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

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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

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Hypoxia Imaging and Outcome After Radiotherapy − Clinical Results

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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.

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Translational Aspects of Hypoxia Modification

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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.