radiotherapy, the PET data must be spatially co-registered to the planning CT data set. Therefore, the PET images must be acquired with the patient in the treatment position, on a flat couch top, with immobilization devices, and using markers at skin positions visible in the image. For this purpose, combined PET/CT scanners with increased bore size and flat-bed inserts are preferable. The initial lymphoma volume on the pre-chemotherapy PET/CT-scan must be contoured on the planning CT-scan done after chemotherapy, and image fusion may be employed to allow pre- and post-chemotherapy images to be combined.

Myeloma: MRI is superior to PET in the assessment of bone marrow involvement, whereas PET/CT is superior for the detection of extramedullary disease. Hence, they may supplement each other in the evaluation of the extent of disease. This is particularly important for the differentiation between solitary plasmocytoma, which may be curable by local radiotherapy, and multiple myeloma, where systemic treatment is indicated and radiotherapy is only palliative.

Leukemias: Only very few publications exist, but PET may be of value in detecting extramedullary infiltrates guiding treatment both in the primary and the recurrent situation.

98 INVITED

Role of PET in clinical trials of novel therapies in haematology

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FDG-PET/CT scans have been clearly demonstrated to be the most sensitive and specific imaging modality currently available for patients with lymphoma. Nevertheless, the extensive published literature provides little guidance as to the optimal use of this technology. Although widely applied for staging, assessment during and following treatment and for posttreatment surveillance, data prospectively validating PET in those settings are limited. Moreover, PET results may be confounded by issues such as variation in interpretation among readers, necessitating the requirement for central review in clinical trials. The positive predictive value is relatively low as a result of a large number of false positives related to timing of the scans, the regimen being used, infection, sarcoidosis, inflammation, and others. In 2007, the International Harmonisation Project standardized interpretation of PET scans and provided recommendations for the use of PET in clinical trials (Cheson, et al J Clin Oncol 25;579–586, 2008). For patients with routinely FDG-avid, curable histologies (e.g. diffuse large B-cell lymphoma (DLBCL) and Hodgkin's lymphoma (HL), PET scans should be done prior to and following therapy. However, for other histologies, PET scans should only be considered if complete remission is a primary study endpoint and the scan was positive prior to therapy. Post-treatment surveillance PET/CT scans are not cost-effective and should not be routinely performed.

Numerous studies demonstrate that a PET scan performed after one or more cycles of therapy is a better predictor of outcome than standard prognostic scoring systems; however, whether altering treatment on the basis of that information improves outcome remains a critical clinical question. Thus, numerous risk-adapted treatment strategies are under investigation to reduce the amount of unnecessary therapy for patients with favorable disease, and to improve the outcome for poor-risk patients. In North America, protocols are accruing patients with limited stage, bulky, or advanced stage HL who are being treated with standard doses of adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) and further treatment determined by the results of a PET scan after two cycles of therapy. Similar trials are ongoing in Europe. Early interim PET scans are also being evaluated as a surrogate endpoint for expediting evaluation of new agents. For example, in the CALGB Lymphoma Committee, patients with previously untreated follicular lymphoma undergo a PET/CT scan following one cycle of a biological doublet and the results correlated with outcome.

Thus, at present, in clinical practice PET should be reserved primarily for the pre- and post-treatment evaluation of the curable, FDG-avid lymphomas. Application of this technology to other settings must first be prospectively validated. It is the goal of current and planned clinical trials to better establish the role of PET/CT in the management of patients with lymphoma leading to improved outcome.

Scientific Symposium (Tue, 22 Sep, 09:00−11:00)
Recent breakthroughs and future directions

99 INVITED

SIOP brain tumour trials

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Brain tumours are the leading cause of solid tumours in paediactrics and a major cause of cancer related-death during childhood. They represent a specific challenge for increasing cure rates while decreasing the morbidity related to the diseases and to the treatments. The SIOP-Europe brain tumour committee conducts collaborative projects in all the main subtypes of paediatric brain tumours (low and high grade glioma, medulloblastoma/primitive neuro-ectodermal tumours, ependymoma, intra-cranial germ cell tumours, craniopharyngioma, atypical teratoid rhabdoid tumours) as well as studies upon quality of survival.

The recently closed SIOP- Europe Brain tumour committee studies will be presented, as well as the ongoing studies and the current projects.

We will insist upon:

- the upper age limit which makes some studies opened not only for children and adolescents but also for young adults, especially for medulloblastoma and intra-cranial germ cell tumours
- the introduction of selected biological parameters that may help to therapeutic stratification in some childhood brain tumour subtypes

100 INVITED

Improving outcomes in Wilms tumour: an update from the SIOP Renal Tumours Study Group

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With current approaches to risk stratification, approximately 15% of children with Wilms tumour eventually die of their disease while half are exposed to treatments that carry a significant risk of late sequelae. The philosophy of improving treatment is therefore changing emphasis from improving overall survival to maximising relapse free survival while minimising risks of late effects for an individual patient, i.e "cure at least cost". This is particularly important for the young children affected by Wilms tumour (median age 3 yrs), who are more susceptible to permanent long term side effects that may only become apparent years after treatment has ended.

The current trial of the SIOP Renal Tumours Study Group, SIOP WT 2001, continues the philosophy of reducing treatment intensity for the majority, with a randomised question about the need for doxorubicin in the post-operative chemotherapy for stage II and III, intermediate risk histology Wilms tumours. This randomisation is expected to close to recruitment at the end of 2009. The answer to the trial question will require long term follow up to fully assess the balance of risks of removing a potentially cardiotoxic drug from front line therapy.

This trial has also introduced a new 'high risk' category based on the histological response of the blastemal component of Wilms tumour to pre-operative chemotherapy. Preliminary analysis of the outcome of this subgroup, which represents ~8% of all Wilms tumours, shows that EFS for localised disease is improved by intensifying chemotherapy to the 'high risk' stratum. However, when metastatic at diagnosis, outcomes are as bad as for diffuse anaplastic tumours, with EFS of ~30%, despite intensive chemotherapy with a 4 drug regimen.

Future strategies involve better definition of the molecular characteristics of 'blastemal type' Wilms tumour and assessment of prognostic biomarkers, including those currently used by the Children's Oncology Group (allele loss on chromosomes 1p and 16q) for risk stratification. These associated biological studies should complement histological risk stratification and identify practical markers of resistant blastema to simplify diagnosis of this entity, which is currently very time consuming for pathologists. Recent analyses by genomic profiling have shown an association of copy number changes in *MYCN* with the SIOP 'high risk' Wilms tumour categories. Gain of *MYCN* is emerging as a finding in several other childhood cancers

beyond neuroblastoma, where it was originally described. Emerging therapies directed at MYCN function in other tumours should be considered for testing in high risk Wilms tumour. Such novel therapeutic strategies, together with a risk-stratified, protocolised approach to treatment of relapse, are expected to continue to improve outcomes for children with Wilms tumour and to allow the majority to be cured without late sequelae.

102 INVITED

Germ cell tumour trials: recent advantages and future directions

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Germ cell tumors (GCTs) are heterogeneous and vary with respect to clinical presentation, histology and biology. Two incidence peaks are observed within the pediatric tumors; during infancy and early childhood, mainly as teratomas and yolk sac tumors that predominantly arise in the sacrococcygeal region or testes and in the second decade predominantly as mixed malignant gonadal, mediastinal and CNS germ cell tumors. Histology and age correlate with the genetic profiles. In malignant GCT of children <10 years an isochromosome 12p has rarely been found, whereas aberrations at chromosomes 1, 6, and 20 and the sex chromosomes occur most often. This requires a multimodal treatment including the pediatric oncologist in cooperation with the appropriate surgical disciplines and the radiotherapist. During the past, a dramatic improvement of the prognosis of malignant GCTs in the adult and the pediatric population has been achieved. This progress is mainly attributed to the utilization of a cisplatinum-based combination chemotherapy. The first pediatric trials have been designed based on the experience in malignant testicular GCT in adults. These studies have soon revealed the particular clinical and biological features of childhood GCT. Therapy is more specifically tailored to the pediatric setting by stratification of chemotherapy according to risk groups in respect to the parameters age, histology, primary site and stage. From the 1980ies, the pediatric protocols for testicular and nontesticular GCTs included cisplatinum- and etoposide based chemotherapy regimens. As a result of the excellent event-free survival rates above 80% the cumulative chemotherapy could be step-wise reduced to currently 4 to 5 cycles in poor prognostic patients which did not affect outcome. Under protocol guidelines complete tumor resection is the most important risk factor therefore. In locally advanced or metastatic tumors a neoadjuvant approach is used as it facilitates complete tumor resection and thereby reduces the need for second look surgery. In most of the running protocols an expectant watch-and-wait strategy is recommended for patients with completely resected low stage tumors. This spares chemotherapy in approximately 25% of patients with malignant GCT. Special emphasis has to be given to extragonadal teratoma with malignant microfoci as in half of all relapsing teratoma patients of the pediatric age group malignant histology (yolk sac tumor) is predominant.
In recent years biologcal understanding of the disease has let to a distribution between pediatric and adult type germ cell tumors which vary in their appearance as well as in their biological behaviour. In the future it is hoped to have new prognostic biological markers to distinguish between good and poor risk patients.

103 INVITED

SIOPEL Liver Trials – Recent breakthroughs and future directions

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The International Childhood Liver Tumour Strategy Group – SIOPEL – was founded in 1988 under the umbrella of the International Society of Paediatric Oncology (SIOP). Its main aim is to promote basic and clinical research on childhood malignant neoplasms of the liver, mainly hepatoblastoma (HB) and hepatocellular carcinoma (HCC).
The principal mission of the SIOPEL group is to develop comprehensive clinical research programs on childhood HB and HCC, and to foster world-wide cooperation in this field.
The SIOPEL group has so far completed two generations of prospective clinical trials and a phase II studies which resulted in 28 publications so far:

- SIOPEL 1 – 1990/1994
- SIOPEL 2 – 1994/1998
- Phase II study on High dose Cyclophosphamide – 1996/2001
- A prospective randomised clinical trial on standard risk hepatoblastoma − SIOPEL3 SR-HB – 1998–2005
- A prospective single arm trial on high risk hepatoblastoma – SIOPEL 3 HR-HB – 1998–2004
- A prospective single arm trial on the hepatocellular carcinoma family of tumours; SIOPEL 5 – 2005–2008.
- A Phase II study on Irinotecan – 2003–2008

Past SIOPEL activity has led to introduction of preoperative chemotherapy for hepatoblastoma with an increase of patients survival from 30 to 70%, as well as development of the world-wide adopted PREtreatment Tumor EXTension assessment (PRETEXT). With time and consecutive generations of trials proposed therapy has become more refined, switching from initial 'one for all' approach into patients' stratification based on previously identified prognostic factors and more customized treatment.
Presently the group is running:

- A new study on high risk hepatoblastoma; SIOPEL 4 – opened 2005.
- A new single arm trial for standard risk hepatoblastoma; SIOPEL 6 – opened 2007.
- A prospective single arm trial in cooperation with the Indian Paediatric Oncology Society – SIOPEL RCN – opened 2009.
- The group also runs an international tissue bank for childhood liver tumours.

SIOPEL group is planning to further improve therapeutic approach to primary pediatric liver tumors by redefining risk groups, possibly including biological prognostic factors, as well as to address an issue of long term toxicities. In particular we are aiming at:

- Creating global retrospective database of patients with liver tumors – CHIC (Childhood Hepatic Tumors International Cooperation) project in cooperation with with North American COG, German GPOH and Japanese JPLT groups.
- Starting new global worldwide study for hepatocellular carcinoma (to replace SIOPEL 5) – based on sorafenib.
- Forming an international network of laboratories dedicated to develop new drugs and running pharmacologic research in vitro and in animals on childhood HB and HCC.
- Preparation of new studies for the High Risk Hepatoblastoma and Refractory/Relapsed Hepatoblastoma.
- Participation in ongoing and new basic research projects:
  - serpin SCCA (Squamous Cell Carcinoma Antigen) role in liver tumors
  - tissue array prognostic significance in hepatoblastoma
  - Protein expression analysis and its prognostic significance in hepato-blastoma

The major challenge for the group is the lack of solid funding in the light of constant expansion of the trial portfolio and increasing number of centers participating in studies, as well as insufficient administrative and secretarial support. Another major challenge is to overcome obstacles associated with opening of the new trials facing the European Clinical Trials Directive and lack of the institution willing to take the role of a formal European sponsor.

104 INVITED

I-BFM SG trials on childhood ALL

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Acute lymphoblastic leukemia (ALL) is the most frequent malignancy in childhood. The International BFM Study Group (I-BFM SG) is an informal forum for all relevant study groups investigating and treating childhood ALL in Europe, Japan, and South America. The Annual Meeting also comprises active observers from other study groups worldwide. Besides providing the opportunity for scientific discussion of research, diagnostics and treatment of ALL in general, the I-BFM SG forms an umbrella for conduction of cooperative clinical trials and research activities on rare subgroups. In that context, trials on treatment of infants with ALL (Interfant) and of children with BCR/ABL positive ALL (EsPhALL) are being conducted, and a cooperative trial on childhood relapsed ALL (EuReALL) is being planned.
ALL at the age younger than 1 year constitutes a distinct clinical and biologic entity: Most leukemias contain MLL involving translocations, tolerance to treatment is a special issue in this early stage of life, and prognosis is inferior compared to other ALL subgroups. The large