142 INVITED

Chemoradiation as neoadjuvant treatment: which schedule is best?

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The standard of care for pre-operative chemoradiation (CRT) is the use of a fluoropyrimidine (fluoro) combined with pelvic irradiation to a dose of 45−50.4 Gy. This is based on the results of three pivotal European trials. The EORTC 22921 and the French 9203 trials both demonstrated a significant reduction in local recurrence (LR) when concurrent 5 fluorouracil (5FULV) was added to pelvic irradiation giving a total dose of 45 Gy. A German trial demonstrated a significant reduction in LR, acute and late toxicity in favour of pre-op CRT when it was compared with post-op CRT.
The phase III evidence therefore supports the use of an intravenous 5FU (+/−LV) concurrent CRT. Following these trials both phase I/II and III trials have focussed on the improvement of the concurrent CRT schedule. This includes the evaluation of oral fluoro, the addition a second chemotherapy drug or a monoclonal antibody to fluoro CRT. Relatively few studies have developed pre-operative schedules that combine a period of systemic dose chemotherapy in combination with concurrent CRT.
Oral fluoro CRT is now in common use based on direct phase II evidence and indirect phase III trial evidence demonstrating equivalence of an oral fluoro when compared with 5FU/LV as both adjuvant and first line metastatic treatment. Based on phase I/II studies the oral CRT schedule is either 5 or 7 days per week.
Multiple phase II studies demonstrate acceptable toxicity and encouraging early measures of efficacy based on histopathological downstaging when either oxaliplatin or irinotecan is added to fluoro CRT. There is a lack of mature outcome data from such studies and the inevitable concern that phase II studies have small sample sizes and possible selection bias. Two phase III (the STAR and ACCORD) trials recently reported (ASCO 2009) an increase in actue toxicity but no significant difference in the rate of pCR when oxaliplatin fluoro CRT was compared with fluoro CRT.
Phase I/II studies have evaluated the addition of either an EGFR or a VEGF inhibitor to the CRT schedule. To date these studies have demonstrated acceptable toxicity although there are limitations in interpreting the information on efficacy due to both sample size constraints and an emphasis on early histopathological measures of downstaging. We currently lack a validated early outcome measure that correlates with long term outcome. Although pCR, tumour regression grade and the circumferential margin are all considered useful measures of "downstaging" there is no evidence that validates these measures as a reliable surrogate end point for long term outcome.
It is therefore important to emphasize that it is most unwise to change routine clinical practice based on phase II data from studies that intensify CRT. Evidence of benefit from well designed phase III studies is essential to justify and increase in treatment related toxicity. The importance of high quality phase III trial design will be illustrated.
Phase II designs of novel CRT recognize the opportunity to integrate a component of systemically active chemotherapy combined with CRT and examples of such studies and future clinical trial design will be discused.
At present the standard of care for pre-op CRT remains fluoro CRT. Positive results of ongoing phase III trials are required before any alteration in this standard is considered.

143 INVITED

Late complications of local multimodality treatment

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Functional outcome of rectal cancer treatment is often poor. In order to get insight in the etiology of anorectal and urogenital dysfunction after rectal cancer treatment, long term functional outcome was evaluated and risk factors were identified. In addition, the surgical anatomy of the nerves to the levator ani muscle was studied to evaluate a possible role in the development of incontinence problems after total mesorectal excision (TME).
Methods: Data were obtained from the database of the Dutch TME trial, in which patients with resectable rectal cancer were randomized to total mesorectal excision (TME) with or without preoperative radiotherapy (PRT). Questionnaires concerning functional outcome were completed preoperatively and at several time points until five years postoperatively. Sexual dysfunction, urinary dysfunction and faecal incontinence (only in patients treated with low anterior resection) were evaluated in 526, 785 and 339 patients, respectively.
Results: Increase of general sexual dysfunction, erectile dysfunction and ejaculatory problems was reported by 76.4, 79.8 and 72.2 percent of male patients, respectively. Risk factors were nerve damage, blood loss, anastomotic leakage, PRT and the presence of a stoma. In female patients increase of general sexual dysfunction, dyspareunia and vaginal dryness was reported by 61.5, 59.1 and 56.6 percent, respectively. This was associated with PRT and the presence of a stoma.
Long-term difficulty in bladder emptying was reported by 30.6 percent of patients and was associated with preoperative difficulty in bladder emptying, peroperative blood loss and autonomic nerve damage.
Long-term urinary incontinence was reported by 38.1 percent of patients and was associated with preoperative incontinence and female sex.
Long-term faecal incontinence was reported by 48.7%. Risk factors were preoperative faecal incontinence and PRT. Faecal and urinary incontinence were significantly associated with each other.
Conclusion: Sexual, urinary and anorectal dysfunction are frequent problems after TME. Associated risk factors demonstrate that it can be mainly attributed to surgical (nerve) damage with an additional effect of PRT. Patients should be informed preoperatively and education of surgeons in pelvic neuroanatomy and crucial anatomical dissection planes may provide the key to improvement of functional outcome.

144 INVITED

Quality control of rectal surgery, a must?

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The surgeon is an important factor in obtaining excellent outcomes in rectal cancer. The ability to identify and follow the appropriate plane and avoiding perforating the resection is critical to reducing local recurrence and ensuring an optimal outcome.
Evidence supporting the importance of mesorectal plane surgery comes from the Dutch TME trial, CR07 and the Mercury study. Such studies suggest improvements in surgery but there is more that can be done. In abdominoperineal resection, in most studies, the frequency of incomplete excision and perforation is too high. This is due to the wrong planes being followed and can be overcome by changing the planes and the operating position of the patient. In a recent series of 175 levator excision abdominoperineal operations operated on by 9 European surgeons the rates of incomplete excision and perforation were markedly reduced by such changes. Simple photography and cross sectional slicing allows pathologists to assess the planes of surgery achieved to help surgeons consistently operate in the correct plane. Such records should be mandatory part of the pathological examination of colorectal cancer

Scientific Symposium (Tue, 22 Sep, 14:45−16:45)
Biological imaging for adaptive radiotherapy

146 INVITED

Biological imaging in treatment planning

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Apart from disease staging, the most widespread use of functional imaging in radiotherapy is target volume delineation. For example, the PET tracer 18F-FDG is considered to be of great utility for target segmentation in lung and head and neck cancers. For other cancers, more specific biomarkers that target the amino acid metabolism or cell membrane receptors have proven to be valuable. In addition, some MRI techniques like diffusion-weighted imaging or dynamic contrast imaging supply geometrical information in some tumour entities.
However, deriving the accurate shape of a tumour from biological images is fraught with problems regarding spatial resolution of the imaging equipment, signal-to-background ratio and image sensitivity. In order to provide reliable target delineation, both the image acquisition protocols and the segmentation algorithms have to be tuned meticulously to this task.
Although target delineation is the main use of biological imaging, a variety of physiological and biological tumour properties can be imaged which may influence therapy optimization or patient selection. Recently, hypoxia, perfusion and repopulation have attracted considerable attention. With respect to these properties, tumours appear very variable both within an individual and the population. Concepts have been proposed to adapt the therapy to the observed heterogeneity of the tumours in an individual or for patient selection for additional, more aggressive treatments. In many instances, it has been shown that the biological image can be transformed into a directed escalation of the radiation dose in the target, the intent being increased efficacy of the treatment or reduced side-effects compared to a dose escalation to the entire tumour. These attempts to image guided 'dose painting' meet with further difficulties regarding the quantification of the

images, the understanding of the significance of the imaged physiological properties with respect to treatment outcome and the reproducibility of the imaging prior to and during treatment.
Treatment adaptation to the heterogeneous response of the tumour to therapy can be based on pre-treatment imaging and, potentially more reliably, to consecutive scans during therapy. Although response monitoring appears appealing, first the challenges of providing reproducible quantitative images and image registration for possibly shrinking tumours have to be met. Again, increased dose to the most slowly responding volumes of the tumour or selection of patients for alternative yet more toxic therapies are an option.
Concluding, biological imaging can be used for radiotherapy treatment planning both in a qualitative manner, e.g. for target delineation, and a quantitative manner, e.g. for directed dose escalation or response monitoring. The demands on the quality of the imaging equipment and image analysis software are huge and reliable methods are still being developed. Nevertheless, biological imaging bears great potential both for the optimization and individualization of radiotherapy.

147 INVITED

Clinical status of bio-imaging for radiotherapy

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Bio-imaging leads to the characterization and quantification of cellular and sub-cellular metabolic pathways and allows to better understand the complexity of tumour biology. It includes nuclear medicine techniques as well as magnetic resonance imaging using dynamic contrasted enhancement or spectroscopic analysis or molecular contrast agents.
These new imaging techniques had been widely employed in many fields of oncology giving additional information compared to anatomical imaging, traditionally based on computed tomography (CT) and magnetic resonance imaging (MRI). In radiation oncology growing interest towards molecular imaging has developed in the last few years.
Positron emission tomography (PET) with the tracer 18F-fluorodeoxy-glucose (FDG) has shown to have a clinical impact on diagnosis and staging of several cancer types being also recommended by international cancer practice guidelines. Using FDG-PET in pre-treatment evaluation, radiotherapy with curative intent may be precluded in patients with previously undetected metastases and changes in gross target volumes (GTV) and planning target volumes (PTV) as well as in dosage and schedules can be recorded since a better delineation of loco-regional disease is offered by these imaging modalities. This leads to the new concept of biologic target volume (BTV).
Therefore, bio-imaging may help to visualize sub-volumes characterised by functional parameters involved in radio-resistance such as hypoxia, proliferation and cancer metabolism and to discover the biologic behaviour of the tumour, monitoring the response to therapy and the molecular changes in tumour biology during treatment. These intriguing opportunities may support dose escalating strategies and multimodal approaches.
PET tracers such as 18F-fluoromisonidazole (FMISO), 18F-fluoroazomycin-arabinoside (FAZA) and 60CU (II)-diacetyl-bis (NA-methylthiosemi-carbazone) and dynamic contrast enhanced (DCEMRI) have been evaluated as hypoxia tracers.
Still several uncertainties remain regarding the most appropriate tracer to use, the method of quantification, how to manage setup variation and target movements, the image processing and particularly the different image registration methods (rigid and not rigid algorithms), the various approaches for definition of volumes of interest (VOI) in GTV contouring and finally the best way to apply this imaging to radiotherapy tumour response.
In conclusion clinical data support the role of molecular imaging in staging and planning for radiotherapy but for individualized treatment in the form of biologic image-guided radiotherapy results from preliminary clinical trials have to be awaited and further analysis are required.

148 INVITED

Functional imaging methods for oncology

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The primary goal of what is now termed "Molecular Imaging" is the visualisation pathological processes at the cellular level, often long before disease symptoms become clinically apparent. The ability to do this confers two major benefits: earlier diagnosis of disease and targeting of individual therapy. Both PET and SPECT have been used in this way for many years, but with limited spatial resolution. In very recent years the idea of molecular MRI has evolved, with the advantage of considerably greater spatial resolution than either PET or SPECT. Typically, diagnostic MRI has relied on the effects of pathology on the water molecules in the tissue, and as a consequence has provided indirect and, frequently, rather non-specific information on the underlying processes. With the advent of molecular MRI we now have the ability to gain information on the expression, upregulation or downregulation, of specific molecules associated with pathology.
In principle, any ligand (intracellular, extracellular or vascular) could be targeted, but there are significant challenges to crossing cellular barriers with the majority of MRI contrast species currently in use. Thus, endovascular targets represent the most accessible and, hence, most widely studied targets to date. The vascular endothelium plays an essential role in normal vascular physiology, and its functional phenotype is dynamically responsive to pathological stimuli. Many of the vascular endothelium's functions are mediated by surface adhesion molecules that can be rapidly upregulated, and this is a common feature of acute neurological disease. These molecules provide an accessible tag with which we can identify the presence of disease within the brain using our new MRI contrast agents. We have discovered that we can detect adhesion molecules using ligand-targeted MRI contrast agents early in the progression of experimental brain disease [1–5]. Moreover, we are able to do this at a time when the presence of pathology is undetectable by either existing imaging methods or clinical scoring.
There is now evidence to suggest that tumour cells use inducible endothelial adhesion molecules to promote their adhesion to the vascular endothelium. Both VCAM-1 and E-selectin have been found to be upregulated in a number of tissues containing metastases, and we have recently demonstrated VCAM-1 upregulation in human brain tissue containing breast cancer metastases. However, the role of such adhesion molecules in metastasis development remains unclear. In this talk I will discuss the various novel targeted contrast agents that we have been developing in Oxford and our recent studies in models of brain metastasis, which indicate the potential of molecular MRI for acute tumour detection and monitoring of therapy.

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149 INVITED

Validation of bio-imaging methods for radiotherapy

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Pre-clinical evaluation of biological imaging is important to validate markers such as hypoxic markers in the context of curative radiotherapy. Outcome after fractionated irradiation is determined by several factors: the number and intrinsic radiation sensitivity of tumour stem cells, repopulation, reoxy-genation, recovery from sublethal damage, and redistribution. Over the last years we studied different biomarkers for proliferation (BrdU), vasculature (CD31), perfusion (Hoechst33348), and hypoxia (pimonidazole) in a panel of 10 different head and neck squamous cell carcinomas in nude mice. The data were correlated with local tumour control probability after clinically relevant irradiation with 30 fractions within 6 weeks. In parallel, single dose irradiations were performed. In the studied panel of tumour models analysis Pimonidazole binding correlated with local tumour control after fractionated irradiation but not with radiobiological hypoxia. CD31 and perfusion were not correlated with local tumour control or radiobiological hypoxia. Radiation sensitivity to single dose under clamped hypoxia correlated strongly with sensitivity to fractionated irradiation and with Pimonidazole binding. Our data indicate that evaluation of biological imaging using clinically relevant fractionation schedules and endpoints allows preclinical validation of biomarkers in the context of curative radiotherapy. Pimonidazole binding predicts local tumour control after fractionated irradiation. The data suggest that Pimonidazole doesn't reflect radiobiological hypoxia but rather the number and/or radiation sensitivity of tumour stem cells.
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