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.

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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.

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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.

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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