function of DCs in patients with cancer. We investigated whether osteosarcoma cell lines have an inhibitor effect on DC1 and DC2 *in vitro*, by analysing the expression of co-stimulatory molecules.

Material and methods DC1 and DC2 were selected from healthy donors' mononuclear cells and plated with or without different concentrations of osteosarcoma cell lines (SJSA, U2OS, SAOS, HOS and MG-63) in presence of GM-CSF and IL-4 for DC1 and of IL-3 for DC2. GM-CSF, IL-4, IL-1β, IL-6, PG-E2 and TNF-α were added at DC1, and LPS at DC2, for the maturation. In both the experiments we analysed the DC2 surface for CD40-80-83-86-DR by flow cytometry.

Results We obtained a high decrease of DC maturation. With DC1, the inhibition is more evident for CD80, CD86, CD40 and DR, but less so for CD83. With DC2, there is a strong inhibition of CD80, CD83, CD86 and DR, while a minor effect is evident for CD40.

Conclusions Osteosarcoma cell lines have a strong impact on DC maturation and, therefore, they highly interfere with the DC essential immune function as antigen presenting cells.

6. Nutlin 3a in combination with prevailing chemotherapy gives promising results in sarcoma cell lines

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Introduction Nutlins are selective small molecule inhibitors of the p53-mdm2 interaction, and can displace the p53 protein from the complex with mdm2, thus stabilizing the p53 protein. Treatment with Nutlin induces apoptosis and cell cycle arrest in several tumours, specifically those with amplification of the MDM2 gene. This amplification is frequent in sarcomas and results in the lack of normal p53 activity, although p53 is normal in virtually all cases where MDM2 is amplified. In our study we have investigated the effectiveness of Nutlin 3a in combination with doxorubicin or cisplatin to see whether this could reduce the amount of drugs needed in a toxicity perspective and to investigate if the combination also could be effective also in tumours without the mdm2 amplification, where the p53 pathway in many cases is deranged.

Material and methods The study was performed on 4 different cell lines with wt p53; OSA and T778 (ampl mdm2), U2OS and RMS13 (normal mdm2). The cells were exposed to different combinations and ratios of Nutlin 3a, doxorubicin and cisplatin for 120 hours. Cytotoxicity was evaluated by the sulphorodamine B assay and the type of drug interaction was assessed using the method of Chou and Talalay.

Results Nutlin 3a and doxorubicin produce a synergistic effect (combination index <1) both in cell lines with and without amplification. The combination effect of Nutlin 3a and Cisplatin was less clear.

Conclusion Our study gave promising results with the combination of Nutlin and chemotherapy, e.g. doxorubicin, both in sarcomas with and without mdm2 amplifications.

7. Comparative genomic hybridization profiling in pleomorphic soft tissue sarcomas

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Pleomorphic soft tissue sarcomas like the leiomyosarcoma (LMS), malignant fibrous histiocytoma/undifferentiated pleomorphic sarcoma (MFH) and pleomorphic liposarcoma are characterized by complex karyotypes and lack of specific reciprocal translocations. Array based comparative genomic hybridization was applied to 18 LMS and 37 MFH in order to characterize copy number changes affecting these pleomorphic tumors. 32K microarrays with tiling coverage and high resolution produced from BAC clones were used. The LMS and MFH shared similar genomic imbalances. The most common recurrent gains, present in 50–60% of the samples, were at 1q21-q22, 5p14-p15, 7p22, 19p13, 20q13.33, and 21q22.3. Loses on 2q37, 9p21, 13q14, and 16q12 were most recurrent. High levels of DNA amplification were detected in multiple short regions including 1p31.3-p32.2, 2q14.1-q14.3, 3p11.2-p12.1, 4q12, 5q11.1-q12.1, 11q22.3, 14q32.33, and 19p12-p13.11. Significant losses of chromosomes 2, 10, and 13, and gains of 1p, 5p, 7, 19, and 20q were also detected. Among the genes present in the amplification peaks were *CDK4* and *MDM2*, whereas *RB1* and *CDKN2A* were among the genes frequently deleted. In conclusion, complex but recurrent alterations were identified and included novel genes as well as those previously implicated in soft tissue sarcoma tumorigenesis.

8. Luciferase imaging of a Balb/c mouse syngeneic metastatic osteosarcoma model

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There is a great need for clinically relevant animal models to study the metastatic spread and to validate novel approaches for the control of systemic disease in osteosarcoma (OS). Here we report the development of a syngeneic (Balb/c) murine model of OS using a cell line (OS50L) originally derived from a spontaneous murine tumor (Schmidt et al., 1989). OS50L cells were engineered to express Luciferase as a reporter gene and were injected orthotopically in the distal femur of syngeneic BalbC mice. Luciferase bioluminescence allowed the monitoring of primary tumor growth throughout the first 3 weeks from injection and, within 5 weeks, revealed the appearance of spontaneous pulmonary metastases in 100% of the mice.
This animal model of OS faithfully recapitulates some of the most important features of the human malignancy, such as metastatization to the lung, and has the added value that progression of the tumor can be monitored by non-invasive imaging in living mice. These features make it a valuable tool to improve our understanding of the biology of the tumor, to identify molecules which may inhibit its growth/prevent its metastatic spread, or to validate new treatments.

9. Identification of the NG2 Proteoglycan-Collagen type VI Interplay as a Pro-Metastastic Factor in soft tissue sarcomas and design of approaches for the exploitation of NG2 as an immunotherapeutic target

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Metastases of soft-tissue sarcomas show a >5-fold increase of NG2 proteoglycan, a primary surface ligand for collagen type VI (Col VI), when compared to the primary lesion(s). RNAi knockdown of NG2 in sarcoma cells specifically impairs their motile and invasive capabilities in response to Col VI matrices, whereas forced expression of the proteoglycan enhances their metastatic potential in wild type animals, but not in Col VI knock-out mice. The combined use of animals carrying single- and double gene deletions chemically-induced carcinogenesis allows for the definition of the tumour initiating/propagating versus pro-metastatic role of NG2. Higher dissemination capabilities of NG2-expressing sarcoma cells are associated with accentuated intravasation and the use of dominant-negative mutant cells defines the relative involvement of the extracellular Col VI-binding domain and the cytoplasmic cytoskeletal adapter tail of the proteoglycan in the tissue dissemination process. Phospho-proteomics shows that the Col VI-NG2 interaction triggers defined signalling cascades and DNA microarray screens clarify some of the transcriptional modulations in NG2-overexpressing cells. Antagonists of the cell signalling pathways engaged by NG2 are currently exploited in vivo and, in parallel, immunomodulatory dendritic cell-derived peptides of the proteoglycan are being elaborated for putative therapeutic vaccination approaches of sarcoma patients.

10. Plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) levels as new marker for drug-induced cardiotoxicity

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Background The incidence of cardiotoxicity following anthracyclin treatment of adult and childhood cancer varies according to the method used for its detection (TnI, TnT etc.). Recently it was shown that plasma levels of NT-proBNP is a new and useful marker for cardiac failure. In fact, recent studies reported a correlation from NYHA class (I–IV) and increased plasma levels of NT-proBNP. We assessed the prevalence of LVEF reduction and its possible association with plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) levels, in asymptomatic patients treated with anthracyclines.

Patients and methods Asymptomatic adult and children patients who had received anthracyclines during their treatment for cancer were evaluated. The LVEF was determined by M-Mode echocardiography. Additionally the patients' plasma NT-pro BNP levels were determined.

Results Preliminary data show that high prevalence of reduced LVEF is associated with increased NT-proBNP levels. The NT-pro BNP levels in patients with reduced LVEF were higher than those measured in patients without LVEF reduction (0.38 ± 0.02 versus 0.12 ± 0.01 pmol/mL respectively, p=0.009). A cut off NT-pro BNP level of 0.2 pmol/mL could differentiate patients with LVEF reduction from those with normal or greater than expected LVEF.

Interpretation In asymptomatic patients who have received anthracyclin chemotherapy, high NT-proBNP levels could be an early indication of subclinical cardiotoxicity and open a possible role of this marker for the screening of this subset of patients.

11. Increased risk of malignancies in a population-based study of 820 soft tissue sarcoma patients

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Introduction Soft tissue sarcomas (STS) have been associated with various rare cancer syndromes and have been described to occur at increased frequencies in survivors of childhood cancer, but also adult patients with soft tissue sarcomas have been suggested to have an increased risk of multiple primary malignancies.

Material and methods We studied the risk of multiple primary malignancies in a population-based cohort of 820 patients with primary STS of the trunk wall or extremity. Syndrome-associated and radiation-induced sarcomas were excluded. Primary malignancies after the STS diagnosis was analyzed by means of Standard Morbidity Ratio (SMR), with the Southern Swedish population as reference. The analyses were stratified by sex, calendar year, and 5-year age groups.

Results Among the 820 patients, 203 tumors were identified before or after the STS. 131 individuals (16%) developed 1 additional malignancy and 33 (4%) developed 2 or more primary malignancies in addition to the STS.

Conclusion An increased risk of multiple primary malignancies following the STS was identified (SMR=1.25; 95% CI=1.03–1.51; p=0.02). The only specific tumor type that had a significantly increased risk was STS (SMR=18; 95% CI=8.–34; p<0.001). In summary, 20% of the patients developed at least 1 additional malignancy and a particularly increased risk of development of a second primary STS was identified.

12. The Scandinavian Sarcoma Group (SSG) experiences from ongoing intergroup trial EURAMOS 1

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Introduction Impact of new therapies in osteosarcoma patients will probably be small, and only assessable in large patient populations. Thus, in order to conduct a study with a reasonable fast accrual time, intergroup collaboration is necessary. We will discuss SSG trial centres experiences from the ongoing joint protocol, EURAMOS 1, of 4 osteosarcoma intergroups.

Results The protocol writing took about 4 years. Thus, time gained in a faster accrual might be lost in the process of protocol writing. Compromises were made. One of those were to define a Common Data Set (CDS), but allowing for intergroup specific CRFs. SSG does not have experience in conducting randomized clinical trials under ICH/GCP guidelines and EU directive 2001/20/EC. Therefore, extensive learning was needed. For instance, the planned internal auditing of the data centres, necessitated a set up of general Standard Operating Procedures for data management, and a study specific Data Management Plan. During this work, the CDS was thoroughly reviewed, and some suggestions of amendments to CDS were done. This working process has been slow, since possible changes needs to be approved by all intergroups.

Conclusion EURAMOS 1 have involved a lot of effort and administrative work. However, there has been a great learning process.

13. Status of the European and American Osteosarcoma Study, EURAMOS-1

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Background Euramos-1 is a joint protocol of 4 multinational groups (COG, COSS, EOI, SSG) aimed to optimize treatment of osteosarcoma.

Patients and methods Patients aged <41 y with operable high-grade osteosarcoma are eligible, including patients with operable metastases. All patients receive a 3-drug combination of methotrexate, doxorubicin, and cisplatin preoperatively (MAP). Postoperative treatment is stratified according to histologic response. Poor responders are randomized to either continue MAP or MAP with addition of ifosfamide /etoposide. Good responders continue with MAP and are randomized to interferon maintenance therapy or not. As part of the infrastructure a Common Data Center and Safety Desk have been established. A Quality of Life project is launched as part of the protocol.

Results As of December 31st, 74 patients from 43 institutions in 8 participating countries were registered into the trial. In Scandinavia 11 patients from 5 institutions in Norway and Sweden has been recruited and 3 have been randomized by Feb 28th. The trial is now also open for recruitment in Denmark and Finland.

Conclusion The Euramos-1 protocol for operable osteosarcoma made possible through extensive international collaboration has been successfully launched in 14 countries including 4 Scandinavian countries.

14. A Scandinavian Sarcoma Group (SSG) treatment protocol for adult patients with high-risk soft tissue sarcoma of the extremities and trunk wall

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Introduction From January 1998 through 2005 the SSG has treated 93 patients with high-risk soft tissue sarcoma (STS) in a prospective multicenter trial (SSG XIII) with chemotherapy and accelerated/hyper-fractionated radiotherapy. The regimen consisted of 6 cycles of doxorubicin 50 mg/m^2 + ifosfamide 5 g/m^2 with dose modification based on nadir values. Dependent on surgical resection margins 36 Gy or 45 Gy (1,8 Gy per fraction, 2 fractions daily), were given interpolated with chemo-therapy. Inclusion criteria were presence of at least 2 of the 3 prognostic factors: tumor size >8 cm, necrosis, and vascular invasion. The preliminary survival data is promising, and toxicity seems moderate. Based on these results, and data supporting the prognostic importance of peripheral tumor growth pattern (pushing vs infiltrtive), the SSG is planning a new protocol for high-risk STS with a modification of the current system of prognostication.

Methods and results 519 pathology reviewed STS in the SSG registry were included in a retrospective analysis of the prognostic factors size, vascular invasion, necrosis, infiltrative growth pattern, depth and malignancy grade. Based on the relative importance of the prognostic factors, a novel system for prognostication was found to accurately identify patients at risk for metastasis, and clearly separate high-risk and low-risk groups among grade III–IV tumors. Tumors with vascular invasion are a priori considered as high-risk and following this selection, a further stratification into risk-groups is based on the presence of 2 of the 3 factors tumor size >8 cm, necrosis, and infiltrative tumor growth. A local recurrence during the first year after primary treatment also renders the tumor high-risk, irrespective of prior classification.

Conclusion In an impending adjuvant protocol for high-risk STS the SSG suggests use of an inclusion decision tree based on the following criteria: 1. vascular invasion 2. presence of at least 2 of the risk factors: size >8 cm, necrosis, infiltrative growth and 3. local recurrence within 1 year as a cause for alternative, later inclusion. 6 cycles of doxorubicin 60 mg/m^2 and ifosfamide 6 g/m^2 will be given interpolated with hyperfractionated, accelerated radiotherapy. A preoperative treatment proposal will also be presented.

15. Prognosis and therapeutic targets in the Ewing family of tumors – sixth framework programme- 1st year update

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This project will through collaborative studies define prognostic markers and new therapeutic targets in the Ewing's sarcoma family of tumors (ESFT) to provide rigorous scientific justifications for the development of clinical trials for this rare disease. The main objective of the project is to evaluate the prognostic relevance of selected markers (EWS/FLI-1, secondary genetic alterations, CD99, IGF-IR, NOVH, erbB-2 and TTF1) and the effectiveness of therapeutic approaches targeting some of these molecules. During this first year we have obtained some clear answers with respect to prognostic and therapeutic relevance of erbB-2, CD99 and IGF-IR. In addition the genetic profile of experimental models with differential metastatic ability have identified some new prognostic molecular markers that appear to have statistical significance (Gal3BP, Hint1, calnexin). Cytogenetic profiles of cell lines and tumor samples identified some novel small deletions and amplifications. Two tissue arrays have been constructed and are now available for the analysis of some new other genes. Finally the project is taking steps in the construction of new therapeutic tools, such as antisense oligos against EWS/FLI1 in new, more effective vectors and chimerized antibody against CD99.

16. Soft tissue sarcoma in adolescents and young adults

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Background Adolescents and young adults (AYA) are often diagnosed with cancer at advanced stage and have low enrollment in clinical cancer trials. The EURAMOS protocol for osteosarcoma includes all patients aged <40 y. Pediatric treatments have historically had more chemotherapy in their protocols than adult regimens. Young patients are likely to tolerate a more intensive treatment then older adults and might therefore be considered for a more intensive treatment.

Patients and methods At Umeå University Hospital we have treated patients aged 18–30 with soft tissue sarcoma according to pediatric protocols including 3 neoadjuvant courses of chemotherapy, surgery, and 6 postoperative chemotherapy courses with concomitant hyperfractionated radiotherapy and 6 months maintenance low-dose chemotherapy. Data from the SSG registry was analysed from 1984–2004 comparing soft tissue sarcoma patients aged 18–30 (n=273) to those >30 years at diagnosis (n=3122).

Results The AYA group tolerated the prolonged chemotherapy from pediatric protocols well without any severe toxicity. The SSG registry data showed that the AYA group had significantly higher frequency of advanced disease at diagnosis, also more often deeply situated tumors and had different sarcoma types compared to adults aged 30 or older. Extents of surgery and radiotherapy frequencies were similar between the groups but chemotherapy was significantly more frequently used in the AYA group. The tumors were more often of low grade and the AYA group still had better event-free and overall survival than the older age group.

Conclusions Patients aged 18–30 have a different spectrum of tumors and if their survival is going to be improved they ought to be enrolled in clinical trials in collaboration between adult and pediatric sarcoma groups as they tolerate more intensive chemotherapy.

17. Most benign lesions around the knee do not need filling following curettage?

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Introduction Benign lesions around the knee are usually filled with autograft, allograft or bone substitute following curettage. Is the filling really needed for healing?

Patients and methods 146 benign cysts around the knee were treated by curettage and left empty to consolidate without supplementation. 83 (57%) of the patients were male. The average age was 27(1–71) yr. Mean follow-up was 4 (0.5–20) yr. The average cyst size was 63 (3–240) cm^3. The histological diagnoses included GCT (47%) followed by chondroblastoma (14%), ABC (13%) and enchondroma (6%).

Results Clinically the result was good or excellent in 90% of the cases. There was good consolidation of the defect evident radiologically in almost all of the cases. There were 14 (10%) fractures identified on postoperative radiographs. The average size of these defects was 108 cm^3 compared with 58 cm^3 for defects without fracture (p=0.003). All but 2 fractures were managed non-operatively.

Conclusion Large benign lesions around the knee can be managed with curettage alone. Defects larger than 50 cm^3 carry a risk for postoperative fracture.

18. Multifocal ossifying fibromyxoid tumor, benign or malignant? Follow up using scintigraphy?

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Background Ossifying fibromyxoid tumor was first described by Enzinger et al 1989. The tumor is composed of small round cells within a myxoid matrix. Transition toward hyaline fibrosis and osteoid formation is seen in almost half of the cases. Positive staining for vimentin, S-100 is found in more than one third of the cases. Local recurrence is common. Recurrence at multiple sites have been reported in a few cases. We present a case (male, now aged 65) with ossifying fibromyxoid tumor with local recurrence and occurrence at multiple sites - a multifocal benign lesion or a malignant lesion?

Case story During 1971–1981 the patient was operated on, at a local hospital, 3 times because of locally recurrent (left shoulder) 4–5 cm large tumors with calcifications. The microscopic diagnoses were leiomyomas with calcifications.
In 1987 a third large local recurrence with calcification was removed by a wide resection. The tumor expressed S-100 and vimentin and showed similarities to clear cell sarcoma. Postoperative radiotherapy was given. In 1999 he developed a tumor in the left groin, removed by a wide resection. The microscopic appearance was similar to that in the previous tumors but the diagnosis was at this time considered to be multifocal ossifying fibromyxoid tumor. The patient has since been operated because of a new local recurrence in the left shoulder and occurrence of a tumor with ossification in the right groin. This lesion had increased uptake at scintigraphy (Tc-99m – hdp), performed for the firs time, and which we will try for screening in the future.
We suggest this rare entity be included in the SSG Registry for further studies.

19. Successful treatment of a child with a Ewing-like, t(15;19)-positive bone tumor: Implications for the diagnostic impact of genetic analyses

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Introduction Ewing tumors are difficult to distinguish from other round cell tumors. One potential differential diagnosis is poorly differentiated carcinoma with the translocation t(15;19) (q13;p13), resulting in a *BRD4/NUT* fusion gene. Typically, this tumor affects children or young adults, with a predilection for midline head and neck or thoracic structures, and the outcome is invariably fatal.

Materials and methods and results A 10-year-old boy presented with a tumor in the iliac bone that was diagnosed as Ewing tumor, and the patient was treated according to the SSG IX protocol. Cytogenetic analysis had shown a t(15;19) (q13;p13) as the sole change, which at FISH-analysis was found to result in rearrangement of both *BRD4* and *NUT*. Morphologic, immunophenotypic, and ultrastructural re-examination did not disclose any epithelial differentiation.

Conclusions t(15;19)-*BRD4/NUT*-positive tumors may arise in locations more typical for other pediatric tumours, such as Ewing tumor, and they do not always display epithelial differentiation. More importantly, our patient has remained in complete continuous remission for 13 years, demonstrating that some patients with t(15;19)-positive tumors may be successfully treated. Finally, these results highlight the question to what extent the diagnosis of, and treatment strategy for, Ewing tumors should be based on tumor cell morphology or genetic signature.

20. Specific T-cell therapy for very high risk osteosarcoma patients

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Introduction We studied the possibility of generating osteosarcoma specific cytotoxic T lymphocytes (CTL) and their function and specificity.

Material and methods We used osteosarcoma cells lines or dendritic cells (DC) pulsed with osteosarcoma lysates or with MAGE, SSX and SART-3 peptides to stimulate healthy donor mononuclear cells, by adding different cytokine combinations (IL-2, IL-7, IL-12 and IL-15). After 3 stimulations we evaluated the phenotype (CD3, 4, 8, 16, 56), the specificity (by ELISPOT Assay) and the cytokine secretion (by FlowCytomix Kit) of the CTLs.

Results We succeeded in developing CTLs, which are CD8+, specific for osteosarcoma cell lines, which do not recognize autologous PHA blasts or K562 cell line, and which secrete IFN-gamma. In particular, CTLs generated with osteosarcoma cells lines not only recognize the line used, but also 4/5 of the other osteosarcoma cell lines tested. CTLs generated with autologous DC pulsed with osteosarcoma lysates secrete IFN-gamma only against the line used for the stimulation; CTLs generated with autologous DC pulsed with peptides recognize all the osteosarcoma cell lines and some of the peptides alone.

Conclusions T-cell therapy for the osteosarcoma is feasible and we will shortly be setting up a clinic protocol.

21. Liposarcoma – outcome based on 243 patients from the SSG register

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Introduction We analyzed local recurrences, metastases and survival in patients with liposarcoma of the trunk wall and extremities diagnosed 1986–1998 and reported to the SSG Register from sarcoma centers in Norway and Sweden. After review of 319 patients by the SSG Pathology Board the diagnosis was retained in 243 patients.

Results 26% had recurrent disease, i.e. 9% had local recurrence only, 12% had metastases only and 5% had both. Among low-grade lesions, the local recurrence rate was only 10 % despite intralesional or marginal margins in 56% and only 12% had postoperative radiotherapy. Among high-grade lesions the local recurrence rate was 21%. Only 59% with intralesional or marginal margin had radiotherapy. The local recurrence rate was 22% in Grade IV tumors with wide margins but without radiotherapy.
The 10 years metastasis-free survival was 0.9 in the low-grade group and 0.7 for high-grade. Overall, 16% of the patients died because of tumor.

Conclusion Radiotherapy can not be recommended routinely in low-grade liposarcomas. In high-grade lesions radiotherapy is indicated after intralesional and marginal margins and should be considered after wide margins.

22. Results from the Scandinavian Sarcoma Group, SSG XIV, Osteosarcoma trial

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Introduction The SSG XIV trial was based on the experience from previous SSG and ISG-SSG studies and was aimed to improve outcome in classical osteosarcoma.

Patients and methods Patients with extremity localised high-grade osteosarcoma with no metastases at presentation were eligible. All patients received a combination of methotrexate, doxorubicin and cisplatin preoperatively. Good responders continued with the 3-drug combination whilst poor responders were salvaged with addition of 3 courses of high-dose ifosfamide.

Results From March 2001 to Dec 2005 71 patients were recruited. 5 patients were excluded due to a revised diagnosis to clear cell sarcoma (1) or metastases at presentation (4). With a median follow-up of 34 months for survivors the projected 3-year event-free survival and metastases-free survival are 71% and 75% (± 12%) respectively. 8 patients are dead due to osteosarcoma (5) or treatment related (3). There is no difference in outcome between males and females (p=0.7). In univariate analyses outcome is better for good than poor histological responders (p= 0.03).

Conclusion The preliminary survival data compares favorably with previous SSG osteosarcoma trials. Good histologic response is associated with good outcome.

23. GIST mainly has an infiltrative growth pattern supporting surgery with wide margins whenever possible

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Introduction There is no consensus on the role surgery in patients with GIST in the era of Imatinib. Unfortunately has recurrent disease been recognized even after adjuvant therapy and furthermore do patients continue to develop resistance to the drug even though survival has dramatically increased. This means that surgery still has an important role in the treatment of GIST. In other sarcoma tumors has there long been known the importance of wide margins in order to decrease local recurrence rate.

Patients and results In order too investigate the importance for this in GIST tumors we analysed the growth pattern in GIST tumors at our institute. Of the 117 patient known to us were growth pattern only examined in 26 patients. Of these had 18 infiltrative growth and 8 had pushing border. In the group of patients with infiltrative growth had 3 patients intraabdominal recurrence whereas non in the group with pushing border. Metastasis developed in 5 patients in the infiltrative group and in 3 in the pushing group.

Conclusion Among the patients that had tumors with infiltrative growth 3 patient developed local recurrence while none of the patients with pushing border. There was no difference in the groups in developing distant metastasis. Even though this study is much too small it still show that most of these tumors had an infiltrative growth pattern supporting that they as other sarcoma tumors should be operated with wide margins whenever possible in order to achieve microscopic free margins. Furthermore, were local recurrence found only in the group of tumors with infiltrative growth that further strengthen this hypothesis.

24. Chondrosarcoma in patients with hereditary multiple exostoses

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The reported risk of malignant transformation in hereditary multiple exostoses (HME) is 1 to 3%.

The last 15 years we have operated 7 patients with this type of chondrosarcoma, 4 located in the pelvis and 3 in the shoulder. The median age at diagnosis was 25 (19–45) yr, and the duration of symptoms 5 (3–9) yr. All patients had large tumors, and were treated with extensive resections: 2 hemipelvectomies, 1 type I+II+III resection, 1 type I resection, 1 proximal humerus resection, 1 scapulectomy and 1 shoulder disarticulation. All tumors were low-grade, and there are no recurrences.

All patients had been informed about the usual complications of HME, but none of them were adequately informed about the increased risk of malignant transformation or had any follow-up. According to Campanacci (1999) all patients should be followed for life, monitoring the deeper exostoses (pelvis, spine) with serial radiograms every 2–3 years. No center in SSG has such screening programs.

After treating these 7 young patients with major resections of low grade tumors which should have been detected earlier, we want to discuss better follow-up routines including clinical investigation and radiological surveys for patients with HME.

25. Dedifferentiated chondrosarcoma – results of a European wide study

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Introduction We have investigated prognostic factors in 317 patients with dedifferentiated chondrosarcoma from 8 European centres.

Patients and results The mean age was 57 (15–89) yr and the most common site was the femur (46%). 25% of patients presented with a pathological fracture and 23% had metastases at diagnosis. 30% of patients received chemotherapy with 47% under 60 having chemotherapy compared with 10% over 60. One third of this group had neoadjuvant chemotherapy and the rest had adjuvant treatment. 88% had surgery with limb salvage used in 80%. Local recurrence was related to adequacy of surgical margins, arising in 8% with wide margins and 28% with marginal margins. The overall survival was 38% at 2 years and 24% at 5 years. In patients without metastases at diagnosis these figures were 43% and 26%. Poor prognostic factors for survival were: Metastases at diagnosis, amputation or no operation, marginal margins, local recurrence, age over 60 and pathological fracture at presentation. Chemotherapy did not produce a survival benefit.

Conclusion Dedifferentiated chondrosarcoma carries a dismal prognosis. Early diagnosis and complete surgical excision still offer the best prognosis for this condition.

26. What is the optimum follow up regime for sarcoma patients?

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Introduction There is considerable uncertainty about how best to follow up patients following treatment of a sarcoma. Studies in the USA have shown that the cost of follow up for the same condition can vary 43-fold at different centres.

Method and results We carried out an investigation of sarcoma clinicians in the UK to assess if there was consensus about the best follow up. Although most clinicians agreed that follow up was valuable the frequency of this and the investigations varied widely for identical clinical scenarios. This resulted in a potential 20-fold difference in cost between the most aggressive follow up regime with regular cross sectional imaging and the least intensive (clinic follow up only).

Discussion There is a need for a randomized controlled trial to identify the value of follow up and whether there is any place for intensive or even decreased follow up regimes. We propose a trial that will investigate this and invite comment about it's acceptability across Europe. The trial will have three arms with intensive, standard and patient focussed follow up and patients will be stratified by the depth of the tumor. Endpoints will include quality of life, cost equivalence, local recurrence and survival.

27. Quality of life and mental distress in survivors of extremity bone sarcoma

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Purpose To evaluate the Quality of life and level of mental distress in survivors of extremity localized osteosarcoma and Ewings sarcoma (EBTS).

Patients and methods At minimum of 5 years after treatment, 130 (72 males) EBTS answered a questionnaire containing SF-36, Hospital Anxiety and Depression Scale (HADS), Fatigue questionnaire (FQ) in addition to questions about demographic data. The median age at follow up was 29 (15–57) yr. Median time since diagnosis was 13 (6–25) yr. Limb sparing surgery was performed in 60%. SF-36, HADS and FQ findings were compared to age and sex adjusted norm data.

Results 52% were married/cohabitant, and 42% had completed a college/university degree. 67% were working full or part time. The EBTS had lower scores in all the physical dimensions of SF-36 compared to their norm sample ($p<0.001$). The males had also lower scores in two of the mental dimensions (Social Functioning, $p=0.04$ and Role Emotional, $p=0.008$). We did not find any significant difference in the level of anxiety nor depression for male EBTS compared to the norm, but female EBTS had a higher anxiety level ($p=0.04$) than their norm sample. The male EBTS had higher physical ($p=0.003$) and total fatigue ($p=0.004$) than norm.

Conclusion At long-term follow-up the female EBTS show a higher anxiety level, the males have more fatigue and all have reduced physical functioning compared to the norm.

28. Psychological support during chemotherapy in patients with sarcomas

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Background Psycho-oncology is based on the principle that disciplines' integration is essential to carry out a system of care facing the whole patient's needs. This discipline is particularly addressed to patients with a psychological uneasiness independent from a psychopathological illness but as a result from a traumatic condition due to cancer experience. Sarcomas frequently affect young-adult people who are planning their future and in many cases are active in job. Therapies could cause changes, also irreversible, in body-scheme, in quality of life, in job capability and in family balance. Those problems require a psychological support in many cases.

Patients and methods Since May 2004, in our Department 53 patients (median age 57 (19–71) yr, 29 men) with sarcoma have been followed by psycho-oncology service. All of them were treated with chemotherapy (21 with palliative intent, 18 in adjuvant and 14 in neoadjuvant settings). All patients were subjected to HADS (Hospital Anxiety and Depression Scale) questionnaire. All of them received an interview, 6 patients more than 1 (2–4).

Results We found these psychological disorders: anxiety, more frequently in patients during adjuvant and neoadjuvant therapy (56%). Difficulty in coping with the new situation, especially in the youngest people (two thirds between 18 and 40 yr). Their greatest worries consisted on the loss of working identity and family problems management. Depressive disorder involved different types of patients (44%) and the problem was more frequent in advanced or metastatic disease.

Conclusions Patients taken in care since the first treatment and followed during the whole period of chemotherapy developed a better coping style during the whole period of therapy and follow-up. Our findings confirm the importance of psychological support to increase adherence to the therapy and to improve the quality of life.

29. Terminal phase in patients with advanced sarcomas: a perspective study for a better assistance

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Background Sarcoma are rare tumors, with an incidence <1% of all neo-plasms. Very few data are available on the clinical and psychological needs of sarcoma patients in the terminal disease phase when the goal is no more cure or prolongation of life, but control of symptoms related to the disease progression.

Methods As a specialized interdisciplinary group we have started to treat the patients with soft tissue and bone sarcomas since 1994. We have recorded in a perspective study the problems of the terminal patients from 1998 until 2005. We have followed 178 patients (median age 57 yr, 95 men) with sarcomas in terminal phase for at least 3 months with median PS 50 Karnofsky. 143 had soft tissue sarcomas, 28 osteosarcomas, and 7 Ewing sarcomas. Extremities were the origin of the disease in 34% of the cases, abdomen in 29%, trunk in 22% and other sites in 15%. Site of recorded metastases: lung in half of the patients One third of the patients had inoperable primary tumors or local relapse.

Results During the last month of their lives patients complained of: pain 79%, dyspnoea 49%, anxiety 17%, gastrointestinal obstruction 25%, anorexia 51%, bleeding 8%. 57% of the patients died at home, 43% at the hospital. To control pain, dyspnoea and other symptoms, radiotherapy (43%), supportive care (100%) and palliative chemotherapy (36%) were used. Psycological support was offered to two third of the patients as well as physical rehabilitation (57%).

Conclusion Supportive care of patients with advanced sarcomas is an underestimated aspect in clinical oncology. We have shown that these patients have specific needs, in some aspects, different from those of patients with the most common cancers. A complex, multidisciplinary approach is necessary to improve the assistance and quality of life of these patients.

30. The Scandinavian Sarcoma Group Skeletal Metastasis Registry. Functional outcome and pain after surgery for bone metastases in the pelvis and extremities

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Background Few authors have reported function and pain after surgical treatment of patients with bone metastases. In 1999 the Scandinavian Sarcoma Group (SSG) initiated the Skeletal Metastasis Registry as a multi-centric, prospective study to provide a scientific basis for treatment recommendations.

Patients and methods We analyzed function and pain in 530 patients (mean age 65 yr) operated on (599 operations) for non-spinal skeletal metastases at 9 SSG centres. 7% were operated for more than 1 metastasis. Carcinoma of the breast, prostate, kidney and lung were the dominating primary tumors.

Results 25% of the patients died within 6 weeks after operation. 11% of the patients had complications. 6% had a reoperation. In patients surviving more than 1 year the reoperation rate was 12%. 92% of the patients had no, light or moderate pain at 6 weeks (first control) and 6 months follow-up. Patients using opioids were reduced from 40% preoperatively to 30% at 6 months. In patients with metastases in pelvis or lower extremity 79% were walking with or without crutches at 6 weeks and 88% at 6 months. More patients with metastases in proximal femur were mobile at 6 weeks and 6 months when treated with prosthesis than with internal fixation. 77% of the patients had a good or moderate Karnofsky performance score 6 weeks after operation and 85% 6 months after operation.

Discussion Palliative surgery for bone metastases improves function and decrease pain. Most operated patients had metastases in the pelvis or lower extremity with increased mobility after surgery. Prosthetic replacement seems to do better than internal fixation for metastases in the proximal femur. We need to analyze function and pain earlier than 6 weeks postoperatively to determine the expected survival time limits for surgical treatment of bone metastases.

31. A new strategy for preoperative radiotherapy of retro-peritoneal sarcoma

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Introduction Surgery remains the only potentially curative therapy for retroperitoneal liposarcomas (RPLS) but fails in about 50–70% of patients. Classically preoperative radiotherapy (RT) involves the *entire* tumor volume (figure 1): yet this may *not* be necessary when the tumor has only displaced adjacent organs *without* invasion and will be easily resected. We suggest a new approach of preoperative RT for RPLS with the Clinical Target Volume (CTV) limited to the contact area between the tumor mass and the posterior abdominal wall in order to minimize the irradiation in the high-dose region of the abdominal organs at risk for toxicity.

Material From June 2001, 18 patients diagnosed with RPLS have been treated following a pilot protocol of preop EBRT, 50 Gy/2 Gy/fr: the CTV was restricted to the posterior abdominal wall region judged to be at higher risk for local relapse (figure 2). All patients underwent CT-based simulation and Conformal or Intensity Modulated Radiotherapy (IMRT). Toxicity was evaluated during and after treatment (NCI-CTC scale).

Results The planned RT treatment was completed without severe toxicities and a total surgical resection was possible in all patients 14 (5–25) days after the end of the preop EBRT with resection of adjacent viscera in 16 patients. A postoperative gastric bleeding and perforation was successfully treated. At a follow up of 3–45 months 1 patient developed an in-field local relapse (left paravertebral space), another lung metastases.

Conclusion This strategy is feasible and well tolerated: the rate of resecta-bility is not compromized by limiting the preop CTV to the posterior wall.

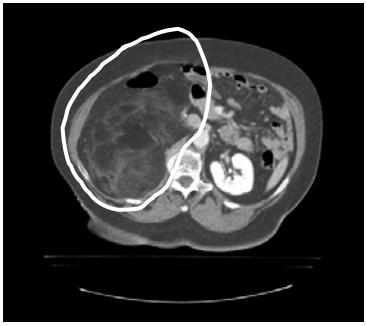

Fig. 1

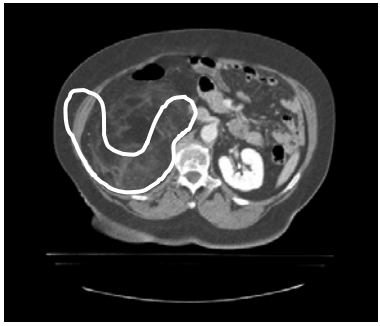

Fig. 2

32. Update from the EURO-E.W.I.N.G. 99 Trial

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The EURO-E.W.I.N.G. 99 trial is stratified into 3 risk strata, i.e. R1: patients with good response to 6 courses of primary VIDE (vincristine, ifosfamide, doxorubicin, etoposide) chemotherapy and all small (<200 ml tumor volume) irradiated tumors; R2: patients with poor response (>10% viable tumour) and/or large irradiated tumors and patients with pulmonary metastases at diagnosis; R3: multifocal or skeletal disease at diagnosis. R1 patients are randomized for either cyclophosphamide or ifosfamide maintenance chemotherapy, R2 for either conventional VAI (vincristine, actinomycin D, ifosfamide) or busulfan/melphalan high-dose therapy with autologous stem cell rescue, and R3 patients are advised to receive busulfan/melphalan high-dose therapy with autologous stem cell rescue following VIDE induction chemotherapy.
As of February 2006, 1702 patients were registered into the trial from the participating groups: GPOH, SFCE, UKCCSG, and EORTC. 535 patients were randomized for R1, 235, for R2. The study is still ongoing and the results are blinded. 92 of 535 R1 patients and 73 of 235 R2 patients have presented with an event. With respect to R3, in particular younger patients and patients with a smaller number of skeletal foci seem to have benefited from busulfan/melphalan high-dose therapy with stem cell rescue.