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

K.M. Brindle[1]. [1]*University of Cambridge, Department of Biochemistry, Cambridge, United Kingdom*

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.

References

[1] Brindle, K. New approaches for imaging tumour responses to treatment. Nature Rev. Cancer 8, 1−14 (2008).
[2] Krishnan, A. S. et al. Detection of cell death in tumors using MRI and a gadolinium-based targeted contrast agent. Radiology 246, 854–862 (2008).
[3] Day, S. E. et al. Detecting tumor response to treatment using hyperpolarized 13C magnetic resonance imaging and spectroscopy. Nature Med 13, 1382–1387 (2007).
[4] Gallagher, F. A. et al. Magnetic resonance imaging of pH in vivo using hyperpolarized 13C-labeled bicarbonate. Nature 453, 940–943 (2008).

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

T. Wiggers[1]. [1]*University Medical Center Groningen, Surgical Oncology, Groningen, The Netherlands*

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.

References

[1] Verhoef C, van der Pool AE, Nuyttens JJ, Planting AS, Eggermont AM, de Wilt JH. The "liver-first approach" for patients with locally advanced rectal cancer and synchronous liver metastases. Dis Colon Rectum. 2009;52:23−30.
[2] Mentha G, Roth AD, Terraz S, Giostra E, Gervaz P, Andres A, Morel P, Rubbia-Brandt L, Majno PE. 'Liver first' approach in the treatment of colorectal cancer with synchronous liver metastases. Dig Surg. 2008;25:430−5.
[3] Pestieau SR, Sugarbaker PH. Treatment of primary colon cancer with peritoneal carcinomatosis: comparison of concomitant vs. delayed management. Dis ColonRectum. 2000;43:1341−6
[4] Poultsides GA, Servais EL, Saltz LB, Patil S, Kemeny NE, Guillem JG, Weiser M, Temple LK, Wong WD, Paty PB. Outcome of Primary Tumor in Patients With Synchronous Stage IV Colorectal Cancer Receiving Combination Chemotherapy Without Surgery As Initial Treatment. J Clin Oncol. 2009. [Epub ahead of print]

221 INVITED

The role of the radiation oncologist

V. Valentini[1]. [1]*Pol. Univ. "A. Gemelli", Cattedra Radioterapia – Istituto di Radiologia, Rome, Italy*

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

are well designed, the study group well defined and the treatments and assessment of long term outcome (including toxicity) are standardised.

Keynote Lecture (Wed, 23 Sep, 11:15−12:00)
Insights into the cancer cell, stem cell interface through systems biology

223 INVITED

From RNAi screens to molecular function: A systematic pipeline for gene function in mammalian cells

F. Buchholz[1], M. Theis[1], D. Krastev[1], M. Slabicki[1], L. Ding[1]. [1]*Max Planck Institute, Institute for Molecular Cell Biology, Dresden, Germany*

RNAi screens typically deliver a large number of candidate genes that play a role in a biological process. The validation of these candidates and the dissection of the molecular mechanism are often time consuming and cumbersome. Hence, RNAi libraries employed during the screening process should be of high quality to avoid tedious downstream work. We have developed endoribonuclease prepared (e)siRNAi libraries for efficient and specific RNAi screening. The advantages of esiRNAs will be discussed and example screens will be presented. We have also developed a pipeline using BAC recombineering technology and tissue culture transgenesis to streamline the analysis of hits identified in large scale RNAi screens. Together, these resources represent a seamless pipeline for the systematic analysis of mammalian genes.

Special Session (Wed, 23 Sep, 13:30−14:30)
What is new in the pathogenesis of urothelial cancer?

224 INVITED

Hereditary factors in bladder cancer

L. Kiemeney[1]. [1]*Radboud University Medical Centre Nijmegen, Department of Epidemiology and Biostatistics & HTA, Nijmegen, The Netherlands*

First degree relatives of patients with bladder cancer have a two-fold increased risk of bladder cancer but high-risk bladder cancer families are extremely rare. There is no clear Mendelian inheritance pattern that can explain the increased familial risk. This makes classical linkage studies for the mapping of susceptibility genes impossible. The disease is probably caused by a combination of exposure to exogenous carcinogens and a large number of susceptibility genes with modest effects.
Genome-wide association studies (GWAS) are better suited to identify these genes. Three of these studies are ongoing of which one reported the first results. In this presentation, an overview will be given of hereditary factors in bladder cancer and the relevance of the results of the GWAS will be discussed.

225 INVITED

Histopathological profile of bladder cancer

A. Lopez-Beltran[1]. [1]*Reina Sofia University Hospital, Department of Pathology, Cordoba, Spain*

Bladder tumors represent a heterogeneous group of cancers that include those that are:
1. Papillary in nature and limited to the mucosa (Non-invasive, stage Ta).
2. High grade and flat confined to the epithelium (Non-invasive, stage Tis)
3. Invasive into the lamina propria or submucosa (Early invasive, stage T1)
4. Invasive into the muscularis propria or beyond (Invasive, stage T2-T4).

The natural history of these bladder cancers is that of recurrence of disease and progression to higher grade and stage disease. Furthermore, recurrence and progression rates of superficial bladder cancer vary according to several tumor characteristics, mainly tumor grade and stage. The most recent World Health Organization (WHO) classification of tumors of the urinary system includes epithelial abnormalities and metaplasia as well as urothelial dysplasia and carcinomas in situ as flat lesions. The papillary lesions are broadly subdivided, following the current WHO classification, into benign (papilloma and inverted papilloma), papillary urothelial neoplasia of low malignant potential and non-invasive papillary carcinoma (low or high grade). Invasive papillary carcinoma and non-papillary (solid) carcinomas are subdivided into low and high grade neoplastic lesions. Each of these lesions is defined with strict morphological criteria to provide more accurate information to urologists and oncologists in managing patients. There is still debate in the literature as to whether the 2004WHO system should be the only one to be used in clinical practice. The key points of the latest World Health Organization (WHO) classification of non-invasive urothelial tumors are: a. The description of the categories has been expanded in the current version to improve their recognition, b. One group (papillary urothelial neoplasm of low malignant potential) with particularly good prognosis does not carry the label of 'cancer', c. It avoids use of ambiguous grading such as grade 1/2 or 2/3 (according to the WHO classification published in 1973, d. The group of non-invasive high grade carcinoma is large enough to contain virtually all those tumors that have biological properties (and a high level of genetic instability) similar to those seen in invasive urothelial carcinoma. e. This scheme is meant to replace the 1973 WHO classification. From the practical point of view, the use of both the 1973 and the latest WHO classifications is recommended until the latter is sufficiently validated. This presentation summarizes the recent literature concerning important issues in the pathology and the clinical management of the patients with bladder urothelial carcinoma. The initial proposal of the WHO has been achieved with most reports clearly recognizing that categories are better defined than in previous classifications. Questions such if PUNLMP remains as a clinically useful category or if this category should be expanded including all low grade Ta lesions (PUNLM and Low grade papillary carcinoma) as a wider low malignant potential neoplastic category not labelled as cancer needs to be discussed in the near future. In this presentation, emphasis is placed on macroscopic appearance, and synchronous or metachronous presentation (field disease vs. monoclonal disease with seeding), classification and microscopic variations of bladder cancer with clinical significance, TNM distribution and the pathologic grading according to the most recent WHO proposal.

226 INVITED

Genomic alterations in urothelial carcinoma subgroups

M. Knowles[1]. [1]*Cancer Research UK Clinical Centre, St James's University Hospital, Leeds, United Kingdom*

Bladder tumors are heterogeneous in their histopathology and clinical behaviour. Currently, assessment of risk for recurrence and progression to invasive disease is not precise and response to specific therapies cannot be predicted accurately. It is anticipated that a thorough knowledge of the molecular alterations that are involved in the development and progression of bladder cancer will lead to greater predictive power and the application of targeted therapies. The current state of knowledge of genomic alterations found in urothelial carcinoma will be summarised.

Special Session (Wed, 23 Sep, 13:30−14:30)
Immune system and ovarian cancers

228 INVITED

Antigen specific active immunotherapy for ovarian cancer

H. Nijman[1], C.J.M. Melief[1], C.A.H.H. Daemen[2], N. Leffers[3]. [1]*Groningen University Hospital, Department of Gynaecologic Oncology/CMCV4th floor, Groningen, The Netherlands;* [2]*Groningen University Hospital, Department of Microbiology, Groningen, The Netherlands;* [3]*Groningen University Hospital, Department of Gynaecologic Oncology/CMCV4ht floor, Groningen, The Netherlands*

Introduction: Epithelial ovarian cancer is the most frequently diagnosed malignancy of the ovaries. Standard therapy consists of cytoreductive surgery, an attempt to remove as much tumour bulk as possible, followed by platinum-containing chemotherapy. Although initial response rates to primary therapy are high, the majority of patients with advanced stage disease relapse. The observation that survival rates were higher in patients with certain intra-tumoral immune cells (i.e. T-lymphocytes), suggested that the stimulation of anti-tumour immune responses, i.e. immunotherapy, might be a useful approach to improve the prognosis of patients with ovarian cancer. In this survey, the feasibility of antigen-specific active immunotherapy is evaluated. As immunotherapy is a relatively novel treatment strategy for ovarian cancer, not only randomised controlled trials, but also early phase studies were included in this review.
Material and Methods: Thirty studies evaluating antigen-specific active immunotherapy in 1230 patients with ovarian cancer were identified with a systematic search of study reports published between 1966 and 2008. Information on clinical responses, survival, immunological responses, and adverse events was available for 18, 18, 29, and 22 studies respectively.
Results: the most frequently described strategy (1134 patients in 14 studies) was the administration of antibodies targeting CA-125, better known as a tumour marker for ovarian cancer. Most of these studies were