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**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.

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**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.

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**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

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**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