decade enabling the delivery of high radiation doses, reducing side-effects in tumour-adjacent normal tissues. While increasing local tumour control, current and future efforts ought to deal with microscopic disease at a distance of the primary tumour, ultimately responsible for disease-progression. This talk will explore the possibility of bimodal treatment combining radiotherapy with immunotherapy. L19 targets the extra domain B (ED-B) of fibronectin, a marker for tumor neoangiogenesis, and can be used as an immunocytokine when coupled to IL2. We hypothesize that radiotherapy in combination with L19-IL2 provides an enhanced antitumor effect, which is dependent on ED-B expression.

**EXPERIMENTAL DESIGN:** Mice were injected with syngeneic C51 colon carcinoma, Lewis lung carcinoma (LLC), or 4T1 mammary carcinoma cells. Tumor growth delay, underlying immunologic parameters, and treatment toxicity were evaluated after single-dose local tumor irradiation and systemic administration of L19-IL2 or equimolar controls.

**RESULTS:** ED-B expression was high, intermediate, and low for C51, LLC, and 4T1, respectively. The combination therapy showed (i) a long-lasting synergistic effect for the C51 model with 75% of tumors being cured, (ii) an additive effect for the LLC model, and (iii) no effect for the 4T1 model. The combination treatment resulted in a significantly increased cytotoxic (CD8(+)) T-cell population for both C51 and LLC. Depletion of CD8(+) T cells abolished the benefit of the combination therapy.

**CONCLUSIONS:** These data provide the first evidence for an increased therapeutic potential by combining radiotherapy with L19-IL2 in ED-B-positive tumors. This new opportunity in cancer treatment will be investigated in a phase I clinical study for patients with an oligometastatic solid tumor. An animation summarizing our results is available at https://www.youtube.com/watch?v=xHbwQuCTkRc.

**REFERENCE:** Zegers CM1, Rekers NH2, Quaden DH3, Lieuwes NG2, Yaromina A2, Germeraad WT4, Wieten L5, Biessen EA6, Boon L7, Neri D8, Troost EG2, Dubois LJ2, Lambin P2. Radiotherapy combined with the immunocytokine L19-IL2 provides long-lasting antitumor effects. Clin Cancer Res. 2015 Mar 1;21(5):1151-60.

**SP-0576**

*The contribution of cancer stem cells to tumour radioresistance*

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For a number of tumour types there is increasing acceptance that cancer stem cells play an important role in tumour initiation and recurrence after treatment. In line with this model, increasing evidence indicates that cancer stem cells exhibit resistance to conventional cytotoxic agents. In the case of glioblastoma, an incurable primary brain tumour associated with dismal prognosis and devastating effects on quality of life, a series of influential publications have demonstrated that the radiation resistance of glioblastoma stem-like cells (GSC) is associated with constitutive upregulation of the DNA damage response (DDR). In this presentation I will outline the evidence supporting this model, and present new data that elucidates the relative contributions of DNA repair and cell cycle checkpoints to this phenotype. Subsequently I will investigate the effects of inhibiting various components of the DDR, alone and in combination, and discuss the potential clinical application of a number of promising new small molecule inhibitors.

**SP-0577**

*Novel Insights in radioresistance of head and neck cancer*

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Recent technological advances in DNA sequencing with greater speed and resolution at lower costs has provided new insights in cancer genetics. The next-generation sequencing (NGS) technology is tremendously facilitating the in-depth genome-wide search for genetic alterations which might significantly contribute to aggressive and/or treatment-resistant phenotypes of cancers, thereby establishing the basis for improvement of cancer treatment. We hypothesized that NGS should also be useful for dissecting the molecular mechanisms of radioresistance in squamous cell carcinoma of the head and neck (HNSCC). We therefore applied the technology of targeted NGS to clinical samples from two multicenter studies of definitive and adjuvant cisplatin-based chemoradiation of locally advanced HNSCC. We evaluated whether by molecular profiling using targeted NGS it is possible to prospectively discriminate between patients who clearly benefit from chemoradiation and those with poor locoregional control and reduced overall survival after such treatment. Our studies could confirm previous reports of poor efficacy of radiotherapy in HNSCC tumors harboring TP53 mutations. For the first time, we identified additional mutations in other genes as predictive biomarkers of outcome after chemoradiation.

The talk will summarize the results of NGS studies in HNSCC and other carcinoma models, thereby focusing on studies in which specific molecular mechanisms involved in radio-/chemoresistance have been addressed. It will present unpublished results from functional studies in preclinical models in which we are evaluating the mode of interaction of distinct genetic variants with radio-/chemoresistance. Concepts of how to integrate the results from NGS into novel personalized treatment strategies for HNSCC will be discussed.

**Symposium with Proffered Papers: Towards Personalised Radiation Oncology (PRO)**

**SP-0578**

*New technologies for genomic tumour profiling*

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Massive parallel sequencing technologies (also: next generation sequencing) have revolutionized our understanding of the genomic and transcriptional makeup of malignomas. Aided by equally impressive developments in sequencing- and chip-based epigenetic tumor profiling and developments in mass spectrometry which allow for a comprehensive proteomic and metabolomic profiling we are now able to draw fairly comprehensive multi -omics landscapes of individual tumors both from tissue but increasingly also from blood or circulating tumor cells. However, many issues remain still challenging when it comes to a translation of these findings into a potential clinical outreach. This includes matters of tumor heterogeneity specifically with respect to tumor evolution in the metastatic setting as well as under therapeutic pressure. Other widely unresolved issues include the usefulness of identified drivers as novel targets for therapy or as predictive biomarkers and strategies to implement broad high throughput genomic testing into individualized patient care. Specifically the latter issue will decide which of these multi-omics technologies will take the step from tools merely for biological research profiling to advanced and modern routine clinical care.

**SP-0579**

*Gene expression profiles in tumours for PRO*

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Gene expression profiles hold great promises for PRO (Personalized Radiation Oncology), yet very few - if any - are implemented in routine clinical practice and used as predictive biomarkers for treatment decisions in radiation oncology.
Several challenges needs to addressed before gene expression profile can be approved as a predictive biomarker by regulatory bodies like the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA). In an ongoing trial, EORTC-1219 (ClinicalTrials.gov ID: NCT01880359), a 15-gene hypoxia profile (1,2) is being tested prospectively. One of the primary aims of the study is to provide data for regulatory approval of the gene profile as an accompanying biomarker for the use of the hypoxia modifier Nimorazole.

The development and ongoing validation of this 15-gene profile will be used as a general example of the challenges for implementing gene expression profiles in PRO. Different strategies for identification of relevant gene expression profiles will be discussed together with the challenges of validating the predictive value of a gene expression profile. The requirements for a quick and robust test for the gene expression profile working on simple routine FFPE (formalin-fixed, paraffin-embedded) sections will also be discussed. Finally, some of the regulatory and patent issues related to gene expression profiles will be commented upon.


SP-0580 GWAS, SNPs and normal tissue toxicity for personalised radiation oncology
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A key challenge in radiotherapy is to maximise radiation doses to cancer while minimising damage to surrounding healthy tissues. As toxicity in a minority of patients limits the doses that can be safely given to the majority, there is interest in developing a test to measure an individual’s radiosensitivity before treatment and predict their likelihood of developing toxicity. A biomarker that predicts a cancer patient’s risk of toxicity could be used to personalise dose prescriptions or to offer alternative treatments. Many approaches have been studied to measure radiosensitivity. The development of omics technologies underpinned genome wide association studies (GWAS) attempting to identify genetic variants reported as single nucleotide polymorphisms (SNPs). The advantages of the approach include: a genetic test will be easier to implement clinically than a functional assay; a genetic test will not suffer from the poor reproducibility associated with some radiosensitivity testing methods; and SNPs are the most common type of genetic variation and so easiest to identify. Omics technologies offer promise, but to have an impact on radiotherapy practice research must identify biomarkers that replicate across cohorts. Robust replication needs big data, which is only possible with large collaborative efforts. The need for big data was addressed by establishing an international Radiogenomics Consortium. Achievements of the consortium include: pooling cohorts to increase statistical power and identify definitively whether individual SNPs are associated with risk of toxicity; producing guidelines to improve the reporting of radiogenomics studies; identifying approaches for analysing data from heterogeneous cohorts involving different toxicity reporting scales and treatment regimens; and establishing studies collecting standardised data to improve our ability to detect more SNPs. Work over the past three years showed it is possible to pool heterogeneous cohorts and has identified several SNPs associated with risk of toxicity. Large collaborative projects in the cancer predisposition field involving analysis of ~100,000 participants shows that sufficient SNPs can be identified to generate a polygenic risk profile for clinical implementation. For example, men in the top 1% of the distribution of a 74-SNP polygenic risk score have a 4.7 fold increased risk of developing prostate cancer. Key challenges for the radiation oncology community are to collect data on the cancers to identify enough SNPs to generate a polygenic risk profile and to increase understanding of the need for endpoint dependent versus independent profiles.

SP-0581 Integrative data analysis for PRO
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Personalized Radiation Oncology (PRO) integrating omics technology is a rapidly developing concept that will have an enormous impact on oncologic treatments and specifically radiation therapy in the near future. Tumor behaviour and outcomes related to oncologic treatments are related to several factors of which connections are nowadays poorly known. Different branches of medicine have developed their own lines of research which are sometimes difficult to be interpreted, difficult to be integrated with classical clinical factors and for these reasons difficult to be translated into clinical practice. In clinical prediction and decision making process, results provided by omics are rarely used, whereas clinicians usually use clinical and imaging data for understanding tumor behaviour, predicting patients’ outcomes and for choosing the “right treatment” for a specific patient. Randomized clinical trials enclose patients with characteristics chosen beforehand and usually omics informations are rarely or never included. This lead to a potential missing of several information that could refine prediction and thus promote personalized treatments and to an erroneous outcomes prediction that can lead to inappropriate treatment decisions for a specific patient. Integrative data analysis has the potential to correlate data of different origins (genetic, radiology, clinic…) with patient’s outcomes and to create a consistent dataset useful to obtain a trustful analysis for the Decision Support System. The DSS can easily be applied in clinical practice helping the Radiation Oncologist to utilize several information that otherwise would be excluded in the process of decision making. The possibility to predict the outcome for a certain patient in combination with a specific treatment with more accuracy, will lead to better identification of risk groups and thus better treatment decisions in individual patients, but it will also stimulate research focused on specific risk groups which try to find new treatment options or other combinations of treatment options for these subgroups. These treatments will be more personalized, which will not only save patients from unnecessary toxicity and inconvenience, but will also facilitate the choice of the most appropriate treatment . The resulting predictive models, based on patient features, enable a more patient specific selection from the treatment options menu and a possibility to share decisions with patients based on a more objective evaluation of risks and benefits. Finally, considering the important role that predictive models could play in the clinical practice, clinicians must be aware of the limits of these prediction models. They need to be internally validated taking into account the quality of the collected data. An external validation of models is also essential to support general applicability of the prediction model. Therefore structural collaboration between different groups is crucial to generate enough anonymized large databases from patients included or not in clinical trials.

OC-0582 Gene signatures predict loco-regional control after postoperative radiochemotherapy in HNSCC
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Gene signatures predict loco-regional control after postoperative radiochemotherapy in HNSCC