profiles that reflect different stages of B-cell development. Specifically, the germinal center B cell-like (GCB) DLBCL shows some features of physiological germinal center B-cells such as expression of BCL6 and the process of ongoing somatic hypermutation of the immunoglobulin genes. Conversely, the activated B cell-like (ABC) DLBCL shows features of post-germinal center B-cells such as the expression of IRF4 and activation of the NFkB pathway. In the CHOP treatment era, patients with ABC DLBCL had inferior survival times compared to patients with GCB DLBCL, and this survival difference appears to be still evident in the R-CHOP treatment era. The definition of the GCB and ABC DLBCL subgroups based on their transcriptional profiles is supported by underlying genetic alterations, many of which cluster within each subgroup. BCL2 translocations and 2p amplifications (c-rel locus) are almost exclusively discovered in GCB DLBCL, whereas amplification of the BCL2 locus, mutations/deletions of PRDM1 and deletions of the CDKN2 tumour suppressor locus frequently occur in ABC DLBCL. More recently, deep sequencing strategies have identified an ever growing number of additional genetic mutations that occur predominantly in GCB or ABC DLBCL. Mutations of the polycomb-group oncogene EZH2 and alterations of the acetyltransferase genes CREBBP and EP300 are predominantly associated with the GCB DLBCL subgroup. On the other hand, mutations/deletions in key genes of the NFkB pathway including A20, CARD11, TRAF2 and TRAF5 are a feature of ABC DLBCL, in which chronic active B-cell receptor signaling can be observed as a consequence of frequent mutations in the B-cell receptor signaling molecules CD79B and CD79A. Approximately 30% of ABC DLBCL carry MYD88 mutations that lead to activation of the NFkB signaling cascade, but also to activation of the JAK/STAT pathway. Ongoing sequencing efforts in DLBCL are likely to identify additional key mutations that might help to explain the heterogeneity of DLBCL and that may lead to the development of novel therapeutic concepts.

134 INVITED

A Molecular Portrait of Follicular Lymphoma

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The clinical diversity of follicular lymphoma (FL) is manifest by a wide range in patient survival and unpredictable risk of aggressive transformation. This variability is reflected in a heterogeneous group of secondary (epi-)genetic changes that typically accompany the hallmark t(14;18) and over-expression of BCL2. As profiling tools have become more sophisticated, we are starting to deliver the 'first draft' of an exceedingly complex portrait of the disease which includes fundamental roles for epigenetic reprogramming and cross-talk between the tumour and its microenvironment.
High throughput genetic profiling has developed many aspects of FL research. *Genome Wide Association Studies* have detected novel susceptibility loci, rs10484561 and rs6457327, on chromosome 6p in the immune gene-rich human leukocyte antigen region and follow the demonstration that immune response in FL can predict outcome. This had been established using *gene expression profiling* that characterised Immune Response I and II signatures that reflect the composition of non-malignant infiltrating immune cells in the tumour. Within the malignant cells, the identification of recurring regions of chromosomal aberrations and the corresponding gene targets is set to accelerate with the introduction of *high throughput sequencing* strategies. *TP53* mutations are linked with poor outcome in the disease, although at 6% these are relatively infrequent and a more important target will be *TNFRSF14*/*HVEM* on 1p36, mutated in 20% of FL, and which functions as a potential inhibitory modulator of BCR signalling. The demonstration of mutations in key histone methyltransferases, *EZH2* and *MLL2*, and the acetyltransferase genes, *CREBBP* and *EP300,* suggest that a shift from gene activation to gene repression may be a pre-requisite for onset of FL. This is consistent with *methylation profiling* studies, which show repressive hypermethylation at 7% of gene promoter regions in these tumours.
These advances come at a time when the assumption that each episode of FL reflects the emergence of a more aggressive sub-clone of cells from an existing FL population is under review. By tracing the genetic changes in sequential FL biopsy samples it transpires that recurrent episodes of disease may originate from a more undifferentiated B-cell population. It is a real possibility, therefore, that FL arises from this pool of progenitor B cells and that many of the (epi-)genetic events described can directly influence these cells and are responsible for the clinical features of the disease. That said, we are still some way off from understanding how such diverse changes complement each other to give rise to FL and influence patient outcome.

Scientific Symposium (Sun, 25 Sep, 09:00−11:00)
Multidisciplinary Quality Assurance

135 INVITED

Quality Assurance of Oral Compliance

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Cytotoxic agents block the growth of cancer cells by influencing cell metabolism during the cell cycle so that cell division and reproduction is inhibited. The mechanisms of cytotoxic action are likely to lead to carcinogenic, mutagenic and teratogenic effects. It is suspected that even the smallest doses of cytotoxic agents have an irreversible and cumulative effect and, although they do not have a threshold value, they represent a low but nevertheless clearly defined risk as a consequence.
Over the last few years, impressive progress has been made in the treatment of cancer, not only in research and clinical application but also in clinical and pharmaceutical practice. There has been a massive increase in the number of cytotoxic and supportive drugs for cancer and with the ongoing development of novel therapeutic agents, many of which can be taken orally, it has become increasingly vital that drugs that can be toxic to healthcare workers are prepared, transported and delivered as safely as possible. The role of the hospital pharmacy is paramount in this process.
The quality standard for oncology pharmacy service, developed in Germany, has become the working standard throughout Europe. Rules and guidelines, which may help to ensure uniform safety and quality, need to be defined for all areas involved in handling cytotoxic agents. However, there is still a long way to go before uniformly high standards of safe preparation are achieved across Europe.
The quality assurance and documentation in the diagnosis and treatment of tumours become increasingly important. As the interdisciplinary approaches are standardized in terms of treatment protocols and clinical pathways adequate quality assured multi-professional care of patients with oral cancer chemotherapy is therefore urgently required.
Nationwide training started in Germany already in May 2010, in order to improve the knowledge of pharmacy staff on selected oncological and pharmaceutical topics (e.g drug interactions in oncology, specifically pharmaceutical oncology case studies, side effects of cancer).
Nearly 20.000 Pharmacists and Technicians in community and hospital, which contribute to increase drug treatment safety in oral cytostatic therapy and provide information and counseling services for people with cancer in pharmacies will be targeted in Germany by ESOP speakers from September 2011 in three main topics in the following month.
Based on the knowledge about tumour, the pharmacology of prescribed oral cytotoxic drugs and the relevant supportive care, patient-specific recommendations can be given and documented.
Physicians and pharmacies together with patients will be able to afford on this basis, an active contribution to improving the pharmaceutical care of cancer patients locally and for the oncology outcomes research as well as to improve the adherence for increasing quality of life while the continuously treatment.

136 INVITED

Quality Assurance Through Outcome Registration in Colorectal Cancer − an ECCO Initiative for Europe

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In recent years there have been significant improvements in cancer treatment. Besides effective (neo)adjuvant treatment regimes, new surgical techniques made a big contribution to these improvements. Standardised and quality controlled surgical trials seem to have a positive effect that reaches further then the patients and doctors that participated in the study. Good examples are the Dutch TME trial and the Dutch D1-D2 Gastric Cancer Trial. In both trials standardisation and quality of surgical treatments was continuously emphasised by means of masterclasses, supervision and visitation with lasting positive effects.
However, most patients are treated without being enrolled in clinical trials. Furthermore, elderly patients or those with multiple comorbidities are often excluded from trials, leaving little evidence for the treatment of these categories of patients. Therefore, to improve quality of care for the entire patient population, a comprehensive audit could be a more effective instrument. In Europe, several national rectal cancer audit registries have been established of which all showed positive and very economic effects on outcome of surgical care. Despite these laudable efforts there is still a wide variation in treatment outcome between countries, regions and institutions, which calls for a European audit on cancer treatment outcome.
Urged by these arguments, the European Society of Surgical Oncology (ESSO) initiated an international, multidisciplinary, outcome-based quality

improvement program which is fully embraced by the European CanCer Organisation (ECCO). Initially, the focus will be on colorectal cancer. In the first period of 2 years the registration will make use of currently existing audit systems for colorectal cancer as in Norway, Sweden, Denmark, the United Kingdom, the Netherlands and Belgium, and start a benchmarking process. The national audit coordinators will provide access to their national databases and will form a multidisciplinary Steering Committee. The second period starts after the development of the European registration system. The data will be continuously used for benchmarking and internal feedback among participants. Afterwards, this experience will be used to extend the audit to other solid malignancies such as breast, gastric and oesophageal cancer. Data and experiences with colorectal audits will be discussed but indicate vast improvements of outcome.
Conclusion: Recent developments in quality assurance in surgical oncology have resulted in improvements that have a greater impact on survival than that of any of the adjuvant therapies currently under study. A European audit could advance future improvements and spread these to every cancer patient in Europe. The ECCO has recognised the importance of quality assurance and has created a framework to develop a European audit. As such, ECCO has established a strong, multidisciplinary organisation with a commitment to improve cancer care in Europe. All information about this project can be found on the website:
www.canceraudit.eu. Persons involved in the treatment of colorectal cancer and interested in joining or contributing to this European colorectal audit ECCO project can contact the authors at anytime.

137 INVITED

Quality Assurance of Radiotherapy

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Objectives: In Radiation Oncology, QA systems are based on audits, which can be either internal or external to the Institution. Internal audits can, for instance, track intra-fraction and/or inter-fraction variations (e.g., variations in prostate position in function of rectum and bladder volumes). In this latter case, actions will be taken to match simulation and treatment settings, and random or systematic differences will be reported and recorded by the staff of the treatment unit. External audits can be national or international, performed on site or at QA review centers. They can be institutionally oriented, for instance, to check the accuracy of the beam calibration performed by the center. They can also be performed in the framework of prospective clinical studies, and conducted by experts of cooperative groups.
Material: In this case, the parameters requested and/or deviations investigated by the QA provider use to encompass: a) a definition of GTV, CTVs and PTVs; and b) an identification of isodose distributions underdosing GTVs, under/overdosing PTVs and/or overdosing critical organs such as, for instance in head and neck oncology, the spinal cord, brain stem, optic nerves and chiasm, etc.
Methods: At least two quality systems are essentially proposed to the investigators: the “dummy-run” and the “individual case review”, which were developed within EORTC. These procedures investigate both the compliance of individual institutions to the protocol guidelines and treatment accuracy. As regards the former one, in the very early phase of a trial activation, participating centers are given a number of reconstructed slices of the anatomical region of interest, including target volume contours, and asked to generate the irradiation plan them according to the protocol guidelines. As regards the latter one, it is based on the collection of images and data specific to individual cases treated in the framework of a given protocol. It generally includes diagnostic CT-scans, MRI and/or PET scans, planning CT-scans, treatment plans with dose distribution in target volumes. It is performed at the completion of the treatment (final review), but can also be “interventional” and scheduled at the very early phase of a trial activation.
Results: The clinical outcome of QA programs conducted in the framework of trials is not always easy to quantitate in terms of efficacy results or impact on quality of life. Examples of direct relationships between poor compliance to protocol guidelines and poor clinical results will be presented, especially as regards regimens combining radiation and drugs.
Conclusions: Among the main messages retrieved from a recent past, it can be shown that poor quality irradiation invalidates the scientific rationale of randomized trials of combined modality treatment, and centres enrolling only a few patients are the largest source of quality problems. Therefore sites involved in clinical research need to be rigorously credentialed prior to enrolling patients and interventional review should ideally be done before RT commences. At community level, doing well what we already know is more important than seeking incremental gains through new treatments.

Scientific Symposium (Sun, 25 Sep, 09:00−11:00)
Novel Oncoproteomic Technology

138 INVITED

Label-Free Mass Spectrometry-Based Proteomics for Biomarker Discovery and Validation in Tissues and Biofluids

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Background: Colorectal cancer (CRC) is the second leading cause of cancer death in the Western world. Detection of CRC at an early stage of disease is associated with a much better prognosis for the patient, and is a realistic approach to reduce CRC mortality rates. Several randomised trials have shown that FOBT screening, ie detection of blood-derived haem in feces, reduces CRC mortality by ~16%. Nevertheless, the FOBT test performance is relatively poor, and it is commonly recognized that sensitivity and specificity of non-invasive CRC screening tests need to be improved, for which novel biomarkers are urgently needed.
Label-free mass spectrometry-based proteomics in (pre)-clinical samples and tumour proximal biofluids is emerging as a powerful, versatile approach for discovery of tissue-derived biomarkers with close association to the disease.
Aim: The aim of our studies is to identify novel protein biomarkers that can be used for development of a stool-based, blood-based, or molecular imaging-based screening test for early diagnosis of CRC.
Approach: Proteomics targeted to “biomarker-rich” compartments (proximal fluids, cell surface, nucleus) using a label-free GeLC-MS/MS workflow and spectral counting for protein quantitation. We have shown that this workflow is reproducible and outperforms other commonly used workflows in terms of the total number of identified proteins and the total number of reproducible identified proteins (Piersma et al., J.Proteome Res. 2010; Albrethsen et al., Mol. Cell. Prot., 2010).
Results: We have analyzed three different CRC model systems: 1) Proximal fluids of a mouse model for human sporadic CRC, which lacks variation due to genetic heterogeneity and allows to compare tumour-to matched control-samples; 2) Secretomes, exosomes and cell surface fractions of a panel of five human CRC cell lines; and 3) Proximal fluids and nuclear fractions of human colon adenoma and carcinoma tissues combined with patient-matched control tissues.
By combining proteome profiles of proximal fluids obtained from different CRC model systems we succeeded to identify tens of candidate biomarkers for stool-based or blood-based early detection of CRC. By combining cell surface proteomics with transcriptomics of adenomas and carcinomas we identified candidate biomarkers for molecular imaging of adenoma-to-carcinoma progression.
Outlook: We are currently validating these candidate biomarkers by IHC, ELISA and Selective Reaction Monitoring mass spectrometry using large series of clinical samples, in order to compose a *panel of biomarkers* with high sensitivity and specificity for CRC early detection and screening.
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139 INVITED

High Resolution Mass Spectrometry-Based Proteomics for Metabolism and Cancer Research

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Recent Breakthroughs in mass spectrometry based proteomics enable the detection adn quantification of thousands of proteins in complex mixtures. In addition, these methodes allow for the quantification for global analysis of changes of posttranslational modifications, such as phosphorylation. The basic principles of the methodology will be discussed using examples of metablism and cancer research.

140 INVITED

Clinical Proteomics in the Early Detection of Breast Cancer

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The completion of the human genome as well as the explosion of novel technologies within genomics, proteomics and functional genomics promise