Imaging challenges following newer treatment options: are companion diagnostics required in neurooncology?

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Contrast-enhanced MRI is the method of choice for follow-up imaging in patients with brain tumors, but its specificity is low despite outstanding spatial resolution [1,2]. Importantly, the differentiation of treatment-related changes from actual tumor progression following newer treatment options such as immunotherapy using checkpoint inhibitors or vaccines is challenging by anatomical MRI alone [2–4]. Specifically, inflammation with intratumoral T-cell infiltrates triggered by immunotherapy may lead to highly variable MR imaging findings including contrast enhancement that may suggest tumor progression. Moreover, neuroimaging changes induced by these treatment options may also hamper a reliable response assessment.

Therefore, there is a great need for companion neuroimaging diagnostics in neuro-oncology, which, either as a single modality or in combination with other imaging techniques, may improve the diagnostic accuracy. It has been demonstrated in numerous studies that the both most frequently used advanced imaging techniques perfusion-weighted MR imaging (PWI) and PET using radiolabeled amino acids can be a helpful adjunct for the diagnosis of treatment-related changes in patients with malignant glioma or brain metastases predominantly after radiotherapy or chemoradiation [5–7]. Additionally, more recent data have suggested that both MRI and PET radiomics has a great potential to add valuable diagnostic information in patients with brain tumors [8,9]. In particular, it has been demonstrated in patients with brain metastases that combined radiomics derived from both amino acid PET and MRI encodes more important diagnostic information for the diagnosis of treatment-related changes secondary to radiotherapy than either modality alone [10].

Due to the increasing use of immunotherapy in neurooncology, initial results suggest that amino acid PET using O-(2-[18F]fluoroethyl)-L-tyrosine (FET) has the potential to identify pseudoprogression in patients with melanoma brain metastases [11] treated with the checkpoint inhibitor ipilimumab. In a larger series of patients with melanoma or non-small cell lung cancer brain metastases treated with checkpoint inhibitors or targeted therapy combined with radiotherapy, FET PET seems also to be of value for both response assessment and diagnosis of pseudoprogression related to inflammation triggered by immune responses [12].

Moreover, 'Immuno-PET' using PET probes specific for T cells or immune checkpoints such as the programmed cell-death receptor 1 or ligand 1 (PD-1, PD-L1) is currently in the focus of attention [13]. Initial first-in-human studies suggested that tumor PD-L1 and PD-1 expression can be quantified noninvasively using [^{89}Zr]nivolumab or [^{89}Zr]atezolizumab PET in patients with various extracranial cancer types [14,15] as well as in brain metastases [14]. Furthermore, Antonios and colleagues showed that clofarabine radiolabeled with fluorine-18 as a PET probe for the enzyme deoxycytidine kinase, which is overexpressed in immune cells such as $CD8^+$ T lymphocytes, is helpful to differentiate immune inflammatory responses from other sources of contrast-enhancement on MRI [16]. This has been demonstrated in patients with recurrent glioblastoma treated with dendritic cell vaccination and PD-1 blockade [16].

Taken together, in the light of newer treatment options such as immunotherapy, the present literature suggests that companion neuroimaging diagnostic methods have a great potential for the challenging diagnosis of treatment-related changes and the assessment of treatment response. However, the number of available studies is still low and only little data is available concerning the evaluation of imaging findings following various immunotherapy approaches for brain tumors using these methods. Additionally, the available results are still based on a low number of patients and, additionally, have frequently a more explorative character. In terms of validation of neuroimaging findings following immunotherapy, the extraction of tissue samples obtained by biopsy for neuropathological evaluation is desirable and should be performed more frequently in the future. In the case of medical contraindications for biopsy, liquid biopsies, i.e. the extraction of tumorassociated markers (e.g. cell-free tumor DNA, circulating tumor cells) in cerebrospinal fluid or blood plasma, seem to be a promising alternative diagnostic method.

In conclusion, to confirm and to further evaluate the reported encouraging imaging findings, further studies withstandardized imaging protocols and data evaluation in a higher number of patients are warranted.

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