or by binding to the anchoring protein (RACK1), which leads to HIF-1α degradation.
Two HIF-1α chimeric reporter systems were developed that allowed us to investigate HIF-1α stabilization/degradation in different cell lines, both in culture and in xenografts. A comparison between HIF-1α/Fluc and HIF-1α(ΔODDD)/Fluc expression levels, as measured by bioluminescence imaging (BLI), demonstrate important differences between non-tumorigenic NIH3T3 and HEK293 reporter cells and tumorigenic PTEN-defective U87 cells. Non-tumorigenic NIH3T3 and HEK293 cells had low basal normoxic-levels of HIF-1α/FLuc expression that were readily detectable by BLI, but not by immunoblotting. In contrast, tumorigenic U87 reporter cells had high basal levels of HIF-1α/FLuc expression, and responded to hypoxia and hypoxia-mimetics as well. A significant reporter response was observed in animals bearing U87/HIF-1α/FLuc xenografts following an i.p. injection of $CoCl_2$, but not in animals bearing U87/HIF-1α(ΔODDD)/FLuc or native FLuc expressing (control) xenografts.
Immunofluorescence analysis of HIF-1α/FLuc subcellular localization and trafficking in reporter-transduced cell lines compared well with that of endogenous HIF-1α in wild-type cells. A bi-exponential BLI profile of HIF-1α/FLuc protein degradation was observed, indicating that both "rapid" and "slow" clearance mechanisms were operative. The half-time of the rapid clearance phase in these cells was ~3−6 min and consistent with the currently accepted half-life of HIF-1α (~5 min) under normal non-hypoxic conditions; a second slow clearance phase (~200 min) was newly identified. The immunofluorescence and kinetic profile analysis of HIF-1α/FLuc degradation suggests that the rapid and slow components of degradation are compartmentalized. Although the mechanism of HIF-1α shuttling between nucleus and cytoplasm is poorly understood, it is clear that HIF-1α subcellular distribution and degradation are regulated in a cell-specific manner, with significant differences between normal cells and cancer cells.

19 INVITED

Application of Hypoxia Imaging in Radiation Treatment Planning

U. Nestle[1], N. Wiedenmann[1], M. Hentschel[1], V. Jacob[1], S. Bucher[1], M. Mix[2], S. Adebahr[1], C. Offermann[1], W. Weber[2], A.L. Grosu[1]. *[1]University of Freiburg, Department of Radiation Oncology, Freiburg,[2]University of Freiburg, Department of Nuclear Medicine, Freiburg, Germany*

The appearance of tumour hypoxia is a common feature of solid tumours that is negatively correlated with prognosis and local control. Among other mechanisms, hypoxia-mediated radioresistance has been identified as a major obstacle for achieving permanent tumour control after radiotherapy. Derived from experimental studies, hypoxic mammalian cells are known to be up to 3 times less radiosensitive than euoxic cells. The elimination of tumour hypoxia has been a long standing therapeutic target. The PET tracers ^{18}F-fluoromisonidazole (F-MISO) and ^{18}F-fluoroazomycinarabinoside (FAZA) have been developed to provide a non-invasive tool for visualizing tumour hypoxia by positron emission tomography (PET). Accrdingly, tumour hypoxia assessed by PET has been found to be correlated with the risk of locoregional failure as well. Studies show F-MISO PET to be associated with a higher risk (HR 7) of locoregional failure after radiochemotherapy compared to non-hypoxic tumours [Rischin et al., JCO 2006]. One approach to target unfavorable tumour characteristics such as tumour hypoxia is the 'dose painting' concept. Thereby the radiation dose is selectively escalated within the most aggressive tumour areas. For hypoxia targeted radiation treatment hypoxic tumour subvolumes are derived from the hypoxia PET and treated with an increased radiation dose ('boost') using intensity modulated radiotherapy (IMRT) treatment planning. By selectively boosting hypoxic tumour cells the tumour control probability (TCP) is supposed to increase as shown by radiobiological considerations. Treatment planning may be based on baseline hypoxia as well as residual tumour hypoxia assessed at different timepoints during a timecourse of radiation treatment. However, radiation-induced tumour reoxygenation and dynamic changes in tumour oxygenation need to be considered. Data on the dynamics of tumour hypoxia during radiation treatment is scarce. Follow-up PET scans of tumour hypoxia during standard radiochemotherapy in locally advanced SCC of the head and neck will therefore be presented as well as examples and technical considerations for hypoxia besed treatment planning. While the role of hypoxia PET as a diagnostic tool is well established, the suitability and feasibility of a hypoxia based dose painting needs to be thoroughly discussed and addressed in clinical trials.

Scientific Symposium (Sat, 24 Sep, 11:15−13:15)
Long Term Follow Up in Childhood and Adolescent Cancer

20 INVITED

Pan-European Network for Care of Survivors After Childhood and Adolescent Cancer (PanCare)

L. Hjorth[1], J. Byrne[2], A. Georgiev[3], R. Haupt[4], L. Kremer[5], G. Levitt[6], P. Pisani[7], R. Skinner[8], E. Sugden[9]. *[1]Division of Paediatric Oncology & Haematology, Department of Paediatrics Lund Skåne University, Hospital Clinical Sciences Lund University, Lund, Sweden; [2]Boyne Research Institute, Drogheda, Ireland; [3]Law Firm Alexiev Georgiev Shalamanov, Sofia, Bulgaria; [4]Epidemiology and Biostatistics Section Scientific Directorate, Gaslini Children's Hospital, Genova, Italy; [5]Department of Paediatric Oncology, Emma Children's Hospital/AMC, Amsterdam, The Netherlands; [6]Department of Paediatric Oncology, Great Ormond Street Hospital for Children NHS Trust, London, United Kingdom; [7]Department of Epidemiology, Universitá di Torino, Torino, Italy; [8]Department of Paediatric and Adolescent Haematology/Oncology, Royal Victoria Infirmary, Newcastle upon Tyne, United Kingdom; [9]Department of Paediatric and Adolescent Haematology/Oncology, Oxford Radcliffe Hospitals, Oxford, United Kingdom*

Background: Recognising the need for a voice in Europe for survivors with late complications of therapy for childhood and adolescent cancer, PanCare was founded to be the pan-European Network that addresses all aspects of childhood cancer survivorship.
Material and Methods: In March 2008, PanCare (Pan-European Network for Care of Survivors after Childhood and Adolescent Cancer) was founded by 26 doctors and scientists from 14 European countries at a meeting in Lund, Sweden. The" Erice statement" was adopted as backbone of PanCare vision and mission.
Results: Seven meetings of the Network have so far been held. At present, PanCare has members from 26 European countries plus Canada and Japan. Most are paediatric oncologists; second most common are epidemiologists; followed by radiation oncologists; survivors psychologists; parent representatives; paediatric neurologists; paediatric and adult endocrinologists; nurses (too few!), medical students and one each being a lawyer and representative of a funding body. The PanCareSurFup consortium, based in PanCare, is a 5-year FP7 Health2010 Collaborative Project focusing on epidemiological studies on mortality, secondary malignancies and cardiac disease after treatment for childhood cancer, and on guidelines for survivors and dissemination of results. In addition to this, working groups within PanCare are currently establishing research projects on fertility, quality of life and ototoxicity. PanCare is also a partner in an FP7 funded Network of Excellence led by SIOPE.
Conclusions: PanCare is a multidisciplinary pan-European network of professionals, survivors and their families that aims to reduce the frequency, severity and impact of late side-effects of the treatment of children and adolescents with cancer. PanCare is working to achieve equity of access to care for childhood cancer survivors across Europe, to perform collaborative research and to act as a resource of research based information concerning all late side-effects of cancer treatment. An important aim of PanCare is to work with the European Community and other stakeholders to increase awareness and research about childhood cancer survivors all over Europe. The long-term strategic aim of PanCare is to ensure that every European survivor of childhood and adolescent cancer receives optimal long-term care.

21 INVITED

The Epidemiology of Childhood Cancer Survivors

R. Haupt[1], P. Pisani[2], S. Garwicz[3], M. Hawkins[4], R. Skinner[5], L. Hjorth[3]. *[1]Giannina Gaslini Children's Hospital, Epidemiology and Biostatistics Section, Genoa, [2]University of Turin, Childhood Cancer Registry of Piedmont, Turin, Italy; [3]Skåne University Hospital, Division of Paediatric Oncology & Haematology, Lund, Sweden; [4]University of Birmingham, Centre for Childhood Cancer Survivor Studies School of Health and Population Sciences, Birmingham, [5]Great North Children's Hospital Royal Victoria Infirmary, Department of Paediatric and Adolescent Haematology and Oncology and Children's BMT Unit, Newcastle upon Tyne, United Kingdom*

Background: As a result of the ever-increasing success rates achieved in recent decades in pediatric oncology, an increasing number of children and adolescents have successfully overcome their cancer experience and have reached or are entering adulthood.

Materials and Methods: The prevalence, age and tumour type distribution of childhood cancer survivors has been estimated in some western countries while for others exact estimation is lacking. Reports from some cancer registries from the North of Europe have been compared with those from Southern Europe and the United States.
Results: Childhood cancer survival rates have been progressively increasing since the early seventies. In the same period an average 1.1% annual increase of cancer incidence has been observed in most countries. This leads to an increasing proportion of members of our society being long-term survivors of childhood cancer. In most of the western countries, the figure has been estimated to vary between 1 subject in 750–1200. Figures may vary among European countries based on differences in survival rates observed in the previous years in Northern, Southern and Eastern Europe.
In the United States the prevalence of childhood cancer survivors was estimated at 328,000 subjects in 2005, with a median age of about 30 years, 12% of which are already 50+ years of age. Detailed figures for Europe have not been published; it is reasonable to estimate that they are between 300,000 and 500,000. This number will rise rapidly due to continued improvements in survival. Based on a conservative estimate of 75% of currently treated cases becoming long-term survivors we predict that each year about 8,000 new long-term survivors will be added to the European population. The distribution of childhood cancer survivors by tumour type is slightly different from incidence data, and reflects variability in success rates obtained for treatment of different childhood tumours.
Survivors of childhood cancer are at increased risk of considerable morbidity and even mortality due to late adverse effects of their previous treatment and the frequency of late complications continues to rise as the length of follow-up increases. Cohort studies show that about 30% have a serious or potentially severe late complication.
Conclusions: The population of childhood cancer survivors constitutes a small but important proportion of our population. It is continuing to increase in size and attained age and it should be carefully monitored to assess health status.

22 INVITED

Transition From Paediatric to Adult Care − Models of Care

E. Frey[1]. [1]*St. Anna Children's Hospital, Late Effects Clinic, Vienna, Austria*

The importance of transition from paediatric to adult care is constantly increasing in all pediatric subspecialities, but there are some special issues concerning adult survivors of childhood and adolescent cancer. In most chronic diseases, the specialists which are needed during adulthood are working in similar fields like during childhood; for instance a child with diabetes will need a specialist for diabetes also during adulthood. The cancer survivors need a comprehensive Care System, including different specialists, according to the allready existing late effects, or for screening for possible occuring late effects. The late effects can affect different organ systems and the timeframe of the onset of late effects differs very much; therefore we have to screen lifelong. The number of survivors is constantly increasing and also the knowledge about late effects during adulthood. On one hand we have sufficient knowledge about late effects which can occur in the first twenty years after the end of treatment, on the other hand there is still little known about late effects in later life decades. This makes it obvious, that constant research is needed during the whole lifespan of our patients, and to do prospective research concerning new drugs and new treatment regimens.
For coping with these special problems there is an increasing number of different models, offering a comprehensive long term care for adult childhood cancer survivors. In 2009 on behalf of the PanCare working group we sent out a questionnaire to the members asking for transition programs. We sent out questionnaires to 64 clinics in 19 countries, and we got 26 questionnaires back. 9 of these 26 clinics have a transition program, but none was really content with that. The main problems are: the definition of risk groups, lack of guidelines and low interest of adult specialists in collaboration. Some programs are more focused on the general practitioners and some on the clinical centres, where the patients have been treated. These different models have different advantages: the collaboration programs with the general practitioners are preferred by the patients, the programs driven by a Clinical Program are creating reliable data for research.
The future tasks will be to create programs with easy access for the former patients and with reliable data transfer to scientific centres, further to define risk groups and requirements for transition programs, creating guidelines and tools for the patients themselves, to become "specialists" for their individual after care.

23 INVITED

Late Complications After Cancer in Childhood and Adolescence

G. Levitt[1]. [1]*Great Ormond Street Hospital, Oncology, London, United Kingdom*

Background: As survival rates improved there became a realisation that cure came at a cost to the survivor. As yet cancer treatment is not cancer cell specific and therefore normal tissue damage occurs. This is particularly so in the vulnerable young child who still has considerable growth and development potential to fulfil.
Extensive research has been conducted by both epidemiologists and clinicians into the health outcomes in survivors of childhood and adolescent cancer. With overall survival of childhood cancer now >80% and a sustained survival of >50% over the last two decades, this has enabled valuable long term data to be collected.
Methods: Analysis of causes of late deaths in large multicentre and population based studies across continents and in association with tumour types, age at diagnosis and era of treatment has provided important data. In tandem with the mortality studies have been large epidemiology and more detailed clinical based studies reporting on long term morbidity.
Results: The late deaths studies have identified the increased risk of premature deaths compared to the matched population. This increase is maintained over more than three decades. A substantial proportion of the deaths have been due to the treatment in particular radiation therapy and certain chemotherapeutic groups (alkyating agents and anthracyclines). The majority of deaths were due to second malignant tumours with cardiovascular and pulmonary disease following behind.
The morbidity studies identify 25% of survivors are at risk of severe or life threatening illnesses with more 60% exhibiting some treatment related effects. The conditions reported are very varied covering all organs and systems and depend on the treatment received, age at diagnosis and at time of study and gender of the patients. In addition the length of follow-up is a risk factor for certain effects as damage although occurring at the time of treatment can may manifest many years later.
Conclusion: This priceless data can be used to inform clinicians enabling them to provide appropriate long term care for survivors to maximise their quality of life. In addition the highlighting of late effects can be used to assist in developing new treatment protocols with improved outcomes. Continuing the study of survivorship will inform the new goal to provide personalised medicine taking into to account individual susceptibility to treatment related organ damage thereby minimising late effects.

24 INVITED

ICCCPO (the International Confederation of Childhood Cancer Parent Organisations) − the Survivors Perspectives

A.K. Kienesberger[1], S.K. Karner[1]. [1]*Österreichische Kinder-Krebs-Hilfe, Österreichische Kinder-Krebs-Hilfe, Wien, Austria*

Background: The Survivors Perspective concerning long-term follow-up is increasingly an important topic within the paediatric oncology. This fact leads ICCCPO and in particular survivors representatives of the International Childhood Cancer Survivors Network (ICCSN) to deal with this topic.
Material and Methods: Since the last years parent organisations try to work together with survivors about the development of long-term follow-up. The survivors were asked about their point of view. German and Austrian survivors expressed their experiences and wishes concerning the long-term follow up. In the next months survivors from other European countries will be asked.
Results: The long-term follow-up is for the most of the survivors a very important topic, especially for those who have one or more late effects. An optimal long-term follow-up is just as important as the treatment itself. The long-term follow-up contributes to the quality of life of survivors and their families. Until now there doesn't exist a lot of optimal models of long-term follow-up clinics in the European countries. An optimal long-term follow-up should indicate late effects early and take care about this. So that the quality of life of the survivors don't suffer. Just an early identification of late effects and their treatment will also avoid different side effects.
The Information transfer about the life after cancer and possible late effects after treatment should be told at a suitable time. The survivors have to know what is going on, what they have to consider and who the contact person is for them. They should know the schedule of the different screenings, what will be done and what is necessary (latest knowledge).
Just as important as the medical long-term follow-up is the psychosocial aftercare for Survivors. There has to be an offer to support survivors after the treatment.
Conclusions: At this meeting we want to give a detailed overview from the survivors perspective what is needed in future concerning the long-term follow-up.