105 INVITED

Very Rare Cancers in Children − From TREP to EXPeRT

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Malignant tumours are relatively uncommon in children, especially when one compares them to adult cancer. The impossibility to perform meaningful studies on the few patients treated in each centre has encouraged Pediatric Oncologists to search for national and international collaboration to perform research and find support. The products of this increasing collaboration are evident in the progressive raise of the survival results obtained in nearly all pediatric tumours.
Unfortunately some children did not benefit from this effort, i.e. those affected by exceptionally rare tumours. Some of these tumours are typical of pediatric age, such as pleuropulmonary blastoma or pancreatoblastoma, and are very rarely encountered in the daily practice even in large hospital. Others are typical of the adulthood, such as thyroid carcinoma, thymic tumours, renal carcinoma, so pediatric oncologists may feel themselves unprepared to confront with them.
These different entities constitute a group of tumours, and more importantly of children, the pediatric oncology community have found little interest to be involved with. This is reflected in the survival results that did not changed substantially over the years and are unsatisfactory for some hystotypes. To overcome this problem national groups specifically focussing on rare cancers in childhood have been founded. The TREP project that was launched in Italy in 2000 represents a successful model of creating a network dedicated to rare tumours. In fact it provides not only a registry for case registration but also guidelines for the different tumours, and a network of experts that can assist clinicians in patient management. Groups with similar aims have been created more recently in other European countries and, in June 2008, a new cooperative group denominated EXPeRT − European Cooperative Study group for Paediatric Rare tumour, has been founded. The main aim of EXPeRT is to empower the research on rare pediatric tumours promoting collaboration between the founder national groups: Italy, France, United Kingdom, Poland and Germany. Data exchange, retrospective and prospective studies, international recognized guidelines, expert consultation and international case registry are the undergoing initiatives. The formation of similar Groups in other countries is expected and supported. This will hopefully improve the quality of research and the treatment results for children that have been until recent years partially neglected.

Scientific Symposium (Sat, 24 Sep, 16:00−18:00)
New Image Guided Cancer Therapies

106 INVITED

Application of MRI for Radiotherapy Dose Painting

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The treatment with radiotherapy has reached unprecedented levels of accuracy due to the introduction of sophisticated delivery techniques and in-room image guidance to ensure precise targeting. High-quality imaging is essential to realize these treatments. To date, CT is the standard imaging modality for target delineation as well as in-room image guidance. However, a growing number of groups have started to explore the use of MRI for radiotherapy because of its superior soft-tissue contrast.
The use of MRI for in-room treatment guidance is currently investigated in several initiatives. The key advantage of an integrated MRI-accelerator is that imaging of the patient is possible concurrent with the irradiation. This allows on-line monitoring of organ motion and may be exploited for high-precision tumour tracking.
With this high level of accuracy in radiation delivery, the definition of the target for irradiation becomes critical. For tumour delineation and characterization both anatomical and functional MRI techniques are used. At a high spatial resolution, these images can be used to identify the boundaries of the target volume. In particular when combinations of imaging techniques are used, the heterogeneity of a tumour can be assessed. Potentially, this information can be used to modulate the dose in the target, depending on the cell density and biological characteristics of the tumour. This approach is called dose painting.
Also during follow-up, the use of MRI can be of importance. By imaging prostate patients with a PSA relapse after treatment, the location of the recurrent tumour can be compared with the location of the primary tumour and the delivered dose. This makes a more detailed evaluation of clinical outcome feasible, and helps strengthen the end points of clinical trials.
In conclusion, the superior soft-tissue contrast of MRI and its versatility in anatomical and functional contrast leads to an increased use during all stages of a radiotherapy treatment: for tumour characterization and delineation, for treatment guidance and for follow up. This will allow us to take the optimal benefit of high-precision delivery techniques.

107 INVITED

Fluorescence Guided Cancer Therapy

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Substances that emit fluorescence after light activation has provided a powerful tool for imaging both at the subcellular level and the tissue level. The use of fluorescing drugs for cancer diagnosis and therapy is an emerging field and has already been used clinically to guide resection of tumours. In this presentation, approaches for fluorescence guided cancer therapies will be presented with the main focus on photosensitizers as the fluorescing substance. Photosensitizers are light-sensitive drugs that absorb light at specific wavelengths leading to a short-lived high energy-state of the drug. The energy is released either as heat or fluorescence or transferred to oxygen resulting in formation of reactive oxygen species of which singlet oxygen is the most common. The emission of fluorescence makes it possible to use these photosensitizers in diagnosis of i.e. bladder cancer (clinically approved in EU) and the fluorescence guided resection of gliomas (clinically approved in EU).
In addition to diagnosis and therapy, certain photosensitizers can also be used to enhance anti-cancer drug delivery; this strategy is called photochemical internalization (PCI). PCI is an efficient and specific drug and gene delivery technology established in our lab for the light-induced endosomal or lysosomal escape of molecules sequestered in these organelles. PCI of different model drugs has been documented in >80 malignant and non-malignant cell lines and >10 different tumour xenograft models. A clinical phase I/II study, PCI of Bleomycin, primarily enrolling patients with head & neck cancer is in progress. Preliminary results are promising, with strong tumour response observed in all patients (n = 19).

108 INVITED

MRI Guided Focused Ultrasound in Brain

Abstract not received

109 INVITED

MRI-Guided Focused Ultrasound Applications in the Body

F. Busse[1]. [1]*Philips Healthcare, MR-HIFU, Vantaa, Finland*

The ability of High Intensity Focused Ultrasound (HIFU) to generate precise tissue necrosis deep inside the body, using an external applicator, is unique. The key differentiation to other non-invasive techniques is the fact that the passage of ultrasound energy through intervening tissue has no apparent cumulative effect on that tissue. Especially abdominal structures, but also long bones, are promising targets for HIFU treatments, since the coupling of the applicator to the tissue is easily possible through a gel or water filled pads, and also a clear soft tissue pathway of the Ultrasound beam to the target can be found in most cases. When combined with image guidance, especially by MRI, highest clinical effectiveness and safety are expected, for four reasons. a) Targeting accuracy. Since MRI allows temperature monitoring, fine test sonications allow for an accurate positioning of the beam. b) Ablation efficiency. MRI temperature monitoring enables thermal dose mapping, so that tissue is ablated reliably independent of the tissue properties. c) Safety. MRI monitors temperature not only in the target region, but also at critical structures. d) Motion detection and compensation. MR-guided HIFU is clinically established for the treatment of uterine fibroids, with 7000 patients treated so far. The second approved application is the palliative treatment of bone metastasis, which clinically is still in early phase. There are several other body applications in development, from prostate cancer, breast cancers, liver cancer, kidney cancer to pancreatic cancer. There is even research in head and neck tumours ongoing. This article is going to review the most recent technological developments in MR-guided HIFU for prostate, breast, liver and kidney cancer, as well as remaining technical and clinical challenges.

110 INVITED

Image-Guided Radiation Therapy − From Current Concept to Future Perspectives

D. Jaffray[1]. [1]*Princess Margaret Hospital, Radiation Medicine Program, Toronto, Canada*

The field of radiation therapy has undergone a remarkable transformation over the past decade through the rapid and broad adoption of on-line image-guidance techniques. Motivated by early work using electronic portal

imaging and CT-on-rails technology, cone-beam CT has become a staple technology for daily imaging and repositioning of the patient prior to radiation therapy. This imaging technology can localize soft-tissue targets directly or through implanted surrogates and permits localization precision and accuracy on the order of 1 mm for high-contrast, unambiguous objects. More impressive is the fashion in which the vendors have worked to integrate these technologies into the clinical workflow, allowing volumetric cone-beam CT guidance to be performed within a 15 minute treatment slot. These technologies have transformed radiation therapy practice and are enabling the pursuit of more conformal treatments that hopefully will demonstrate reduced toxicity or alternatively success in more aggressive treatments. In addition, these technologies are highlighting the opportunity for further refinements in the treatment paradigm. Treatment induced changes over the course of therapy highlight the opportunity to adapt the treatment during therapy to either assure target coverage, or more likely, further reduce the dose to normal tissues by shrinking the high dose volume to the responding structures. This adaptive paradigm is an area of research that is being investigated. In addition to the impact of IGRT technology on the clinical process, we are also seeing improvements to IGRT performance (better CNR, 4D-CBCT, accurate CT numbers) through the development of second-generation IGRT systems. The value of image-guidance and the desire to provide even greater targeting capabilities, including on-line re-planning, is also motivating the development of MR-guided radiation therapy systems. The current state of IGRT practice and the future of these technologies and their uses will be discussed.

Sunday 25 September 2011

Scientific Symposium (Sun, 25 Sep, 09:00−11:00) Impact of Tumour Hypoxia on Heterogeneity in Radiation Response

111 INVITED

Cellular Responses to Hypoxia and Consequences for Radiotherapy

L. Dubois[1], T. van den Beucken[1], K.M.A. Rouschop[1], P. Lambin[1].
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Efficacy of cancer treatment modalities has been hampered by heterogeneously spread regions of low oxygen. These hypoxic regions are the result of a poorly developed and/or poorly functioning vascular network and influence the tumour cell behavior by activation of several oxygen-sensing pathways. The hypoxia-inducible factor family of transcription factors (HIFs) and its downstream targets, such as carbonic anhydrase (CA) IX is one of the best understood adaptation mechanisms. Since CAIX is implicated in both extra- and intracellular pH regulation, it has been proposed as a potential therapeutic target and recent work using CAIX inhibitors starts unraveling the molecular mechanisms underlying their antitumour effect and the exact role of CAIX in tumour progression. Recently it has been demonstrated that inhibition of CAIX activity could enhance the therapeutic effect of irradiation. Additionally, two other pathways have been implicated in promoting adaptation to low oxygen concentrations. These include inhibition of a central regulator of cellular metabolism, the kinase mammalian target of rapamycin (mTOR) and activation of the unfolded protein response (UPR), a pathway that responds to endoplasmic reticulum (ER) stress. During starvation or hypoxia mTOR activation is reduced resulting in decreased translation and cell growth through hypophosphorylation the eukaryotic initiation factor 4E binding protein 1 (4E-BP1), which increases the association with the cap-binding protein eukaryotic translation initiation factor 4E (eIF4E). Depletion of 4E-BP1 or overexpression of eIF4E sensitized cells to hypoxia-induced cell death, reduced the viable hypoxic fraction within tumours and subsequently sensitized tumours to irradiation. Recent reports have indicated that hypoxia-induced UPR activation enhances autophagy. Blockade of the UPR signaling pathway or autophagy increased hypoxia-induced cell death and decreased cell proliferation during mild hypoxia. Furthermore, this reduced the levels of viable hypoxic cells in tumour xenografts which sensitized tumours to irradiation. Targeting these oxygen-sensing pathways appears to influence hypoxia tolerance leading to a reduction of the hypoxic fraction and a sensitization of tumours to irradiation treatment and is thus an attractive therapeutic option to pursue clinically.

112 INVITED

Hypoxia Imaging and Outcome After Radiotherapy − Pre-Clinical Results

Abstract not received

113 INVITED

Hypoxia Imaging and Outcome After Radiotherapy − Clinical Results

P. Dirix[1]. [1]*University Hospitals Leuven, Radiation Oncology, Leuven, Belgium*

Tumour hypoxia has been shown to be one of the major factors affecting radiotherapy resistance in most types of cancer. As surrounding oxygen levels fall below 5 mmHg, cells become progressively more resistant to radiation. The difference in radiosensitivity between aerobic and hypoxic cells is typically in the range of 2.5 to 3 (= oxygen enhancement ratio). In the absence of oxygen, radiation-induced radicals in DNA may be reversed by donation of hydrogen from non-protein sulfhydryls, leading to less net DNA damage, and thus less cell kill, for the same dose. Even a small fraction of hypoxic cells can dominate the radiotherapy response of the tumour, since the radiosensitive, aerobic cells will be rapidly eliminated, leaving the radioresistant, hypoxic cells.
Non-invasive PET imaging evaluating the gross disease can provide serial quantitative measurement of hypoxia. A number of potential exogenous hypoxic cell markers, labeled with positron-emitting radionuclides, have been studied, including [^{18}F]-fluoromisonidazole (FMISO), ^{60}Cu(II)-diacetyl-bis-N^4-methylthiosemicarbazone (Cu-ATSM), [^{18}F]-fluoroerythronitroimidazole (FETNIM), and several others. Of these tracers, FMISO is certainly the most developed. In head and neck cancer for instance, significant hypoxia as defined by FMISO-PET is present in the majority of patients, and both the degree of hypoxia and the size of the hypoxic volume are independent predictive factors for survival. These data imply that FMISO-PET could be used to estimate the burden of hypoxia and guide treatment intensification (e.g. anti-hypoxic agents or radiotherapy dose-painting). However, considerable variability in the spatial uptake of FMISO between different time-points was observed. These results imply that the hypoxic volume delineated on FMISO-PET consists of a combination of transient and chronic hypoxia components. Dose-escalation on the entirety of such a “shifting” hypoxic volume, based on a single time-point scan, would unnecessary compromise normal tissue sparing with less expected benefit than if the volume were stable. In our opinion, this precludes the use of FMISO-PET to guide radiation dose-escalation until the underlying causes for these apparent changes in intra-tumour radiotracer distribution are fully understood.
Dynamic contrast (DCE) and diffusion-weighted (DW) MRI are promising functional MRI techniques that provide information on the tumour microenvironment and could indicate lesion aggressiveness. Although there are some discrepancies in the reported outcomes, most results suggest that DCE-MRI is particularly suitable for the assessment of perfusion, permeability, and oxygenation. These studies provide evidence that DCE variables could guide new anti-vascular or anti-hypoxic therapies. DW-MRI is rapidly gaining widespread traction as a biomarker for treatment response.

114 INVITED

Translational Aspects of Hypoxia Modification

P.J. Hoskin[1]. [1]*Mount Vernon Hospital, Cancer Centre, Northwood Middlesex, United Kingdom*

Hypoxia modification in the clinical setting has a long history beginning with early work using normobaric and hyperbaric oxygen, followed by the era of oxygen radio sensitizers, and more recently the evaluation of carbogen and nicotinamide. Despite this over 50 years of clinical endeavour has yet to translate into routine clinical care outside very selected specialist centres, despite meta-analysis data confirming an impact on both local control and overall survival in head and neck cancer and the results of the recent BCON study demonstrating an improved survival in bladder cancer patients receiving carbogen and nicotinamide.
There have been many explanations for this failure of the clinical community to embrace hypoxia modification outside the research protocols. Many of the early studies were relatively small by current standards with limited statistical power. In the hyperbaric oxygen studies because of the technical limitations of treatment within a hyperbaric tank, hypofractionated schedules were used and then compared with a more conventional control arm. Toxicity was prominent in some of the sensitizer studies, but the DAHANCA studies of nimorazole showed that non toxic simple drug sensitisation was possible and effective. The magnitude of this effect is at least that of many other widely adopted pharmaceutical interventions such as transtuzumab, cetuximab and bevacizumab and one of the major obstacles to widespread clinical uptake may well be the fact that hypoxia modification uses treatments which are not promoted by the pharmaceutical industry.
Against this background − is there a future for further translational studies of hypoxia modification? The pivotal role of hypoxia in radiosensitization remains unchanged with ever increasing evidence to support this concept.