Hypoxia PET imaging for delineation and response assessment during radiotherapy

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Purpose: To review the current status of hypoxia PET imaging for delineating hypoxic volumes (HVs) inside the gross target volume (GTV) and for radiotherapy (RT) outcome prediction.

Methods: Hypoxia PET tracers currently used in clinical trials are mainly $^{18}$F-FMISO, $^{18}$F-FAZA and $^{18}$F-HX4. Different imaging protocols and methods for delineating HVs will be presented in this talk. Furthermore, results of recent clinical trials will be reviewed where the prognostic value of hypoxia PET imaging before and during RT with respect to outcome as investigated.

In our institution, a clinical phase II trial is currently carried out where to date n=33 head and neck cancer patients were included. Patients were examined using dynamic FMISO PET imaging plus conventional FDG PET imaging in addition to planning CT and eventually MRI before the start of RT. HVs were segmented based on parameters derived from the pharmacokinetic analysis of the dynamic FMISO PET data. Patients were randomized into two treatment arms. Patients in the experimental arm were treated with a 10% dose escalation to the HV whereas patients in the control arm received standard IMRT treatment with 70 Gy in 35 fractions.

Results: Different manual and (semi-)automatic methods for HV delineation based on hypoxia PET data have been used in clinical studies, such as thresholding, tumour-to-background ratio (TBR) based methods, advanced automatic methods or delineations based on dynamic PET imaging. Different contouring techniques for HV definition may result in strongly varying volumes. Recently published clinical trials confirm the prognostic character of hypoxia PET imaging. However, no consensus was found yet with regard to the timing of the hypoxia PET examination. Some studies found that pre-treatment hypoxia PET information was correlated to outcome whereas others stated that hypoxia PET data acquired two weeks into RT had prognostic value. For our hypoxia dose painting trial, a planned interim analysis was carried out after recruiting n=20 patients. Median follow-up time for this group was 36 (11 - 52) months. 5 patients did not show any hypoxia (HV = 0 mL). The mean HV of the hypoxic tumours was 8.6 mL (0.3 - 49.2 mL).

Furthermore, data acquired in this study could confirm a prognostic value of hypoxia PET imaging before and during RT with respect to outcome as investigated.

Conclusion: Hypoxia PET imaging is a very promising tool for the stratification of patients into different risk groups and thus a potentially very interesting molecular marker in the advent of biologically adapted, personalized RT. However, a comparison of results from different clinical trials is difficult due to large discrepancies in terms of imaging protocols and data analysis strategies.

Predictive value of MR spectroscopic imaging for relapse site in GBM and integration in a dose-painting trial

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Pre-RT MR spectroscopic imaging (MRSI) has been described as a promising non invasive tool to depict GBM behaviour and extension. We confirmed this based on data from an in-house prospective clinical trial for GBM, analysing both pre and relapse MRSI and published the predictive value of Cho/NAA>2 (CNR2) regions for the site of relapse. We then elaborated a dose-painting clinical trial aiming to increase dose to CNR2 regions on biopsied or resected glioblastoma. First, as MR spectroscopy metabolic maps are not delivered in a DICOM format, we developed an automated image processing tool for MR spectroscopy data integration onto planning CT.

Then we performed a dosimetric study for each patient, comparing doses to organs at risk with three different treatments: 1) with conventional 3D RT at 60 Gy / 2 Gy fractions targeted to contrast enhancement, CE+2cm) same treatment with an addition SIB IMRT, Simultaneous Integrated Boost with Intensity Modulated RadioTherapy (i.e. 2.4 Gy by fraction on the boost), the boost being the MR spectroscopy abnormalities (Cho/NAA ratio>2 + 1cm) 3) SIB IMRT targeted to MR Spectroscopy abnormalities + contrast enhancement + 3mm. Then the V10 Gy and V40 Gy to normal brain and V54 to brainstem were compared. The dosimetric comparison showed that the doses to organs at risk were lower with increased dose SIB IMRT 72 Gy than with standard 60 Gy conventional RT and equivalent to 60 Gy IMRT. The size of the SIB could be increased to spectral abnormalities + contrast enhancement without increasing dose to organs at risk.

Finally, we started in 2011 a prospective phase III randomized clinical trial SPECTRO GLIO, financed by the French national Cancer Institute (INCa). The goal is the inclusion of 220 patients treated in 9 french centers. Standard treatment delivers 60 Gy/ Temozolomide, targeted to CE+2cm; patients included in the experimental arm receive an additional 72Gy SIB targeted to MRSI abnormalities +1cm and to Contrast Enhancement. The endpoint is survival. This ongoing trial includes a centralized MR spectroscopy post-treatment and CHO/NAA>2 maps integration to planning CT. Target volumes and Organs at risk delineation are also centralized at our institution for all participating centers. An external online quality control of the dosimetry is performed for each patient included in the experimental arm.

Patients undergo MRI and MRSI before and every two months after RT, as well as MR perfusion and diffusion. We recently published a preliminary study of Lactate on MRSI, as lactate is a surrogate of tumor hypoxia and radioresistance. We defined a lactate/NAA<0.4 threshold, having a predictive value for the site of relapse. This data will have to be confirmed on the larger set of data from the Spectro GLio trial as well as MR diffusion and perfusion that are performed longitudinally in this trial.

Conclusion: In our talk we will describe the different steps of a dose-painting clinical trial based on metabolic imaging with MRSI in GBM:

- study of the predictive value for the site of relapse of GBM
- developing a quantification and integration method of the metabolic maps into planning CT
Introduction: In literature the term “dose reconstruction” has been used for several concepts. In radioprotection it is defined as the accumulation of radiation doses received by workers or patients (radiology e.g.). In this presentation the focus is on radiotherapy applications and more concretely on the measure of the actually delivered dose, received by the patient during a dynamic treatment. As treatments are becoming more and more complex, using flattening filter free beams, high dose rates, dose escalation, hypofractionation, and gating or tracking strategies, while irradiating moving geometries, one can expect that the actually delivered dose will deviate from the planned one. Delivery QAs in a homogeneous phantom using in plane gamma analysis do not seem adequate.

Overview delivery QA methods: Setup-uncertainties/robustness: Can be evaluated by convolving the PDF of the tumor position with the dose. Convolving this PDF with the 2-D fluence of each individual beam corrects for the shift invariance assumption. An alternative method is modifying the isocenter position of each individual beam in the RTPlan file for dose reconstruction.

Static delivery QA of a single fraction: In EPID dosimetry the exit fluence measured by the portal imaging device is reconstructed to dose in the patient. On a Tomotherapy machine, the MVCT data obtained during the treatment can be used for this purpose. The method of Feygelman et al uses a phantom measurement-based perturbation map to include the impact of dynamic delivery in the TPS dose. This method can also be used to estimate the impact of patient motion.

Machine log files can be used and dose calculation can be performed on cone beam CT or MVCT.

4D Intra-fraction dose accumulation: The dose corresponding to the original RTPlan is calculated on the different CT phases of the 4D CT. Deformable registration between the phases allows warping the dose to the reference scan for dose accumulation. This does not consider the interplay effect. A more precise approach is to use the machine log files allowing synchronization of the individual CPs with the breathing phase. Phase specific RTPlan files are generated to calculate the phase specific dose. An alternative is the uniform time sampling technique introduced by Litzenberg et al. using a dedicated MC dose calculation engine. Even more precise would be to calculate dose on a 4D cone beam CT.

Inter-fraction dose accumulation: For each individual fraction the log files are used to calculate the delivered dose on the cone beam CT or MVCT images. All fraction scans are deformed to the planning CT for dose warping. The use of congruent energy/mass warping is preferable for this application as the geometry change can be more important.

There remain unanswered questions though: what is the impact of voxels being lost (weight loss, tumor shrinkage, OAR shrinkage, ...). The quantity “dose” might not be optimal for accumulation in shrinking organs.

Conclusion: The dose reconstruction methods are rapidly evolving. Different levels of approximation and accuracy are possible. A further evolution in in-room imaging such as 4D cone beam CT might increase precision and provide the actually delivered dose. This will even be more relevant in proton therapy. The knowledge of the delivered dose might lead to a better understanding of biological effects related to the treatment and to more robust planning strategies. The accumulation of inter-fraction dose remains a challenge where the physical concept of dose probably needs to be replaced by organ specific parameters that can be accumulated, such as the absolute volume of a parallel organ (e.g. the parotids) that receives a dose below a certain threshold.