Advanced Imaging in Glioma Treatment

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Summary

This thesis set out to answer the following question: “Which MRI sequence, PET tracer, or combination of MRI sequence(s) and/or PET tracer(s) is the most accurate for the detection of diffuse glioma infiltration?”.

Chapter 1 provides a general introduction, as well as the aim and outline of this thesis. After a description of the biological and clinical background of diffuse gliomas, we address the difficulty of the detection of diffuse glioma infiltration and the available imaging techniques for the detection of this infiltration. The aims of this thesis are: to discuss the current literature concerning imaging for the detection of diffuse glioma infiltration; to develop quantitative [^{18}F]FET PET parametric maps; to compare the accuracy of different MRI sequences, PET tracers and combinations of MRI sequence(s) and/or PET tracer(s) for the detection of diffuse glioma infiltration; and to quantify such infiltration using histological, molecular and imaging techniques.

In **chapter 2** we systematically review the current literature on the diagnostic accuracy of imaging techniques for the detection of diffuse glioma infiltration. This meta-analysis on 61 studies, describing 3,532 samples in 1,309 patients, has several findings. First, the reporting quality of the studies is suboptimal. Second, the diagnostic accuracy for the detection of diffuse glioma infiltration of standard MRI used in daily practice is better for low-grade than high-grade glioma. Third, the diagnostic accuracy for the detection of diffuse glioma infiltration of standard MRI in high-grade gliomas is lower than MR spectroscopy and PET. Finally, samples without tumor presence from regions without imaging abnormalities (true negative samples) are underrepresented. Based on these findings, we conclude that a prospective study with direct comparison of imaging techniques including true negative samples is needed.

In **chapter 3** we discuss the literature on current available imaging techniques for the guidance of diffuse glioma resection and the localization of brain functions and white matter tracts. We conclude that, although multiple imaging techniques are available, studies directly comparing the guidance of diffuse glioma resection by different imaging techniques are sparse. The results of these few studies suggest that the use of other imaging techniques than the current standard MRI could result in improved survival for patients. Another conclusion

of this review is that direct cortical stimulation remains the gold standard for the localization of important brain functions and white-matter tracts. Imaging techniques, however, are indispensable for surgical planning, including the choice of awake versus non-awake surgery.

Chapter 4 comprises a study of the accuracy of an in-house developed stereotactic drilling technique for diagnostic biopsies and stereo-electroencephalography depth electrode implantation. We included seven patients with 89 depth electrodes implanted and compared the pre-operative neuronavigation planning with the actual position on post-operative CT. The difference between planning and actual position was 3.5mm. Therefore, we conclude that our stereotactic drilling technique is suitable for diagnostic biopsies.

Chapter 5 describes the study protocol for a monocenter prospective diagnostic accuracy study for the detection of diffuse glioma infiltration. Inclusion encompasses adult patients with a newly diagnosed, diffuse infiltrative glioma undergoing resective glioma surgery. Advanced neuroimaging is added to the standard preoperative MRI, and both are used to plan serial neuronavigated biopsies in and around the glioma boundaries. Biopsies are obtained immediately preceding resective surgery and provide histopathological and molecular characteristics of the regions of interest, enabling comparison with quantitative measurements in the imaging modalities at the same biopsy sites.

Chapter 6 examines different tracer kinetic models for the quantification of [^{18}F]FET kinetics in seven patients. The purpose of this study is to identify the optimal model using full plasma input data, as well as to identify the optimal simplified model that does not require arterial or venous blood sampling. The reversible two-tissue compartment model was the optimal tracer kinetic model and showed a strong correlation with the 60-90 min tumor-to-blood ratio, which was therefore identified as the optimal simplified model. There was also a significant, although moderate, correlation between [^{18}F]FET kinetics and cerebral blood flow, determined by [^{15}O]H_2O PET. We conclude that the optimal simplified method is accurate enough to replace the full plasma input method.

Chapter 7 compares multiple parametric maps of [^{18}F]FET kinetics as well as tumor-to-brain ratio maps from different [^{18}F]FET PET time intervals in seven patients. In order to assess the accuracy of the parametric maps, the mean value of the tumor volume was determined with the optimal model from chapter 6 and compared with the mean value of the tumor volume of

the different parametric maps. The quality of each image was assessed as the level of noise, with lower levels of noise representing higher image quality. The parametric maps based on the basis function method provided the best accuracy, while the parametric map based on the Logan method displayed the lowest level of noise. Tumor-to-normal ratio maps provided better accuracy and lower noise if later interval times were used.

Chapter 8 consists of a study directly comparing [^{18}F]FET and [^{11}C]choline PET for the detection of diffuse glioma infiltration in 74 samples from eight patients. The diagnostic accuracy of both the standardized uptake value (SUV) and the tumor-to-brain ratio (TBR) maps of [^{11}C]choline and different time intervals of [^{18}F]FET were assessed. For [^{18}F]FET, the diagnostic accuracy of the TBR was higher than that of the SUV for intervals 40–60 min and 60–90 min. For [^{11}C]choline, there was no difference in diagnostic accuracy between the SUV and the TBR, however, there was a significant difference between tumor and normal samples SUV, but not TBR. The diagnostic accuracy of [^{18}F]FET TBR 60-90 min was higher than that of [^{11}C]choline SUV 20-40 min. We conclude that [^{18}F]FET PET is more accurate than [^{11}C]choline PET for detecting diffuse glioma infiltration.

Chapter 9 presents the results of the direct comparison of diagnostic accuracy of multiple MRI sequences, PET tracers and combinations of MRI sequence(s) and/or PET tracer(s) for the detection of diffuse glioma infiltration in 174 samples from 20 patients. In enhancing gliomas, the combination of ADC with [^{18}F]FET PET detected diffuse glioma infiltration better than T1G MRI and better than [^{18}F]FET PET. In non-enhancing gliomas, no imaging combination detected diffuse glioma infiltration significantly better than standard MRI. FLAIR-weighted MRI was more accurate than [^{18}F]FET PET in non-enhancing glioma. We constructed a probability map of tumor presence based on the combination of ADC with [^{18}F]FET PET, with each voxel representing the probability of tumor presence, ranging from 0 to 100%. We conclude that combining ADC and [^{18}F]FET PET detects diffuse glioma infiltration better than standard MRI and [^{18}F]FET PET in enhancing gliomas, potentially enabling better local therapy.

Chapter 10 quantifies diffuse glioma infiltration using different techniques and assesses intratumoral epigenetic heterogeneity in 133 samples of 16 patients. Diffuse glioma infiltration was quantified as tumor purity using (epi)genetic, histological and radiological metrics. An epigenetic tumor purity metric (PAMES) correlated best with all other metrics.

Also, tumor purity demonstrated high intrapatient spatial variation. Intratumoral epigenetic heterogeneity was analyzed at molecular epigenetic classification level and compared with intratumoral variation in tumor purity. We conclude that apparent spatial heterogeneity in molecular epigenetic classification can generally be explained by variation in tumor purity and generally does not reflect biological variation. Genome-wide intratumoral epigenetic heterogeneity was also analyzed and confirmed the findings at molecular epigenetic classification level.

Finally, in **Chapter 11**, we present the general discussion of this thesis including: the current standard radiological imaging for the detection of diffuse glioma infiltration; imaging combinations for the detection of diffuse glioma infiltration; and quantification of diffuse glioma infiltration. Furthermore, we discuss the future perspectives of a new standard imaging protocol for diffuse glioma and local treatment beyond current standard MRI abnormalities. Finally, suggestions are made for future research.