It is well known that MR data contains detailed information with high tissue contrast and that PET imaging gives molecular/biochemical information with high molecular sensitivity but what is the added value? A major goal with treatment planning is to delineate the tumor volume, which can be done with both MR and PET, but since the both modalities show different characteristics of the tumor the volume might differ between them. Challenges from the imaging point of view will be discussed. The availability to PET/CT is much higher and the challenges with this method are fewer. Some comparison of the two hybrid modalities will be done. The majority of PET studies are done with the tracer fluorodeoxyglucose, FDG, but beyond FDG a large number of tracers are available, all giving information about different biochemical properties of the tumor. A few of these tracers will be presented and discussed.

SP-0127
MR-PET for radiation oncology: the sub-volume opportunities
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Purpose: To investigate the value of combined PET/MR imaging for biologically individualized radiotherapy (RT) planning.

Methods: Hybrid PET/MR imaging offers the possibility to combine molecular information from PET with high resolution anatomical MR imaging. Consequently, a combination of the two different imaging data sets seems promising for improved automatic target volume delineation (TVD). An automatic co-segmentation algorithm has been developed in our institution which derives probabilities of tumor presence by combining PET and MR data. Finally, the PET/MR-based probability maps are segmented to generate RT target volumes. Automatically segmented target volumes were compared to manual delineations from three experienced radiation oncologists. Furthermore, combined PET/MR imaging allows to assess PET and functional MR data at the same time. In the context of a clinical study, diffusion weighted (DW) as well as dynamic contrast enhanced (DCE) MRI were acquired in addition to anatomical images as well as FMISO and FDG PET images. Pairwise correlations of the different functional parameters were calculated in order to analyze for redundancy or complementarity respectively.

Results: Automatic co-segmentation of tumor volumes based on combined FDG PET/MR imaging in head and neck cancer revealed robust and reproducible contours. The comparison of automatic and manual target volumes showed good agreement in terms of volume overlap. Deviation of the automatic compared to the manual contours was in the same order of magnitude as inter-observer variation. Compared to PET-based TVD, additional information from high resolution MR data improves automatic segmentation. A pairwise correlation analysis of parameters derived from FMISO PET, FDG PET, DW- and DCE-MRI on a voxel-level did only show moderate to low correlation coefficients hinting at a complementarity of the different investigated imaging methods. However, large inter-patient variations in terms of pairwise parameter correlations were observed.

Conclusion: Functional and molecular imaging with combined PET/MR has the potential to improve TVD. At the same time, PET/MR allows to assess different levels of biological information which may in the future be important to derive individualized measures of radiation sensitivity. As a consequence, PET/MR imaging opens new doors for personalized RT planning and delivery in the near future.

SP-0128
MR-PET for radiation oncology: the implementation issues
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OC-0129
Nitroglycerin decreases the hypoxic fraction of non-small cell lung cancer lesions
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Purpose or Objective: Nitroglycerin is a nitric oxide donor being investigated because of its potential to increase tumour oxygenation. In phase II trial NCT01213078 nitroglycerin is added to radical radiotherapy in patients with NSCLC stage IB-IV. Using a dedicated hypoxia PET tracer ([18F]HX4; ref: Dubois et al, Proc Natl Acad Sci USA.2011) we investigate the effect of nitroglycerin on tumour hypoxia. Here, we report the results of the first 14 patients that completed the hypoxia scanning program.

Material and Methods: A baseline [18F]HX4 PET scan (4h p.i.) was performed to measure hypoxia in the primary tumour and nodes. At least 48 hours later, a second [18F]HX4 PET scan was taken after application of a nitroglycerin patch (Transiderm nitro 5 mg). Between the two scans, patients did not receive any treatment. The primary tumour and involved nodes were defined on the planning FDG-PET/CT scan and fused with the HX-4 scan for analysis. The tumour-to-blood ratio (TBR) of [18F]HX4 and the Hypoxic Fraction (HF; the fraction of the volume with a TBR >1.4) were calculated for all lesions. The Wilcoxon signed rank test was used to evaluate differences between scan time points.

Results: In 14 patients, the median interval between the scans was 4.5 +/-2.1 days (range: 2-7days). Seven patients (50%) exhibited hypoxia (HX-4 TBR>1.4) in the primary tumour and 4 of 10 patients (40%) had nodal disease with an HX4 TBR>1.4 in the lymph nodes. In total 9/14 patients (64%) showed hypoxia at baseline in the primary tumour and/or the lymph nodes. The effect of nitroglycerin on HX-4 uptake in hypoxic lesions was as follows: in 8/11 volumes (72%) and in 6/9 patients (66%) nitroglycerin administration resulted in a decrease of the TBR of HX-4. Also, the median HF decreased from 12.9% to 1.2% (p=0.029), corresponding to a decrease in the median hypoxic volume of 5.4 cc to 0.5 cc (p=0.033). In the 7 non-hypoxic tumours and 6 non-hypoxic nodal volumes present at baseline, nitroglycerin caused a decrease of the TBR of HX-4 in 5, an increase in 5 and no effect in 3 lesions. None of the non-hypoxic lesions became hypoxic (TBR >1.4) after administration of nitroglycerin.
Conclusion: Nitroglycerin causes a significant decrease in the hypoxic fraction and hypoxic volume of a majority of hypoxic non-small cell lung cancer tumours and metastatic lymph nodes. This promising result encourages further investigation of nitroglycerin as a sensitizing agent in a selected population. CT-based perfusion studies and lab experiments (data not shown) suggest this effect is mediated by an inhibition of mitochondrial respiration rather than a vascular effect.

OC-0130
Biomarker-based hypoxia-adapted radiochemotherapy: preclinical study in HPV+/- H&N cancer xenografts
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Purpose or Objective: Previous in vivo experiments demonstrated that hypoxia and perfusion determined during fractionated RT are associated with local tumour control (LC) in human head and neck squamous cell carcinoma (hHNSCC). In a randomized clinical trial Nimorazole improved LC and survival of patients with HNSCC treated with RT. Biomarker studies using tumour material from this trial indicate that hypoxic tumours predominantly benefit from nimorazole, supporting a predictive value for hypoxia assessment. However, this has not been prospectively evaluated for radiochemotherapy (RCTx) which represents the current standard of care in locally advanced head and neck cancer.

The hypothesis of the ongoing study is that the microenvironmental parameters are also predictive for response to hypoxic cell sensitizing with nimorazole in combination with RCTx.

Material and Methods: We studied 8 different human HPV-negative and -positive HNSCC in a nude mice xenograft model. Irradiation was performed with 30 fractions (fx) in six weeks combined with weekly cisplatin (3 mg/kg i.p.). Nimorazole (0.3 mg/g i.p.) was applied before each irradiation and was started with the first fx or after 10 fx. Effect of nimorazole was quantified as LC 120/180 days after irradiation. For histological evaluation tumour sections were excised unirradiated or after 10 fx with and without nimorazole. Using quantitative image analysis, microenvironmental parameter such pimonidazole hypoxic volume (pHV), relative vascular area (RVA) and perfused fraction of vessels (PF) were determined.

Results: The data of the cell lines show pronounced heterogeneity in the effect of nimorazole on local tumour control (LC) in human head and neck squamous cell carcinoma (hHNSCC). In a randomized clinical trial Nimorazole improved LC and survival of patients with HNSCC treated with RT. Biomarker studies using tumour material from this trial indicate that hypoxic tumours predominantly benefit from nimorazole, supporting a predictive value for hypoxia assessment. However, this has not been prospectively evaluated for radiochemotherapy (RCTx) which represents the current standard of care in locally advanced head and neck cancer.

The hypothesis of the ongoing study is that the microenvironmental parameters are also predictive for response to hypoxic cell sensitizing with nimorazole in combination with RCTx.

Conclusion: Apparently, the decrease of pHV after the first fractions of RCTx has potential as a predictive biomarker for LC for combination of RCTx with nimorazole and should therefore be further evaluated in experimental FMISO analysis and also in clinical trials using hypoxic cell radiosensitisation during RCTx.

OC-0131
miR-875-5p enhances radiation response of prostate cancer cells via EGFR suppression
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Purpose or Objective: There is increasing interest in defining a functional association between miRNAs, endogenous small non-coding RNA molecules that negatively regulate gene expression, and tumor radiation response, with the aim of rationally designing miRNA-based strategies to increase patient radiosensitivity. In this study, we investigated for the first time the ability of miR-875-5p, a miRNA the role of which in human cancer has not been so far investigated, to enhance the radiation response of prostate cancer (PCA) cells.

Material and Methods: The search for miR-875-5p targets relevant to radiation response was carried out by prediction algorithms and confirmed by the luciferase assay. miR-875-5p reconstitution by miRNA mimics in PCA cell lines (DU145 and PC-3) was used to elucidate its biological role. Radiation response in miRNA-reconstituted and control cells was assessed by clonogenic assay, immunofluorescence-based detection of nuclear γ-H2AX foci and single-cell electrophoresis comet assay.

Results: EGFR was predicted by 6 different algorithms and confirmed by luciferase assay as a direct target of miR-875-5p. Given the role of EGFR in determining tumor cell resistance to ionizing radiation by promoting epithelial-to-mesenchymal transition (EMT) and enhancing DNA-dependent protein kinase activity and DNA damage repair, we assessed whether miR-875-5p reconstitution in PCA cells was able to counteract EGFR-mediated radio-resistance. Indeed, miRNA ectopic expression significantly increased the sensitivity of both DU145 and PC-3 cell lines to radiation, as indicated by changes in cell morphology, marked cytoskeleton architecture rearrangements, reduced migration ability and increased mRNA and protein levels of E-cadherin and B-catenin, the two most important molecular players in the EMT process.

Conclusion: Overall, results from this study support the clinical interest in developing a novel therapeutic approach for PCA based on miR-875-5p reconstitution to increase response to radiotherapy.

OC-0132
FoxO proteins and non-functional p53 determine stemness and radiosensitivity of GBM-stem cells
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Purpose or Objective: Dual inhibitors of PI3K and mTOR do not efficiently radiosensitize glioblastoma multiforme stem cells (GBM-SCs). However, p53-proficient GBM-SCs are more...