Editorial Neuro-Oncology

Combined FET PET/ADC mapping: improved imaging of glioma infiltration?

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Conventional MRI is the method of choice for the diagnosis of cerebral gliomas owing to its ability to detect structural changes with high spatial resolution and outstanding sensitivity. In malignant gliomas, the determination of tumor extent is primarily based on the assessment of blood-brain barrier (BBB) disruption as reflected by contrast enhancement after application of paramagnetic contrast media. In gliomas of the WHO grades II or III, which are frequently non-enhancing, estimation of tumor extent relies on signal abnormalities in T2-weighted MRI or in the fluid-attenuated inversion recovery (FLAIR) sequence. It is well known, however, that neither contrast enhancement nor FLAIR abnormalities are specific for neoplastic tissue. Many studies have demonstrated that a considerable amount of the tumor mass may extend beyond areas of contrast enhancement, and that FLAIR abnormalities may exceed the tumor extension.[1] Regarding this clinically important topic, PET using radiolabeled amino acids has attracted attention because tracer uptake is independent of BBB disruption and allows therefore the identification of glioma tissue without contrast enhancement in MRI. A number of biopsy-controlled studies have confirmed the potential of amino acid PET to detect the extent of glioma infiltration [2,3], and the method is currently considered as very helpful to improve tumor delineation of gliomas. Moreover, the Response Assessment in Neuro-Oncology working group (RANO) has recommended the additional use of amino acid PET imaging among other applications to better assess tumor spread.[4] Amino acid PET, however, is only available in a limited number of neuro-oncological centers, and alternative advanced MRI methods such as perfusion- or diffusion-weighted imaging or MR spectroscopy are under continuous clinical evaluation to explore their potential for improved detection of tumor extent. Ultimately, all currently established imaging techniques have limitations and the solution to the diagnostic problems as mentioned above is likely to be best achieved by a combination of different techniques[5], i.e., in a multimodal setting.

In this edition of Neuro-Oncology, Verburg and colleagues present the results of a prospective study which analyzes the accuracy of amino acid PET using O-(2-[^{18}F]fluoroethyl)-L-tyrosine (FET) and multiparametric MRI to detect the extent of gliomas in relation to regional tissue samples.[6] For this purpose, the authors collected 174 biopsies in a series of 20 patients with newly diagnosed gliomas. Besides FET PET and conventional MRI, all patients underwent perfusion-weighted imaging to generate maps of relative cerebral blood volume and blood flow, MR spectroscopic imaging to produce maps of the choline/N-acetyl-aspartate ratio as well as diffusion tensor imaging (DTI) providing maps of fractional anisotropy and the apparent diffusion coefficient (ADC).

The study by Verburg and colleagues is unique in terms of the scope of the functional imaging parameters included. Most previous studies in glioma patients compared amino acid PET with selected MRI parameters only or are lacking from neuropathological validation.

The main result of the study is that the infiltration zone of enhancing gliomas is best reflected by a combination of FET PET and ADC mapping. This is a novel finding, which will further stimulate research on the optimal method to image the extent of these tumors. In particular, the role of ADC mapping is surprising since previous studies showed only a moderate correlation between signal abnormalities and cell density [7], and no relationship between ADC mapping and tumor extent [8] or amino acid PET. [9] Obviously, ADC mapping may play a more relevant role in combination with other imaging parameters.

Nevertheless, the poor result of FET PET in delineating glioma extent in this study is quite astonishing and raises doubt on the results of previous studies. It has to be considered, however, that the group of WHO grade II gliomas is over-represented. While this group of gliomas usually accounts for about 15% of all gliomas, in this study, 40% of the tumors were classified as WHO grade II and 38% of these are negative in amino acid PET which leads to a disproportionately high number of false-negative FET PET findings. The authors addressed this problem by subgroup analyses which confirmed the main findings, but the numbers in the corresponding subgroups are small and have to be considered with caution.

Also unexpected is the low significance of MR spectroscopic imaging, which is favored as an important method for the specific visualization of gliomas. In the study by Verburg et al. spectroscopic data were missing in 36 samples of 14 patients because of limited coverage of the tumor area which reflects an inherent problem of this method in clinical practice. Nevertheless, the potential of this method may not be correctly reflected in the study.

A limitation for the transferability of the findings of Verburg et al. into clinical practice is the fact that the authors do not provide threshold values for FET uptake or ADC values, which can be used for the interpretation of individual patient data. Data evaluation is based on a regression analysis that uses a specific mathematical model to combine the mean values of different imaging parameters. Applying this model to the ADC and FET images results in a probability map for tumor presence, which, however, is not fully convincing. Due to artifacts high probability of tumor tissue is indicated in many areas, which are probably not infiltrated by tumor tissue as addressed by the authors. On the other hand, it has to be emphasized positively that the authors make their software available to the public, which makes it possible to verify and further develop the method independently.

A general limitation of advanced MRI is still the lack of standardization in acquisition, data processing and image interpretation. Consequently, comparability and reproducibility of the findings is often difficult. On the other hand, ADC values derived from DTI have shown a good scan-rescan concordance within scanner types as well as between different manufacturers and field strengths, [10] which is an important prerequisite to transfer the approach by Verburg and colleagues to other clinical settings.

Overall, the study by Verburg and colleagues is a big step forward and should be considered as a blueprint for future efforts to further investigate and promote advanced multimodal imaging in neuro-oncology.

STATEMENT

The text is the sole product of the authors and no third party had input or gave support to its writing.

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