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Letter to the Editor

Assessment of imaging biomarkers in the follow-up of brain metastases after SRS

We have read the article "Long-term metabolic evolution of brain metastases with suspected radiation necrosis following stereotactic radiosurgery: longitudinal assessment by F-DOPA PET" by Cicone et al with great interest.[1] Currently, the number of patients with radiation necrosis (RN) after stereotactic radiosurgery (SRS) of brain metastases is increasing, because new treatment strategies have improved the survival of patients with metastatic disease.[2] To improve long-term monitoring and control of brain metastases after SRS, there is an urgent need for imaging biomarkers to discriminate local progression (LP) from RN during follow-up. Cicone et al address this important issue and report a high diagnostic accuracy of positron emission tomography (PET) using 3,4-dihydroxy-6-[^{18}F]-fluoro-L-phenylalanine (F-DOPA) to differentiate LP from RN in brain metastases after SRS. However, their data need to be interpreted with caution, since their study has several major limitations. Consequently, this raises the question of which criteria are required for imaging studies reporting on RN and LP in brain metastases.

First, in only 20% of all lesions included in the study of Cicone et al, imaging biomarkers were compared to the gold standard histopathology. Furthermore, their definition of RN as <20% neoplastic features is quite arbitrary, since neoplastic features below this value can still represent progressive disease. For the remaining 80% of lesions, clinical course—including the decision to irradiate—was used as the reference standard, which is far from well defined.

Second, the cohort of Cicone et al is too small (30 patients with 34 lesions) to achieve some statistical robustness, and consists of an unequal distribution of LP and RN (29.4% vs 70.6%, respectively).

Third, very few baseline characteristics were described in the selected patients; in particular administered systemic anticancer treatments are missing. This is especially relevant since targeted therapy and immunotherapy will influence the clinical course and affect imaging findings in patients with brain metastases, with or without SRS.[2]

Fourth, the defined inclusion criteria are mainly focused on the selection of patients with lesions suspected for RN, creating a higher pretest probability of RN. Even more selection bias may have been created by limiting inclusion to patients with a Karnofsky performance status >60 and stable extracranial disease, resulting in a cohort that is not representable for the real-world population of brain metastasis patients having undergone SRS. In addition, 10 patients were included from a previous study by Cicone et al[3] that had a different study aim.

To summarize, the exploratory study by Cicone et al lacks the methodological strength to adequately assess the biomarker validity of F-DOPA PET to distinguish between true tumor progression and treatment effects. This raises the need to define minimal criteria for studies reporting on (imaging) biomarkers that potentially allow this distinction. These studies should present cohort studies, with outcome clearly defined. Cases presenting pseudoprogression (PsPD) or RN should either show unequivocal pathology findings or no growth over a clinically relevant period of time (eg, at least 6 months) without a change in anti-tumor treatment, except for steroids or bevacizumab.[4] In case of treatment with steroids or bevacizumab, PsPD is described as the ongoing stabilization or shrinkage for again a clinically relevant period of time after the end of steroid or bevacizumab treatment.[4] Baseline characteristics and information on treatments must be clearly described. The sample size must be robust, representing a realistic clinical population, and allowing statistical analysis with calculation of clinically relevant indices such as negative and positive predictive values and/or negative and positive likelihood ratios. If future studies do not meet such requirements, the field will continue to suffer from small series that lack convincing results and which are unlikely to alter patient management.

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