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

collaborative Interfant Study Group has been founded with the aim to improve survival of these patients by recruiting sufficient patients for prospective randomized trials, forming a platform allowing for integration of new targeted drugs, developing new prognostic factors and improving the understanding of the biologic background of the disease. The Interfant-99 study has been closed in 2006 providing results of 482 patients with an event-free survival (EFS) rate at 4 years of 47%. As major risk factors, MLL translocation, high leukocyte counts, age below 6 month, and response to prednisone could be determined. Within the trial, minimal residual disease could be established as additional relevant prognostic factor. A new protocol Interfant-06 has recently been opened investigating a more AML-oriented therapy for this patient cohort.
3–5% of children with ALL have a Philadelphia-chromosome positive (Ph+) disease with a poor prognosis and EFS rates of 25–30%. The tyrosine kinase inhibitor imatinib specifically inhibits proliferation of BCR/ABL positive leukemias. In the EsPhALL trial, imatinib is used on the basis of the ALL-BFM 2000 HR therapy in all Ph+ patients with high risk features, whereas it is randomized in good-risk patients. About 30 patients per year are recruited. The trial will provide the opportunity to assess in a prospective controlled manner the importance of imatinib in non-HR Ph+ patients.
Relapse it the most frequent adverse event in childhood ALL occurring in about 20% of patients. Within the I-BFM SG, common risk stratification on the basis of conventional risk factors and minimal residual disease has been established. A variety of interesting new compounds has been developed in recent years with targeted activity in ALL. The importance of these drugs needs to be prospectively evaluated in randomized phase III trials before being integrated into frontline therapies. The EuReALL 2010 trial is planned to include patients from nearly all relevant European study groups and some non European groups aiming at a recruitment rate of at least 200 patients per year. This will allow answering randomized questions in standard and high risk relapse ALL separately within 4 years.
In conclusion, the I-BFM SG is the most important European organisation for childhood ALL, and provides an ideal setting for planning and conducting clinical trials in rare subgroups of patients.

Advocacy Session (Tue, 22 Sep, 09:00–10:30)
The burden of cancer

105 INVITED

Recent trends in the burden of cancer in Europe: a combined approach of incidence, survival and mortality for 17 major cancer sites since the 1990 s

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An overview is presented of most recent trends in incidence of, mortality from cancer across Europe since the mid 1990 s thereby interpreting relative survival trends for patients with cancer from the Eurocare study. The fact that the prevalence of cancer (i.e. also comprising ex-cancer) is rising by 3–5% annually does not necessarily imply that the cancer problem is worsening, on the contrary. Given the downward trends in cancer mortality for most major cancer sities in most countries the reverse is rather happening. Thus the combined interpretation avoids the flaws of the separate view. Incidence and survival can be strongly biased by early detection and screening and mortality by other causes of death. Data were obtained in 2008 from cancer registries in 21 European countries on incidence, mortality and 5-year relative survival from the mid 1990 s to early 2000 for cancers of oral cavity and pharynx, oesophagus, stomach, colorectum, pancreas, larynx, lung, skin melanoma, breast, cervix, corpus uteri, ovary, prostate, testis, kidney, bladder, and Hodgkin's disease. Annual percentages of change in incidence and mortality were calculated. Survival trends were analyzed by calculating the relative difference in 5-year relative survival between 1990–94 and 2000–02 using data from the EUROCARE-project. Trends in incidence as measured by population-based cancer registries were generally favorable in the more prosperous countries from Northern and Western Europe, except for obesity, alcohol and UV-related cancers. Whereas incidence of and mortality from tobacco-related cancers decreased for males in Northern, Western and Southern Europe, they increased for both sexes in Central Europe and for females nearly everywhere. Survival rates generally improved, mostly due to better access to specialized diagnostics, staging and treatment. Marked effects of organised or large scale opportunistic screening became visible for breast and prostate cancer in the wealthier countries and possibly also for melanoma. After decades of rises & unfavourable trends, cancer prevention and management in Europe seems to be moving in the right direction, suggesting that the rising awareness during the 80's is paying off. Still, cancer prevention efforts have much to attain, especially in the domain of female smoking and the emerging obesity epidemic. Standards of care can potentially rise by efforts to regionalize, to be documented through cancer registries. Conclusion: a comprehensive approach remains needed to measuring epidemiologic progress against cancer. Lit refs: Cancer Control in Europe: state of the art. Eur J Cancer special issue 2008; 44:1345–89. Survival of Cancer patients in Europe, 1995–2002: the Eurocare 4 study. Eur J Cancer special issue 2009;45:6:901–1084.

106 INVITED

Economic burden of cancer on patients

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In the European Union, one new case of breast cancer is diagnosed every two minutes.
In particular, breast cancer, second after lung cancer, is the most common form of tumour in Europe. 35% of the 275.000 women diagnosed with breast cancer every year are under 55 years of age, and 12% of them are under 45. The high incidence of this type of tumour, together with the relatively young age of the patients, has a major impact not only on the social lives of the patients, but also on their employment and their economical situation now and in the future. With increasing prevalence of survivors it is impostant to shed light on problems facing these persons after diagnosis and treatment. The overall aim of this study was to evaluate the rehbilitation process following a breast cancer diagnosis for women at working age by examing factors related to type of socio-economic status, working condition, life/working satisfaction and their association with return to work.
The Swedish study was distributed as an electronic questionnaire and linked to homepages for several patient-organizations, newspapers and magazines and generally to all institutions connected to cancer. The study was announced threw articles in newsletters, advertisemnet in newspapers and press-release was also sent about this study. In the Swedish study it participated 714 persons and the majority was in the ages 20–60 years old. This gave us an excellent basis for the evaluation of the results.
The study was a part of an European Commission project "Promoting new measures for the protection of women workers with oncolocigal conditions by means of social dialogue and company-level collective bargaining", and gave us good possibilities to compare the results in the participating countries.
The study showed that the women strove to belong to the labour market, but the study also revealed how women's perceptions of the value of the employment changed. The quality of social support received from employers and co-workers differed between women who returned to work and those still sick-listed one-two year after breast cancer treatment. Work situation after breast cancer is still a critical issue, even though a high proportion of these women are able to return to any type of work.
The return to work for women with breast cancer can be part of the transition to a state of well-being, even if women may find that returning to labour market is not particularly easy, either in physical or psychological terms, due to the feelings of tiredness that they may not have had before, and which they try to conceal, and due to anxiety about oncological risk, which remains a constant factor.
The principal finding was that most of the studied women who were working before cancer returned to work after their active cancer treatments were completed. Type of treatment as well as work-related factors, life satisfaction and coping skills were associated with return to work.
The group of women who not return to work or those who change to part-time work have big changes in their economical situation as a burden of their cancer and one of the most important difficulties to overcome consists of the need to strike balance between working hours, medical treatment and the person's individual needs.

108 INVITED

Return to working life with/after cancer

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The quality of life after cancer experience is becoming an increasingly important issue and return to work belongs in this topic. For most survivors, work is a financial and emotional necessity, to help them keep their self-esteem and social support, but work is also a source of stress and can adversely affect health. According to American authors, up to 65% of cancer survivors remain professionally active, but as much as 75% of cancer survivors have to change their working status due to the disease consequences. In Europe there are no data on how many cancer patients return to work and how easy they find it to do so.
Permanent consequences experienced by cancer survivors may be:
- physical consequences – loss of function and structure of organs