enhancing fraction and that in patients receiving VEGF inhibitors whose disease is progressing, the tumours manifest an increasing enhancing fraction. Together, these results highlight the potential of the vascular fraction as a potential predictive biomarker for VEGF inhibitors and we are now testing the additional information gathered by measuring imaging and blood borne biomarkers of angiogenesis.
Taken in conjunction with emerging imaging technologies (e.g. ASL) it is now appropriate to test the predictive value of imaging to determine which patients most benefit from anti-angiogenic agents.

## *Scientific Symposium* (Wed, 23 Sep, 09:00−11:00) FLIMS Symposium and ECCO/EJC Young Investigators Award

**210** INVITED

**The FLIMS Workshop**

W. Steward[1]. [1]*Leicester Royal Infirmary, Department of Cancer Studies and Molecular Medicine, Leicester, United Kingdom*

The 1st Annual Workshop "Methods in Clinical Cancer Research" was held in Flims, Switzerland in 1999 and was based on a similar training workshop held at Vail, USA. This Workshop had been borne out of a concern about the shortage of young clinical researchers and the increasing need to conduct clinical trials with new anticancer agents. The European Workshop was run under the auspices of FECS (now ECCO), AACR and ASCO). Funding was obtained from these organisations and a grant from NCI together with contributions from the pharmaceutical industry. Ten courses have been held with almost 800 graduates attending the Workshops. Each Workshop comprises 35 to 40 highly experienced international clinical investigators and several innovative techniques and teaching methods are utilised aimed at intensively guiding and supervising the students through the process of completing a protocol concept sheet and developing a finished protocol by the end of the Workshop week.
Four educational formats are used. Protocol development sessions involve small groups of students with at least 3 dedicated faculty members and this constitutes the core activity of the Workshop. Support is provided by Faculty members to each student so that the final protocol can be developed. Small group discussion sessions are held during the week to cover specialised topics relating to clinical trials development. Lectures and panel discussions are held on a daily basis to cover a variety of specific topics presented by experts in the field. These give an essential overview of the design and conduct of high-quality clinical trials. Where appropriate, lectures on related topics are followed by a panel discussion or round table sessions. One on one sessions are held during the week for individual counselling and advice on protocol and career development. The selection of participants is highly competitive and undertaken after submission by applicants of a trial concept sheet together with CV and letter of recommendation. International peer review is undertaken and successful candidates are selected following this. Constant monitoring of the success of the Workshop is undertaken. A set of objectives were determined at the outset of the Workshops in 1999 and, encouragingly all have been exceeded. Greater than 80% of protocols written during the Workshop were subsequently submitted, approved and funded for candidates in 2001, 2004, 2005 and 2006. Greater than 80% of protocols have subsequently been submitted and approved by Ethics Committees every year except 2001. The Workshop has proven extremely popular with universal positive feedback and the perception by many that this is one of the highlights of their careers. Several important trials have been developed at Flims and have been published in high impact journals.

**211** INVITED

**Presentation of a Flims study: The diagnostic value of PET/CT for primary ovarian cancer – a prospective study**

S. Risum[1], C. Hogdall[2], A. Loft[3], A.K. Berthelsen[3], E. Hogdall[4], L. Nedergaard[5], L. Lundvall[2], S.A. Engelholm[1]. [1]*Department of Oncology, The Finsen Center Rigshospitalet, Copenhagen, Denmark;* [2]*The Gynecologic Clinic, The Juliane-Marie Center Rigshospitalet, Copenhagen, Denmark;* [3]*PET and Cyclotron Unit Dept. of Clinical Physiology & Nuclear Medicine, Centre of Diagnostic Investigations Rigshospitalet, Copenhagen, Denmark;* [4]*Department of Pathology, The National Biobank Herlev Hospital, Copenhagen, Denmark;* [5]*Department of Pathology, Centre of Diagnostic Investigations Rigshospitalet, Copenhagen, Denmark*

**Background:** To prospectively evaluate the diagnostic value of combined PET/CT for detecting a malignant tumor in patients with a pelvic mass and to identify PET/CT predictors of incomplete/suboptimal primary cytoreduction in advanced ovarian cancer patients.

**Methods:** From September 2004 to August 2007, 201 patients (median age=61 years, range=21–91 years) with a risk-of-malignancy index (RMI)>150 based on serum CA-125, ultrasound examinations, and menopausal state, underwent PET/CT within 2 weeks prior to standard surgery/debulking of a pelvic tumor. Histological diagnoses were compared to the PET/CT results to calculate the diagnostic value of PET/CT in differentiating between malignant and borderline/benign tumors. In 94 ovarian cancer patients the FIGO stage was compared with the stage indicated on PET/CT. Ten PET/CT features were identified and evaluated as predictors of cytoreduction in 66 patients with advanced ovarian cancer.
**Results:** The sensitivity of PET/CT for diagnosing a malignant pelvic tumor was 95% (107/113) and the specificity was 91% (80/88). FIGO stage IV was found in 11% (10/94) of ovarian cancer patients. In 44% (41/94) of ovarian cancer patients, PET/CT demonstrated areas of abnormally increased metabolic activity that indicated stage IV, metastatic disease. Complete cytoreduction (no macroscopic residual disease) was achieved in 38% (25/66) of patients with advanced ovarian cancer. Using univariate analysis, predictors of incomplete cytoreduction were large bowel mesentery implants (LBMI) ($P < 0.001$), peritoneal carcinosis ($P < 0.001$), pleural effusion ($P < 0.003$), ascites ($P < 0.01$) and small bowel mesentery implants ($P < 0.02$). Using multivariate analysis, LBMI was the only independent predictor of incomplete cytoreduction ($P = 0.004$).
**Conclusion:** Combined PET/CT demonstrated high diagnostic value in identifying primary ovarian cancer in patients with a pelvic mass of unknown origin and RMI>150. In patients with advanced ovarian cancer PET/CT located metastases unrecognised by standard staging procedures. In addition, PET/CT predictors of cytoreduction were found. However, those predictors should be used with caution until prospective randomised trials have clarified which subgroup of ovarian cancer patients benefits in terms of survival from neoadjuvant chemotherapy followed by interval debulking.

**212** INVITED

**Presentation of a Flims study: Randomized phase II study of docetaxel/oxaliplatin and docetaxel in previously treated non-small cell lung cancer patients**

O. Belvedere[1,2], A. Follador[2], M. Gaiardo[2], F. Grossi[3], C. Rossetto[2]. [1]*Leeds Institute of Molecular Medicine, University of Leeds, Leeds, UK;* [2]*Dept of Medical Oncology, S. Maria Misericordia University Hospital, Udine, Italy;* [3]*Medical Oncology A, National Institute for Cancer Research, Genoa, Italy*

The development of a research protocol is the core activity at the workshop on Methods in Clinical Cancer Research, sponsored by ECCO-AACR-ASCO and held annually in Flims, Switzerland. At the end of the workshop, the "Flims graduates" return to their home institution with an approved protocol to be implemented in the real world! Obtaining Ethics approval, granting financial support, having the study up and running can be challenging and the successful completion of the study up to a publication should not be taken for granted. This presentation will be given by an Italian Medical Oncologist who attended the Workshop in 2004 and whose life has definitely changed as a consequence of this experience. The talk will chronicle the development and implementation of her Flims protocol for a randomized phase II study evaluating the activity of docetaxel plus oxaliplatin in second-line non-small cell lung cancer (NSCLC); the comparator arm was single agent docetaxel. The study was designed as a one-stage, three-outcome phase II trial (Sargent et al, Control Clin Trials 2001) requiring 21 evaluable patients per arm; primary endpoint was response rate. The study was implemented at the student's home Institution with the support of the Alpe Adria Thoracic Oncology Multidisciplinary group (ATOM group). Fifty patients were enrolled at four Italian centers. It was a positive study: the level of activity for the combination docetaxel/oxaliplatin satisfied the pre-defined study primary endpoint, warranting further evaluation of this combination as second-line therapy for NSCLC. Final results have already been presented at International meetings and the manuscript is in preparation. This is only one of hundreds of trials designed during the Workshop since 1999. Without any doubt, the Flims Workshop is the best training opportunity to learn the essentials of clinical trials methodology: all young oncologists with a major interest in clinical cancer research should be encouraged to attend.

**213** ECCO/EJC Young Investigators Award

**The lessons that can be learned by studying the patterns of local recurrence after primary rectal cancer treatment**

M. Kusters. *Catharina Hospital, Eindhoven, The Netherlands*

**Background:** By determination of the subsite of locally recurrent rectal cancer on imaging and relating these to patient, treatment and tumor variables, the mechanisms of local relapse genesis can be reconstructed. The purpose of this study was to analyze the patterns of local recurrence

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?**

D. Koh[1]. [1]*Royal Marsden Hospital, Department of Radiology, London, United Kingdom*

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**

A. Peet[1]. [1]*University of Birmingham, Cancer Sciences, Birmingham, United Kingdom*

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:

**References**

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**216** INVITED

**Diffusion weighted imaging in the evaluation of response in abdominal tumours**

O.E. Olsen[1]. [1]*Great Ormond Street Hospital for Children, Radiology, London, United Kingdom*

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).