variety of organs and diseases. The intestinal organoids have been shown to be a very powerful tool for the study of Cancer, Cystic Fibrosis and Inflammatory Bowel Disease (Dekkers, Nat Med 2012; van de Wetering, Cell in press). The models represent previously unavailable in vitro models and patient specific samples for drug development, patient stratification and diagnostics. In addition, we recently showed the organoids are amendable to genetic corrections by novel and conventional biochemical techniques such as Crispr/Cas9 (Drost et al., Nature 2015; Schwank et al., Cell Stem Cell 2013). Finally, the in vitro stability of the organoid was demonstrated by the integration after transplantation of human liver cells into recipient mice. This makes the organoid a useful new platform for drug development, for precision medication for patients in the clinic, and a possible new source for cell therapy.

SP-0099
The role of ATM and p53 in normal tissue radiation response
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Following ionizing radiation exposure, double strand DNA breaks activate the ataxia telangiectasia mutated (ATM) kinase, which then phosphorylates a large number of target proteins to orchestrate the DNA damage response. One of the key proteins that is activated by ionizing radiation in an ATM-dependent manner is the tumor suppressor protein p53. Our laboratory has utilized the Cre-loxP system to delete ATM, dependent manner is the tumor suppressor protein p53. Our studies define cell type specific roles for ATM and p53 in different normal tissues in mice. We have also employed reversible in vivo shRNA to temporarily inhibit p53 during radiation exposure. We find that the roles of ATM and p53 in normal tissue radiation response are cell type specific. In bone marrow exposed to radiation, p53 acts to control ATM during radiation exposure. We find that the roles of ATM and p53 in normal tissue radiation response are cell type specific. In bone marrow exposed to radiation, p53 acts to control ATM during radiation exposure.

SP-0100
Radiation sensitivity of human skin stem cells: dissecting epigenetic effects of radiation
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Due to its anatomical localization and high turnover, epidermis is a major target for carcinogens, and skin carcinoma is one of the most frequent human cancers. Ionizing radiation (IR) can induce carcinoma in skin, but the respective roles of keratinocyte stem cells and their progeny in the carcinogenic process is unclear. We characterized cell intrinsic radiosensitivity of keratinocyte stem cells (KSC) to gamma rays. Primary KSC were found radioresistant to high radiation doses (Rachidi, 2007), as well as to low doses. They repair rapidly all types of DNA damage (Harfouche, 2010), both after ionizing radiation and UVB exposure (Marie, submitted), without going to apoptosis. Activated repair was notably due to increased levels of DNA repair proteins and activation of nuclear FGF2 signaling. To evaluate the potential impact of irradiation on the epigenetic status of keratinocyte precursor cells, the Illumina 450K array was used, which measures the methylation level of 480,000 methylation sites (or CpG islands). More than 36 million of GpCs have been identified in the human genome, most of them located directly in gene sequences or in gene promoters. In the present study, analysis of the lists of the modified genes obtained by normalized graph-cut DNA methylation changes over 3 weeks in culture, with 18 genes exhibiting the most discriminant methylation changes at 16 and 23 days after exposure. Six genes were members of the super-family of protocadherins of the alpha type, pointing to alterations of cell-cell interactions. 2) a specific signature of long-term alterations after 10 mGy: 15 specific genes had methylation changes that were discriminant after 16 and 23 days. From their functions, it appears that the major cell responses after 10 mGy were localized at the cell membrane, for processes involved in calcium-related cell adhesion, signaling, energy status and carcinoma development. As a major function of methylation changes is to inhibit transcription, these signatures have been validated by characterizing the expression of the genes found in the signatures. In summary, high and low-dose exposures of immature keratinocytes from human epidermis result in epigenetic changes, part of them being specific to the dose. Methylation changes appear to regulate notably cell functions related to cell-cell interactions, cell adhesion and energy status.

SP-0101
A radiation systems biology view of radiation sensitivity of normal and tumour cells
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Background: One of the main aims of radiotherapy alone or combined with chemo-, immuno- or biologically targeted therapy is the maximisation of tumour tissue eradication whilst preserving the surrounding normal tissue. This requires a deep understanding of the molecular mechanisms of radiation sensitivity in order to identify its key players and potential therapeutic targets. Currently, a paradigm shift is taking place from pure frequentistic association analysis to the rather holistic systems biology approach that seeks to mathematically model the system to be investigated and to allow the prediction of an altered phenotype as the function of one single or a signature of biomarkers.

Methods: In the current study cell culture models of radiation-resistant tumour cells and normal radiation-sensitive cells were investigated by multi-level (genome, transcriptome, miRNA) omics profiling over time and the resulting multi-layer radiation interactome was reconstructed. Validation of key network elements in biopsy-derived multi-omics data from radiotherapy treated HNSCC patients was performed and tested for association with clinical outcome.

Results: Molecular frameworks including signalling pathways, gene sets and immune system wit have been identified and are therefore likely to drive radiation response in tumour and normal cells. Moreover, the identified networks could be used to identify molecular key players and potential targets for the simultaneous modulation
of radiation sensitivity. A subset of these candidate molecules could be validated having an impact in clinical outcome of radiation therapy treated HNSCC patients.

Conclusion: Our study demonstrates that multi-level radiation systems biology allows gaining deeper insights into chief mechanisms of radiation sensitivity, thereby paving the way for targeted individualised therapy approaches in radiation oncology.

Debate: This house believes that progress in the treatment of locally advanced NSCLC will come from:

SP-0102 Radiation treatment intensification
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A large proportion of non-small cell lung cancer (NSCLC) patients are diagnosed with locally advanced (stage III) disease. For this patient group the treatment of choice is definitive concurrent chemoradiation (CCRT). CCRT results in an improved overall survival (OS) compared to sequential chemoradiotherapy or radiotherapy alone because of improved locoregional control. However 2-year OS rates of 30-35% are still poor because many patients develop locoregional failures (about 30%) and distant metastases (about 40%)1. Currently locally advanced NSCLC patients selected for CCRT have FDG-PET scanning and imaging of the brain (MRI or CT scan). Despite this brain imaging with the present chemotherapy regimens used we are faced with the problem of brain metastases in about 10% of the patients within 1 year after chemoradiation.

In several chemoradiation studies it was reported that the Gross Tumor Volume is correlated with OS. This is rational since the tumor volume reflects the number of clonogenic tumor cells that needs to be eradicated. To improve locoregional control the dose prescription could be escalated taking into account the individual Gross Tumor Volumes and tolerances using image guided adaptive Intensity Modulated Radiotherapy (IMRT). However there are radiation oncologists who challenge the usefulness of RT dose escalation and intensification in patients with stage III NSCLC. The outcome of a randomized phase III trial, RTOG 06171, revealed that NSCLC patients within the 74 Gy arm given in 7.5 weeks had worse local control and significantly worse overall survival as compared to the patients treated to 60 Gy arm in 6 weeks2. Patients in all study arms received two additional cycles of consolidation chemotherapy ± cetuximab. So the obvious question is: How do we continue? Dose escalation with prolonged overall treatment time in NSCLC local control has previously been proven disappointing because of accelerated repopulation3. In an individual patient data meta-analysis in patients with non-metastatic lung cancer, which included trials comparing modified radiotherapy with conventional radiotherapy, a significant OS benefit from accelerated or hyperfractionated radiotherapy was reported4. Another issue is the use of consolidation chemotherapy after concurrent chemoradiation. In the RTOG 0617 trial the increase in mortality started < 3 months after randomization during the period of consolidation paclitaxel-carboplatin chemotherapy. Generally taxanes given after RT increases toxicity and the combination of high dose to the heart and consolidation taxane-based chemotherapy might have caused toxic deaths and biased the outcome. RT dose intensification while using modern image guided adaptive IMRT and accelerated schemes is an important area of ongoing clinical research and should not be discontinued.

In Stereotactic Ablative Body Radiotherapy (SABR) much higher biologically equivalent doses are delivered compared to conventionally fractionated RT (typically EQD2 of 70-85 Gy), and has generated outstanding tumor control in early stage NSCLC. For SABR a significant dose-response relationship was observed for prescription EQD2 of 105 Gy or more (2-year LC 96%) or of less than 105 Gy (2-year LC 85%)5. Tumor size and overall treatment time were also important factors influencing outcome.

The tumor control probability of SBRT (small tumor volume) and conventionally fractionated chemoradiation (large tumor volume) were successfully described in a single model6 suggesting that a dose-response relation in NSCLC does exist. Recently there is a growing interest in genetic profiles that predict a patient’s response to radiotherapy, because severe toxicity in a minority of patients limits the doses that can be safely given to the majority. Recent progress in genotyping raises the possibility of genome-wide studies. If we know the normal tissue reactions to radiotherapy by genotype we will really be able to tailor the individual radiation dose.

In conclusion: Besides the unsolved problem of the occurrence of distant metastases there is room for improvement of locoregional control in locally advanced NSCLC patients treated with chemoradiation. In the era of personalized treatment, radiotherapy dose intensification using image guided adaptive IMRT could be directed towards individual tumors and tolerances. RT dose intensification while using accelerated schemes is an important area of ongoing clinical research.


SP-0103 Better systemic therapy
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About one third of patients with non-small cell lung cancer (NSCLC) present with locoregional disease extension in either the mediastinum (T4) or the mediastinal lymph nodes (N2/3). Apart from a fraction in which resection after induction therapy is sometimes considered, selected patients with stage 3 are considered for definitive chemoradiotherapy, administered either sequentially or concomitantly. Despite staging with PET-CT scan and endosonographic mapping of mediastinal lymph nodes and notwithstanding a patient selection for this radical treatment, the outcome in stage 3 is nevertheless moderate with a median survival of 2 years [1]. Progression occurs after a median of 10 months and is due to local relapse or distant metastasis in 30 and 45% of cases, respectively. Any advance in the outcome in stage 3 NSCLC will hence depend on improvements in systemic therapy directed at distant metastasis. The past 10 years have seen important changes in the paradigm of treatment in selected patients with advanced NSCLC, in whom platinum-based doublet chemotherapy used to be the standard of care. The discovery of drugable genomic alterations has introduced precision medicine in oncology. Patients whose NSCLC harbour either an activating EGFR mutation, EML-ALK translocation or ROS1 amplification are now routinely treated with oral small molecule kinase inhibitors of the 1st, 2nd and 3rd generation instead of chemotherapy, with a significant improvement in outcome and a substantial impact on quality of life. Similar, although less pronounced effects have been observed when adding monoclonal antibodies directed at targets associated with angiogenesis or cell growth to the chemotherapy backbone. Unfortunately, the incorporation of these