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

113 INVITED

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.

114 INVITED

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.

Greater understanding of molecular pathways involved in the mediation of the effects of hypoxia open the possibility of targeted therapy based on hypoxia modification. The PARP inhibitor class of drugs has a nicotinamide like effect and will be important to evaluate in the setting of hypoxia modification. Our understanding of hypoxia has led to a greater ability to identify those tumours where hypoxia is prominent. Immunohistochemistry of intrinsic markers, osteopontin, functional imaging, with fluromisonidazole or blood oxygen level dependent MRI and genetic profiling have all been validated in this setting. Future translational studies should harness this new knowledge, identifying patients with clear evidence of hypoxia in the entry criteria and enable a new generation of clinical trials which will establish effective clinical schedules for hypoxia modification. Notwithstanding this the clinical community needs to critically appraise the current evidence and incorporate the proven methods of hypoxia modification already known to result in a survival advantage equal to or greater than many of the new chemotherapy drugs.

Scientific Symposium (Sun, 25 Sep, 09:00−11:00) **Symptom Management**

115 INVITED

How Do Women With Breast Cancer Manage Symptoms of Cognitive Impairments While Undergoing Chemotherapy Treatment?

F. Munir[1], K. Kalawsky[1], C. Lawrence[1], S. Ahmed[2]. [1]*Loughborough University, School of Sport Exercise and Health Sciences, Loughborough Leicestershire,* [2]*Leicester Royal Infirmary, Cancer and Haematology, Loughborough Leicestershire, United Kingdom*

Evidence suggests that women diagnosed with breast cancer experience cognitive changes as a consequence of chemotherapy treatment (Bower, 2008). Much of this evidence comes from self-report data, where women report perceived changes to their cognitive function. In contrast, evidence from neuropsychological measures of cognitive function is mixed with the majority of studies reporting subtle deficits in memory, concentration and executive functioning. It is possible that breast cancer patients are sensitive to subtle changes in cognitive function that current neuropsychological test employed are unable to detect, or that neuropsychological tests may not equate with everyday cognitive problems (Downie et al, 2006). There is moderate evidence that self-reported cognitive problems are more likely to be associated with emotional distress, depression and fatigue than with neuropsychological functioning (Pullens et al, 2010). There may be other variables associated with subjective and objective measures of cognitive function that have not been considered. For example, one area that has not yet been considered is whether patients keep their brain active during chemotherapy which could potentially reduce impairment results on neuropsychological tests. There has been a rise in cognitive-based leisure activities such as the Nintendo brain training game, Sudoku puzzles and other cognitive-based games available on mobile phones and on hand-held technologies such as the IPad. It is possible that some patients undergoing chemotherapy involve themselves with cognitive leisure-based activities while on sick leave. This may result in practice effects when these patients are assessed on neuropsychological tests. This study explored such possibilities, such as what activities patients engage in during chemotherapy treatment. As well as using neuropsychological tests, an in-depth evaluation into what activities women undertook during treatment was conducted in order to gain a better understanding.
Fifty women diagnosed with breast cancer were recruited from a breast cancer clinic in the UK. All completed neuropsychological assessments before, during and after chemotherapy treatment. At the end of their treatment, 31 women were interviewed and asked about their general health and well-being, their coping styles and how they spent their time whilst on sick leave, such as the types of cognitive activities undertaken. Findings suggest that the majority of women self-reported experiencing cognitive changes but only showed a decline on tests of cognitive attention. Nearly half the sample reported engaging in either a cognitive-based activity during their treatment or using compensatory strategies.
The implications for future study designs for assessing cognitive functioning as well as the ways in which women can manage their perceived symptoms of cognitive impairment will be discussed.

116 INVITED

Cough Management in Lung Cancer

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Background: Cough is a common and distressing symptom in lung cancer patients. The clinical management of cough in lung cancer patients is suboptimal with limited high quality research evidence available. The aim of the presentation is to present a clinical guideline developed in the UK through scrutiny of the literature and expert opinion, in order to aid decision making in clinicians and highlight good practice.
Methods: Two systematic reviews, one focusing on the management of cough in respiratory illness and one Cochrane review specifically on cancer, were conducted. Also, data from reviews, phase II trials and case studies were synthesized. A panel of experts in the field was also convened in an expert consensus meeting to make sense of the data and make clinical propositions.
Results: A pyramid of cough management was developed, starting with the treatment of reversible causes of cough/specific pathology. Initial cough management should focus on peripherally acting and intermittent treatment; more resistant symptoms require the addition of (or replacement by) centrally acting and continuous treatment. The pyramid for the symptomatic management starts from the simpler and most practical regimens (demulcents, simple linctus) to weak opioids to morphine and methadone before considering less well-researched and experimental approaches.
Conclusion: The clinical guidelines presented aim to provide a sensible clinical approach to the management of cough in lung cancer. High quality research in this field is urgently required to provide more evidence-based recommendations.

117 INVITED

Bone Disease − Osteoporosis

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Osteoporosis is a major public health problem because of the increased risk of fractures and the resultant morbidity and mortality. Worldwide it is estimated that one in three women and one in five men over fifty will sustain an osteoporotic fracture. In the European Union someone has a fracture as result of osteoporosis every 30 seconds and with an increasingly larger ageing population the yearly number of hip fractures in the EU is expected to more than double over the next fifty years (International Osteoporosis Foundation, 2008).
Bone health is a concern for many patients with breast or prostate cancer because many of their treatments cause bone loss (Cancer Treatment Induced Bone Loss − CTIBL) resulting in osteoporosis or osteopenia. Osteoporotic fractures cause significant disability, pain and even death. Although there is ample evidence of the need for and benefits of screening for osteoporosis to prevent morbidity and mortality this evidence does not always translate into practice (Mac Laughlin, 2010).
Nurses have a significant role in increasing patient's awareness of bone health issues if they are receiving hormone therapy and educating them on diet and lifestyle interventions, prevention of falls and medication management.

118 INVITED

Peripheral Neuropathies Associated With Chemotherapy

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Peripheral neuropathies are common side effects of chemotherapy including taxanes or platinum. Symptoms may come quickly, after a single dose, and often increases with higher doses and number of treatments. The symptoms may be reversible but many patients get irreversible damages to peripheral nerves.
Patients with peripheral neuropathies can experience numbness, a tingling or burning sensation, a loss of sensation or a sense of pain in hands and feet and the symptoms are often symmetric and may give changes in functional ability. Peripheral neuropathies can be dose-limiting and it can be necessary to cancel effective chemotherapy because of these side effects. Today we don't have much to offer these patients other than advices on how to cope and deal with these side effects and to change chemotherapy if possible. By studying literature on studies investigating different drugs that could prevent the onset of peripheral neuropathies in patients receiving platinum- or taxane-based chemotherapies, and by searching for guidelines for prevention and treatment of peripheral neuropathies, the aim is to get evidence-based guidelines for symptom management.