after multimodality treatment of locally advanced rectal carcinoma in the Catharina Hospital in Eindhoven, the Netherlands. The basic treatment principle was preoperative (chemo)radiotherapy, extended surgery and intra-operative radiotherapy (IORT) application to the area most at risk for residual tumor.
Methods: Two-hundred and ninety patients with locally advanced rectal carcinoma who underwent multimodality treatment between 1994 and 2006 were studied. For patients who developed local recurrence, the subsite was classified into presacral, postero-lateral, lateral, anterior, anastomotic or perineal. Patient, treatment and tumor characteristics were related to the subsite of local recurrence.
Results: Thirty-four patients (5-year local recurrence rate: 13.2%) developed local relapse. The most prominent subsite of local recurrence was the presacral subsite; about 40% of all local recurrences. 47% of the local recurrences occurred outside the IORT field. Most recurrences developed when IORT was given dorsally, while least occurred when IORT was given ventrally. Especially after dorsal IORT a high amount of infield recurrences were observed (6 of 8; 75%). In multivariate analysis tumor distance of more than 5 cm from the anal verge and a positive circumferential margin were associated with presacral local recurrence.
Conclusions: Multimodality treatment is effective in the prevention of local recurrence in locally advanced rectal carcinoma. Radicality of the resection is the most important factor influencing local control. IORT application to the area most at risk is feasible and seems more effective in the prevention of local recurrence than application of IORT to the dorsal area. Dorsal tumor location results in unfavourable oncologic results. The mechanism of genesis of the presacral local recurrence is puzzling; several hypotheses speculating its origin are discussed.

Scientific Symposium (Wed, 23 Sep, 09:00−11:00)
New imaging approaches to response assessment in childhood cancer

214 INVITED

Are current tumour response criteria relevant to the 21st century?

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In children with cancers, improved understanding of the molecular basis of diseases and the development of new targeted treatment offer new hope of cures and more effective treatment for a range of childhood malignancies. Accurate assessment of treatment response is critical as it impacts on the choice of treatment and disease prognosis. To date, the most widely used and accepted method of ascertaining tumour response by imaging, is by comparing the measurements of tumour size before and after treatment. Such approach is crystallised in the Response Criteria in Solid Tumours (RECIST) criteria, which was developed from clinical trials data derived largely from adult populations. Although recently revised to a new version (1.1), potential limitations of the RECIST criteria have to be considered when these are applied to the paediatric population.
It has also long been recognised that size measurement based criteria for defining tumour response may not be accurate surrogates for treatment outcomes, such as the time to progression or disease survival. This is particularly important when considering new molecular targeted therapies, which may produce substantial clinical benefits without causing significant tumour size reduction. Thus, there is an urgent need to develop, validate and qualify new imaging biomarkers that reflect biologically relevant end-points, which can be applied to measure the effectiveness of new targeted treatments developed out of better understanding of the phenotypic and genotypic expressions of childhood cancers.
Quantitative functional imaging techniques based on radionuclide imaging, positron emission tomography, MR imaging (e.g. dynamic contrast enhanced imaging, dynamic susceptibility contrast enhanced imaging, diffusion-weighted imaging, MR spectroscopy) and CT imaging (perfusion CT) are now widely used in drug development and clinical trials in the adult population. Such functional imaging techniques are now being investigated in children. Of these, MR imaging derived techniques are particularly attractive as they are free from harmful ionising radiation and can thus be safely repeated. Functional imaging studies yield unique quantitative information that reflect changes in tumour pathophysiology, allowing for a more specific assessment of the consequence of anti-tumour treatment. By selecting the most appropriate imaging biomarker for the mode of drug action (e.g. specific receptor blockade or metabolic pathway inhibition, angiogenesis inhibition, cell death, apoptosis, decrease in tumour metabolism), the detection of drug effects and tumour response to treatment could potetially be maximised. Hence, a developed panel of imaging biomarkers may proof critical for the individualised treatment of childhood cancers in the future.

215 INVITED

Assessing changes in tumour metabolism using magnetic resonance spectroscopy

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Magnetic resonance spectroscopy (MRS) is a technique which can be readily combined with conventional magnetic resonance imaging to measure the levels of various metabolites, lipids and macromolecules in a specified volume of tissue. The most clinically available form is 1H MRS which provides a broad metabolite profile with approximately 15 metabolites being quantitated in brain tumours. Due to the comparative ease of performing 1H MRS in the brain, brain tumours have been the most widely studied tumour group, however, there have also been many studies of prostate cancer and breast tumours. It is well established that 1H MRS metabolite profiles are a powerful characteristic of brain tumours and the use of 1H MRS as a non-invasive diagnostic tool is well investigated. The most impressive results have been obtained by coupling 1H MRS with pattern recognition techniques and large multicentre prospective studies have shown a high level of diagnostic accuracy for many tumour types but a lower accuracy when trying to distinguish between glioblastoma and metastases. Fewer studies have been published in children but small studies indicate that the accuracy is similar. Total choline and mobile lipids have been noted as indicators of tumour aggressiveness and a decrease in choline has been used as an indicator of tumour response to drugs. Similarly, myoinositol correlates with lower grade in gliomas and is a good prognostic marker in pilocytic astrocytomas in children. Animal and cell line studies show particular promise for mobile lipids as early indicators of cell death, however these findings are yet to be verified clinically.
MR spectroscopic imaging allows MRS to be collected from several locations at the same time with a spatial resolution down to 1 cubic cm in the brain using a 1.5T clinical scanner and much higher resolution in the prostate using endorectal coils. Using choline as a marker of active tumour, often as a ratio to another metabolite, has allowed accurate targeting of biopsies and is used commonly in some centres for improving the accuracy of prostate biopsies. MR spectroscopic imaging is also useful for identifying tumour invasion and has detected diffuse tumour outside the regions delineated by conventional MRI. This shows promise in radiotherapy planning.
31P MRS can detect phosphorous containing metabolites and phospho-lipids. It is technically more demanding than 1H MRS but is useful in certain circumstances. Phosphocholine and glycerophosphocholine can be quantitated individually rather than the combined value usually provided by 1H MRS. The ratio of these two metabolites is a powerful discriminant of some tumour types such as medulloblastoma and of response to treatment with the phosphocholine/glycerophosphocholine ratio decreasing in responding tumours.
Dynamic Nuclear Polarisation (DNP) is an exciting new technique for the production of tracer metabolites which can be detected by MRS and has the particular advantage that the parent molecule and its metabolites can be detected separately. The first clinical studies of DNP using pyruvate as a marker of apoptosis are about to start.
Review Articles:

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216 INVITED

Diffusion weighted imaging in the evaluation of response in abdominal tumours

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MRI provides several foundations for image contrast, on of which is diffusion-weighted imaging (DWI). With this technique, protons (in essence the hydrogen nuclei of water molecules) contribute to the MR signal if they are relatively stationary, e.g., if confined intracellularly. They contribute to signal loss if they move within the picture volume element (voxel), which is the case when their diffusion is unrestricted, e.g., in the extracellular space of a low-cellularity tissue. In the MR scanner we can apply both stronger and weaker diffusion weighting, and the relative change in signal can be quantified so that we get absolute numbers for the apparent diffusibility within each voxel; this is called ADC (apparent diffusion coefficient).

Paediatric solid tumours being highly cellular makes DWI attractive. Several studies have demonstrated the feasibility of DWI outside the CNS. In our initial observations (Radiology 2007;245:848−54) we described a significant relation between the tissue cellularity as measured histopathologically, and in vivo ADC. A possible hypothesis was therefore that DWI is a tool for assessing chemotherapy response in solid tumour by observing ADC over time.
Initially we followed a cohort of nephroblastoma patients in our institution with MRI at diagnosis and after six weeks' chemotherapy. The whole volume of all tumours was post processed to provide separate distributions of ADC values before and after chemotherapy. Independently, the histopathological slides were reviewed in accordance with SIOP Wilms-2001. I this pilot we have indeed seen a clear pattern suggesting that tumours that are differentiating, regressive or necrotic shift significantly towards higher ADC values following chemotherapy, whereas tumours that are triphasic or blastematous following chemotherapy do not show such a shift.
The results, although preliminary, are very promising, and deployment as part of future trials should be considered since this may be a unique window for response assessment that is independent of tumour size.

217 INVITED

Detecting tumor responses to treatment using magnetic resonance imaging and hyperpolarized spectroscopy

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Patients with similar tumor types frequently have markedly different responses to the same therapy. The development of new treatments would benefit significantly, therefore, from the introduction of imaging methods that allow an early assessment of treatment response in individual patients, allowing rapid selection of the most effective treatment. We have been developing methods for detecting the early responses of tumors to therapy [1]. This has included a targeted MRI contrast agent for detecting tumor cell death [2] and MR imaging of tumor metabolism using hyperpolarized C-13-labeled cellular metabolites. Nuclear spin hyperpolarization techniques can increase sensitivity in the MR experiment by >10,000x. This has allowed us to image the location of labeled cell substrates and, more importantly, their metabolic conversion into other metabolites. We showed that exchange of hyperpolarized C-13 label between lactate and pyruvate, in the reaction catalyzed by the enzyme lactate dehydrogenase, could be imaged in tumors and that this flux was decreased in treated tumors undergoing drug-induced cell death [3]. We have also shown that tissue pH can be imaged from the ratio of the signal intensities of hyperpolarized C-13-labeled bicarbonate and carbon dioxide following intravenous injection of hyperpolarized C-13-labeled bicarbonate [4]. The technique was demonstrated with a study on a mouse tumor model, which showed that the average tumor pH was significantly lower than the surrounding tissue. Since bicarbonate is already used intravenously in humans, we propose that this technique could be used clinically to image disease and response to treatment.

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Society session (Wed, 23 Sep, 09:00−11:00)
ESSO session − How to manage the patient who presents with stage IV colorectal cancer

219 ESSO Award

How to manage the patient who presents with stage IV colorectal cancer. The role of the colorectal surgeon

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Thirty percent of the patients with primary colorectal cancer presents with synchronous distant metastases. In the majority of cases the liver is the target organ but lung and peritoneum are the other frequently involved organs. This percentage might even increase with the availability of modern imaging techniques in the preoperative workup.
Several aspects are important to define the optimal strategy. This is determined by the presence of symptoms of the primary tumor, the estimation of resectability of both the primary tumor and metastases and finally the condition of the patient.
The colorectal surgeon should be in the lead of the multidisciplinary team making decisions about the right sequence of treatment options. Presently there is no standard therapy although removal of the primary tumor followed by systemic treatment was considered standard in the past.
There is a big difference in the approach between colon and rectal tumors. The first one presents often with obstruction making immediate surgery necessary and the latter one often has a threatened endopelvic fascia making primary surgery without preoperative chemoradiation not feasible.
With the availability of effective chemotherapeutic agents induction chemotherapy has become attractive in the last years. This induction chemotherapy is also used in selection of patients since progressive disease under chemotherapy is a poor prognostic sign. After a good response of the metastases and primary tumor it is attractive to resect the liver metastases first [1,2].
Our group conducts a phase II study in which after a short course radiotherapy (5 times 5 Gray) the treatment is followed by induction chemotherapy (including monoclonal antibodies). After 2−4 cycles a plan is made to treat liver and primary tumor at the same time. If this is not feasible a choice is made to treat either the liver first or the primary tumor, the second procedure is performed after a period of 2−3 months. Initial data show a high response rate and a high percentage of radical resections. This aggressive approach is also justified in patients with synchronous carcinomatosis peritonei [3].
On the other hand if both primary tumor and distant metastases are not resectable systemic treatment only is a valuable option [4].
In summary. As long as metastatic diseases and primary tumor are resectable neoadjuvant systemic treatment followed by radical resection of all tumor sites is advisable. Outcome is similar as in Stage III cases. If incurable disease is present the necessity of surgery should be carefully evaluated.

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221 INVITED

The role of the radiation oncologist

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In the last two decades we have seen major advances in the way patients with rectal cancer are investigated and treated. European investigators have continued to test important questions in the framework of randomised phase III trials with a specific focus on the role of adjuvant radiotherapy. In the last nine years at least seven European phase III trials evaluating the role of adjuvant radiotherapy in rectal cancer have been published. From these trials, we have an evidence base that demonstrates the efficacy of both short course pre-operative radiotherapy and pre-operative concurrent chemo-radiotherapy. Recent data from the Uppsala group have shown that short-course radiotherapy and delayed surgery in T4 tumours based upon MRI-staging also results in a chance of R0 resection, indicating that down-sizing will occur after this treatment regimen and allowing in the meantime an up-front chemotherapy before surgery. There is a paucity of studies that address specific translational questions within the framework of rectal radiotherapy trials. There is an urgent need to prospectively evaluate markers of both efficacy and toxicity with respect to both radiotherapy and concurrent chemotherapy agents. Many of these approaches are underway or planned but it is of paramount importance that future research studies