4 INVITED

Pelvic MRI: how MRI has helped develop new treatments

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The introduction of new radiotherapy and surgical techniques requires close collaboration between clinician and radiologist to optimise the application of imaging. This principle will be illustrated by a review of how MRI has helped implement new therapies for the treatment of cervical and rectal carcinoma. In cervical cancer the selection of patients for uterus-conserving surgery has been optimised by accurate MRI prediction of the relationship of the tumour to the internal os. Also, intensity-modulated radiotherapy (IMRT) has been aided by co-locational imaging between MRI and CT to define the gross tumour volume (GTV). Widespread implementation of pelvic IMRT has been prevented by the lack of a validated method for defining the nodal clinical volume (CTV). Recent work has shown the accuracy of ultrasmall paramagnetic iron oxide particles (USPIOs) in distinguishing infiltrated from normal nodes in gynaecological malignancy. By evaluating 1216 nodal contours, using USPIOs, guidelines for outlining pelvic nodes have been produced.
Multi-institutional studies in rectal cancer show that MRI is equivalent to histopathology in delineating local tumour spread prior to total meso-rectal excision. As the presence of the tumour at the circumferential resection margin affects prognosis, MRI plays a crucial role in the selection of appropriate therapy and has become an effective tool for the identification of patients at risk of incomplete resection.

5 Varian Award

Clinical Varian Research Award Lecture – Repair of DNA double-strand breaks in radiation induced cellular damage

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DNA damage, especially double-strand breaks, can be induced by endogenous or exogenous damaging agents, such as ionizing radiation. Repair of DNA damage is very important in maintaining genomic stability. Incorrect repair may lead to chromosomal aberrations, translocations and deletions. Consequently, incorrect repair might result in oncogenic transformation of cells, which can lead to the development of cancer. Thus, unreaveling the pathways of double-strand break repair is essential in understanding the genetic interactions that lead to oncogenic changes. Biochemical studies have provided insight into the molecular mechanisms by which various proteins, involved in repair of double-strand breaks, perform these essential tasks. The next step ahead is analyzing the relationship between the individual biochemical activities of double-strand break repair proteins and their coordinated action in the context of the living cell. This presentation describes the cellular behaviour and cooperation of the mammalian double-strand break repair proteins Rad51, Rad52, Rad54 and Mre11 after induction of DNA damage by ionizing radiation. Furthermore, the possibility to use detection of these proteins by ionizing radiation-induced foci formation and determination of telomere length as methods that might possibly serve as a predictive assay for measuring individual radiosensitivity in humans, was examined.

6 Varian Award

Clinical Varian Research Award Lecture – Molecular markers of tumor hypoxia: predictors of clinical radiation resistance?

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In the last five years, several groups investigated the role of proteins involved in the "hypoxic response" of tumor cells as molecular markers of tumor hypoxia. The hypoxia-responsive transcription-factor subunit hypoxia-inducible factor-1α (HIF-1α) itself and the products of HIF-1-regulated genes, such as carbonic anhydrase IX (CA IX) and glucose transporter 1 (GLUT1) were most frequently studied as endogenous hypoxia markers by immunohistochemistry, mostly in archival material. Although results were not uniform, the majority of series suggested an association of high marker expression with poor outcome (e. g. overall survival, disease-free survival, rarely local control) or with low tumor oxygenation measured with oxygen electrodes.
In detailed *in-vitro* studies of the accumulation of HIF-1α and CA IX protein in human tumor cell lines, we showed that these markers respond already to very mild hypoxia (e. g. 5% O_2), but have distinct time courses of accumulation and degradation as well as different patterns of response to further decreasing O_2 concentrations. Therefore, an association of marker expression and hypoxic radiation resistance *in vitro* appeared to be cell-type specific. As varying degrees of colocalization of these molecular markers with injected hypoxia markers (pimonidazole, EF5) were observed in tumors, we investigated the effect of manipulating non-hypoxic tumor microenvironment conditions (pH, glucose and serum availability) on the hypoxic HIF-1α and CAIX accumulation *in vitro*. Our observation of a strong glucose dependency corresponds to an immunohistochemical pattern of a lack of endogenous marker expression in hypoxic areas most distant from blood vessels observed by some groups. Despite these limitations, the activation of hypoxia-responsive elements (HRE) by HIF-1 has been successfully used in hypoxia reporter assays and to specifically target hypoxic tumor cells by gene therapy. Targeting HIF-1α pharmacologically is an emerging therapeutic strategy, the success of which will depend on the hypoxic specificity of HIF-1α accumulation.
More recently, osteopontin has been suggested as a plasma marker of tumor hypoxia with a surprisingly strong association with both tumor oxygenation and outcome. Although a ras-activated enhancer has recently been shown to mediate the hypoxia-enhanced transcription of osteopontin, we observed no increase of osteopontin in the culture medium during severe *in-vitro* hypoxia in a panel of human tumor cell lines.
Ideally, hypoxia markers should identify those tumors with the lowest oxygenation and such patients should be treated with effective therapies targeted at hypoxic tumor cells. First reports suggest that this combination may work for pimonidazole and ARCON (accelerated radiotherapy, carbogen, nicotinamide) as well as for osteopontin and the radiosensitizer nimorazole, whereas data on HIF-1-related markers in the context of hypoxia-specific treatment are less promising so far.

ESSO Special session

7 ESSO Award

Rectal cancer treatment in 2005

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Rectal cancer treatment has changed dramatically during the last twenty years. The introduction of more precise surgery (TME technique) as well as a more sophisticated use of radiotherapy has encountered this change.
Staging: Before any patient is treated for rectal cancer it is important to have a proper staging process. First of all the liver and lung have to be scanned to disclose any distant metastases. Secondly, a preoperative MRI will guide the use of radiotherapy and what type of surgical technique. In very tiny lesions (T1-lesions) endorectal ultrasound will disclose whether this is possible or not to do a local excision.
Surgery: The tradition of blunt dissection technique has now been abandoned, mainly due to the risk of high local recurrence rate. It has been proven that the rectal fascia is a barrier for tumour spread and provided that the whole mesorectum and rectum are taken out without any tears of the rectal fascia the local recurrence rate would be reduced dramatically. This technique (TME technique) has been introduced during the last 20 years and the main thing is to follow the avascular anatomical planes and divide the inferior mesentric artery close to the aorta. In tumours situated in the upper third of rectum a TME is probably not necessary and in those cases a resection with 5cm distal margin in the mesorectum is essential. In very low rectal cancers, the 5cm rule is not necessary, since there is no mesorectum harvesting lymph nodes and there is no evidence that a rectal adenocarcinoma will grow more than 5 mm from the macroscopic margin. Consequently, more sphincter preserved procedures can be done if this rule is accepted.
Radiotherapy: Overwhelming data have shown that preoperative radiotherapy is more dose-effective in terms of reduce of the local recurrence rate and also at the end beneficial for survival. Two main options occur. One is the short course with one week treatment and the other is a long course. There are no data indicating that either of them should be the better. An important topic is whether additional chemotherapy to radiotherapy would improve the effect. There are data indicating that the local recurrence rate will be reduced but this has no real impact on survival. On the other hand, it is known that toxicity will increase substantially if chemotherapy is added to radiotherapy.
Another important topic is whether preoperative radiotherapy of preferably chemoradiotherapy will increase the number of preserved sphincters. Uncontrolled data support that but all randomised trials specifically addressing this question have not shown a beneficial effect with chemoradiotherapy compared to radiotherapy.
Future: Based upon available literature the problem with the high local recurrence rates in rectal cancer surgery has been more or less solved. With appropriate surgical technique and selective use of radiotherapy the local recurrence rate should not exceed 5%. However, despite this the mortality due to distant metastases (30% of those operated upon