P1 Cytogenetic and molecular genetic analyses of endometrial stromal sarcoma: nonrandom involvement of chromosome arms 6p and 7p and confirmation of JAZF1/JJAZ1 gene fusion in t(7;17)

F. Micci[1], C.U. Walter[1], M.R. Teixeira[1,2], I. Panagopoulos[3], B. Bjerkehagen[4], S. Heim[1]

[1]Dept of Cancer Genetics, The Norwegian Radium Hospital, Oslo, Norway, [2]Dept of Genetics, Portuguese Oncology Institute, Porto, Portugal, [3]Dept of Clinical Genetics, Lund University Hospital, Lund, Sweden, [4]Dept of Pathology, The Norwegian Radium Hospital, Oslo, Norway
fransesca.micci@hfstud.uio.no

Endometrial stromal sarcomas (ESS) are rare neoplasms with the capacity to both invade the myometrium locally and give rise to extra-uterine metastases. Cytogenetic aberrations have been reported in 22 ESS. Rearrangements of chromosomes 6, 7, and 17 are the most consistent features, with a t(7;17)(p15~21;q12~21) seemingly being a cytogenetic hallmark of these tumors. Recently, the presence in 7p15 and 17q21 of two zinc finger genes was demonstrated that were fused as a result of the translocation.

We describe 4 additional cases of ESS with abnormal karyotypes whose aberrations included structural changes of chromosome arms 6p and 7p. Molecular investigation identified a JAZF1/JJAZ chimeric transcript in the only tumor with a t(7;17), but no such fusion product in another tumor with another 7p15 rearrangement. These findings and the fact that the short arm of chromosome 7, with breakpoints in 7p15~21, was found rearranged in altogether 5 cases beyond the 9 ESS with t(7;17), support the idea that the JAZF1/JJAZ is present in only a subset of ESS and that other 7p15 rearrangements may utilize other pathogenetic pathways in this tumor type. In addition, the clearly nonrandom involvement of 6p21 (rearranged in 7 tumors in which the t(7;17) was not present) suggests that gene(s) reside here that may be of importance in tumor genesis.

P2 Characterization of supernumerary rings and giant marker chromosomes in well-differentiated liposarcomas using a combination of G-banding, CGH, M-FISH, and chromosome-specific FISH

F. Micci[1], M.R. Teixeira[1,2], B. Bjerkehagen[3], S. Heim[1]

[1]Dept of Cancer Genetics, The Norwegian Radium Hospital, Oslo, Norway, [2]Dept of Genetics, Portuguese Oncology Institute, Porto, Portugal, [3]Dept of Pathology, The Norwegian Radium Hospital, Oslo, Norway
fransesca.micci@hfstud.uio.no

Supernumerary rings and/or giant marker chromosomes are often found in connective tissue tumors of low-grade or borderline malignancy, such as well-differentiated liposarcomas/ atypical lipomas. Banding techniques have proved insufficient to identify the genomic composition of such rings and markers, but fluorescent in situ hybridization has shown that they are composed mainly of amplified material from chromosomal segment 12q13-15. This region is known to contain several genes of importance in tumorigenesis, such as MDM2, HMGIC, CDK4, GLI, and SAS, all of which are frequently coamplified in mesenchymal tumors.

We have studied supernumerary ring chromosomes and giant marker chromosomes in lipogenic tumors using the new FISH-based screening techniques comparative genomic hybridization (CGH) and multiplex-FISH (M-FISH) in combination with G-banding and analysis by chromosome- and locus-specific FISH. Our findings demonstrate that chromosome bands 12q13 and 12q21 are always involved; in particular, the CGH analysis showed that 12q21 is the band most often amplified in these chromosomal structures. In three tumors, two dinstinct but close amplicons in 12q could be identified corresponding to bands 12q13-15 and 12q21. Our data also show that the rings may be composed of interspersed sequences from several different chromosome arms, with chromosomal segment 1q21-23 being gained in 12 out of 22 tumors.

P3 Automatic estimation of S-phase fraction in flow cytometric DNA histograms from 259 patients with soft tissue sarcomas – prognostic implications?

P. Gustafson[1], B. Baldetorp[2]

Depts of [1]Orthopedics, [2]Oncology, Lund University Hospital, Lund, Sweden
pelle.gustafson@ort.lu.se

Aim We have earlier shown the prognostic strength of flow cytometric (FCM) S-phase fraction (SPF), manually calculated according to Baisch planimetric principle, for metastasis-free survival in soft tumor tissue (STS) (Gustafson et al 1999). This method does not enable correction for debris or nuclei aggregates appearing in the SPF region. By using an automatic method enabling corrected SPF values for the background disturbances, we have now re-examined all DNA histograms and investigated whether the prognostic value of SPF could be further strengthened.

Materials and methods In DNA histograms from FCM analysis of formalin-fixed and paraffin-embedded STS samples from 259 patients, SPF corrected for debris and nuclei aggregates, and DNA ploidy status were automatically determined with the ModFit Lt 3.1™ software. The SPF-values were categorized into low and high values using an optimized cut-off point for separating the material in good versus poor prognosis regarding 5-year metastasis-free-survival-rate (MFSR). Obtained data were compared with earlier results in which SPF was available in 159 patients.

Results DNA-ploidy status was reported in all samples (diploid n=85, non-diploid n=174). SPF was reported in 181 tumors (reasons for failure were high debris contribution and/or high CV (>8%) and/or small non-diploid cell population). Mean and median SPF were 9.9% and 7.0% (range 0.0 – 44%) respectively. With a cut-off point of 2.0%, 33 tumors had low and 148 had high SPF values. Comparison between the manual Baisch method and the automatic ModFit Lt method (n=153 cases): Spearman rang correlation, r_s=0.89, Metastasis free survival (5 year):

	Cut-point (%)	MFSR (5y) low-risk/high-risk	p-value	late met-rate in low-risk group (low SPF)
Baisch	3.0	0.93/0.54	<0.001	5/8
ModFitLT	2.0	0.97/0.58	<0.001	4/5

Conclusion Both methods give SPF values, equal in prognostic strength regarding 5-year MFSR. The automatic ModFit LT-software estimated SPF values that were marginally better in predicting late metastases in the good risk group. With ModFit LT SPF can be reported more often. Furthermore, SPF values estimated by ModFit LT are reproducible (intra- and inter-observer).

References: Gustafson P, Baldetorp B, Fernö M, Åkerman M. Prognostic implications of various models for calculation of S-phase fraction in 259 patients with soft tissue sarcoma. Br J Cancer 1999; 79(7/8): 1205-9.

P4 Abdominal desmoids: the role of MR

S. Ortori[1], V. Zampa[1], E. Ceretti[2], L. Crocetti[1], C. Spinelli[1], A. De Marchi[3], C. Bartolozzi[1]

[1]Dept of Oncology and Transplants and of the new technology in Medicine, Pisa, [2]Fortis Institute Forte dei Marmi, [3]C.T.O. Turin, Italy

Aim To establish the accuracy of MR in the diagnosis of abdominal desmoids, in the evaluation of their growth and in the discovery of eventual recurrences.

Patients and methods 8 patients underwent MR examination for soft tissue tumors in the abdominal wall; the study protocol included SE T1 weighted sequences, FSE T2, STIR and dynamic study with mdc. The signal intensity was evaluated in relationship to the surrounding muscle intensity.

Results In the T1 weighted, 5 lesion resulted isointense and 3 hypointense to he muscle, while in the T2 weighted all the lesion showed a hyperintense inhomogeneus signal to the muscle with hypointense areas in the context due to the presence of abbondant fibrous tissue. All cases showed a significant enhancement even if in 5 cases it was slow and inhomogeneus and in 3 marked and inhomogeneus. Desmoids have been correctly diagnosed in 7/8 cases. The exact growth of the tumor was correctly identified in all cases. After surgery MR has shown recurrence in 1 patient.

Conclusion MR has been efficient in the diagnosis of abdominal desmoids and in the evaluation of their growth, so permitting a correct surgical plane. The siting, the signal intensity and behaviour of lesion before and after mdc permits the correct diagnosis of the nature of such lesions.

P5 Free vascularised fibula and arthrodesis in the ankle after resection of the distal tibia

S. Skjeldal, T. Lona, C. Trovik, G. Follerås

The Norwegian Radium Hospital, Oslo, Norway
sigmund.skjeldal@klinmed.uio.no

We treated 3 patients with osteosarcoma in the tibia with resection of the tibia including the distal articular surface. A vascularised fibula from the other leg was fixed to the remaining proximal tibia and to the talus by compression screws and a titanium lateral tibial head butress plate (Synthes).

Patient 1 is a 13-year-old boy with a IIB osteosarcoma. He was operated with free margins, no external support was used, and full weightbearing allowed after 8 months. 5 years later there is no evidence of disease. The graft has healed, he walks without support, and has no pain. MSTS functional score 83%.

Patient 2 is a 32-year-old woman with a IIB osteosarcoma, operated with free margins, no external support and full weightbearing after 8 months. 2 years after surgery she was operated for lung metastases. There is no signs of local recurrence, she has no pain, and walks without support. MSTS score 70%.

Patient 3 was a 14-year-old girl with a IIIB osteosarcoma. She had at diagnosis a tumor in the distal femur, a skip lesion in the proximal femur and lung metastases. She was treated with a total femur resection prosthesis (HMRS) and bilateral thoracotomy. 2 years later a metastasis developed in the distal tibia of the other leg.The tumor and the surrounding soft tissue was removed, and a composite vascularised fibular graft with muscle and skin was used for reconstruction. Soft tissue revisions had to be done, the plate was removed after 6 weeks and substituted with screws. A plaster of paris and later an orthosis was used. She had a fracture in the graft which healed, and she could walk shorter distances without support. MSTS score 60%. She died from lung metastases 2 years later.

Discussion Limb salvage after resection of the distal tibia can be performed with a resection prosthesis, allograft, or autograft and arthrodesis. The patients reported show that healing and acceptable function can be achieved by using free vascularized fibula and arthrodesis in the ankle.

P6 Unusual aneurysmal bone cyst

A. Walløe

Orthopedic center, Ullevål University Hospital, Oslo, Norway
anders.walloe@ulleval.no

The patient is a 17-year-old girl. She had experienced pain in her groin for 11 months and with increasing intensity for the last 4 months. She had pain after activity and also at rest but not during the night. The investigations included a radiogram of the hip, MRI and a CT guided biopsy of the lesion. The investigations demonstrated a cortical defect and the tumor invaded the vastus intermedius but not the bone marrow. The patient was operated on in January 2003 and the tumor was removed without any reinforcement of the femur. The patient was immediately free of pain. This case is presented because of the unusual radiograms and MRI pictures.

P7 Childhood sarcoma in Sweden 1960-1998

A.C. Dreifaldt, M. Carlberg, L. Hardell

Dept of Oncology, University Hospital, Örebro, Sweden
lottie.dreifaldt@orebroll.se

Background An increase in childhood cancer incidence has been reported from Europe and US. The Swedish Cancer Registry covers the entire population and has a good case ascertainment. We studied the incidence of sarcoma in children over a 38-year period.

Method All cases of malignant disease in children 0-14 years, reported to the Swedish cancer registry 1960 to 1998, were identified and the cases of sarcoma studied. For each case, information on ICD-7 site code and pathology code was obtained. Annual change in incidence from 1960 to 1998 was estimated using the exponential regression model, and average annual incidence for 1990-1998 was calculated for the different types of sarcoma.

Results Soft tissue sarcoma constitute 5.5% of all childhood cancer, the change in incidence per year was +0.13%, 95% confidence interval (CI) = -0.76, 1.04. The incidence was 0.79 /100 000 person years (py), slightly higher for boys than girls, and highest in the 0-4 year age group. The most common histologies were rhabdomyosarcoma, malignant mesenchymoma, and fibrosarcoma. The most common sites engaged were the head and neck region and hip and lower extremities. For malignant bone tumors, the change in incidence per year over the period studied was +0.21%, 95% CI= -0.81, 1.25. The bone tumors constitute 3.9% of all childhood cancer, osteosarcoma 2%, Ewing sarcoma 1.6% and chondrosarcoma 0.2%. The incidence of osteosarcoma was 0.26/100 000 py and of Ewing 0.20/100 00 py. The incidence was highest in the 10-14 year age group. 74% of the osteosarcomas occurred in the long bones of the lower extremities, the second most common site (13%) was long bones in the upper extremities/scapulae. The sites most commonly affected by Ewing sarcoma were bones in lower extremities, pelvis, and ribs/sternum/clavicle.

Conclusion Childhood sarcoma is a rare disease and few cases occur each year in Sweden. Unlike other types of childhood cancer the incidence of soft tissue sarcoma and bone sarcoma has not increased from 1960 to 1998.

P8 Severe toxicity mainly manifested as GAVE (gastric antral vascular ectasia) in a Ewing patient undergoing HD-BuM and peripheral blood stem cell support

K. Sundby Hall[1], J.P. Poulsen[1], G.F. Lauritzsen[1], D. Torfoss[1], W. Reed[2], I. Taksdal[3], E. Helset[4], K.E. Giercksky[5], S. Kvaløy[1]

Depts of [1]Oncology, [2]Pathology, [3]Radiology, [4]Anesthesiology, [5]Surgery, The Norwegian Radium Hospital, Oslo, Norway
k.s.hall@klinmed.uio.no

A case of severe toxicity from treatment with protocol ISG/SSG IV is reported. A 19-year-old man presented with an inoperable tumor in the right ileosacral region and a metastasis to L3. Biopsy showed a Ewing sarcoma that was confirmed by the presence of EWS-FL11 fusion transcript.

Induction chemotherapy consisted of 7 cycles: Vincristin 7.5mg/m^2, doxorubicin 450mg/m^2, cyclophosfamide 7400mg/m^2, ifosfamide 33g/m^2 and etoposide 600mg/m^2. He developed significant toxicity as repeating neutropenic fever, septicemia and diarrhoea (positive clostridium difficile toxin tests). After the cyclophosfamide and etoposide (mobilizing cycle) signs of capillary leak syndrome occurred (peripheral oedema, pleural effusions, ascites, weight gain 15kg/4 days).

Radiotherapy Hyperfractionated radiotherapy was given to the iliac tumor (54Gy) and to L2-L4 (42Gy) concomitant with ifosfamide (etoposide was omitted due to previous toxicity).

HD-BuM Pneumonia, oral mucositis and hematemesis complicated the post-transplant period. Early gastroscopy revealed dark blood and clots in the antrum. After blood removal, multiple hemorrhagic spots were seen. Resection of antrum and the terminal ileum were done due to continuous bleeding. Histopathology showed dilated capillaries filled with erythrocytes and fibrin thrombi just below the surface epithelium being typical for gastric antral vascular ectasia (GAVE). Total bilirubin increase, weight gain and hepatomegaly occurred as suspicious for veno-occlusive disease (VOD). The bleeding continued, and he developed respiratory failure and died on day 75. Autopsy revealed the same vascular changes in the stomach and the small intestinal remainder.

GAVE is an unusual event of gastric bleeding in marrow transplant patients (ref). Male gender, VOD, oral busulfan and growth-factor use are factors possibly associated with GAVE. Since busulfan may contribute to the development of GAVE, monitoring of serum concentrations of this drug should be warranted.

Ref Tobin RW, Hackman RC, Kimmey MB et al: Bleeding from gastric antral vascular ectasia in marrow transplant patient. Gastrointest Endosc 1996;44 (3):223-9

P9 Treatment of advanced soft tissue sarcoma in clinical practice

N. Wall, H. Starkhammar

Dept of Oncology, Linköping University Hospital, Linköping, Sweden
najme.wall@lio.se

Despite of the poor effects of cytotoxic drugs in treatment of soft tissue sarcomas (STS), the patients often are offered this treatment option. The purposes of this retrospective study were to evaluate therapy effects and to compare our results with published data. The files from 77 patients with locally advanced or metastatic disease, treated during 10 years, was studied. First-line treatments: CYVADIC (cyclophosphamide+vincristine+docorubicin+dacarbazine), n=36, RR= 28%. IVP/ VIG (different combinations of etoposide and ifosfamide ± granulocyte colony-stimulating factor), n=18, RR= 22%. Doxorubicin+ ifosfamide, n=19, RR=5%. Other drugs, n= 4. Second-line treatments: CYVADIC, n=13, RR= 15%. IVP/VIG, n=25, RR=8%. Third-line (n=13), and fourth-line (n=5) treatments resulted in no responses.

Conclusion Chemotherapy in STS has limited effects also according to our study. Because of few patients treated with each drug combination and due to the design of the study, the result from first and second lines treatments do not allow direct conclusions regarding best choice of treatment. The study indicates no benefit of further treatment beyond second line. The need of new drugs and controlled clinical trials is obvious.

P10 Quality of life and long-term morbidity in bone sarcoma patients

L.H. Aksnes[1], H.C.F. Bauer[2], K. Sundby Hall[1]

[1]Dept of Oncology, University Hospital, The Norwegian Radium Hospital, Oslo, Norway,
[2]Dept of Orthopedics, Karolinska Hospital, Stockholm, Sweden
l.h.aksnes@klinmed.uio.no

Introduction The aim of this study is to evaluate functional outcome, long-time morbidity and quality of life (QoL) in patients treated for extremity localized Ewing's sarcoma or osteosarcoma.

Patients The intention is to include 150 patients in Norway and Sweden treated according to the SSG-protocols SSGII, SSGIV, SSGVIII, SSGIX. At the time of follow-up the patients are $\geq$ 15 years old and the observation period is $\geq$ 5 year after end of treatment.

Methods
A. The function is evaluated according to Enneking's system (MSTS) and Toronto Extremity Salvage Score (TESS).
B. Long-term morbidity (cardiovascular disease, renal function, ototoxicity and fertility) is investigated.
C. QoL is measured by a questionnaire consisting of SF-36, HADS, IES, Fatique questionnaire in addition to demographic data.
.
Results Of the 60 Norwegian patients, 25 (16♂ and 9♀) have been examined until April 03. Median age at follow up is 32 years (range 17-52) and median follow up time is 14 years (6-19). Only 1 was treated for sarcoma in the upper extremity. Limb sparing surgery had been performed in 12.

A. Function: Median Enneking Score was 70(20-90) and median TESS score was 87(43-98) with no significant difference between the amputated and limb- sparing ones.
B. Long-term morbidity: 11 had acquired one or more secondary diseases after end of treatment (Heart failure (2), hypertension (4), diabetes (2), renal failure (1), reflux (3), pericarditis (1), hyperthyroidism (1) and depression (2)).
11 patients had S-magnesium below reference limit and needed substitution. Bilateral hearing loss was seen in 17. Four had got children after end of treatment.
C. QoL: 9 had never been married, 12 were married/living with someone and 4 were divorced. 10 patients had education from college or university. 14 were employed full-time, 3 employed part-time, 7 were on rehabilitation and 1 was in high school.

Present status
Norway: The examination of the Norwegian patients will be completed before summer 2003.
Sweden: The investigation will start soon.