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Diffusion MRI as an early marker of response to immune checkpoint inhibitors

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See the article by Song et al. in this issue, pp. 1658–1666.

Immune checkpoint inhibitors (ICIs) have yielded mixed results when recently applied in clinical trials for recurrent glioblastoma.[1–3] This observed variation in response may in part be attributed to increased blood-brain barrier permeability due to the inflammatory response that results from T-cell proliferation and the production of cytokines.[4] The heightened edema and extravasation of contrast agent that ensues mimics the appearance of tumor progression on standard anatomical T1-post-contrast and T2-weighted FLAIR images, presenting a major challenge when trying to accurately assess response to this class of therapy. Although these complications are acknowledged in the criteria for immunotherapy response assessment in neuro-oncology (iRANO), which suggest waiting for 6 months before changing a patient's therapeutic course following immunotherapy,[5] there remains to be a preemptive strategy for distinguishing these beneficial therapeutic responses from underlying tumor progression. Similar to other classes of chemotherapeutics, outcome of patients on these agents can vary widely,[1] which may be partially explained by both our inability to properly identify the subset of patients who would benefit most from ICIs as well as the inflammation-induced heightened permeability of the blood-brain barrier (BBB) mimicking tumor progression.

Despite their demonstrated utility and widespread use in the clinic for several decades, more quantitative or so-called "advanced" MRI metrics derived from physiological imaging are still rarely required in clinical trial imaging protocols. Even when they are recommended, these metrics are often included in exploratory analyses, which can be underpowered because collecting the data is optional and usually only performed in a subset of patients where the data is required as part of their routine site-specific protocol. The two most prominent MRI-derived metrics that have emerged for this purpose are the apparent diffusion coefficient (ADC), which is derived from diffusion-weighted MRI and reflects underlying tumor cellularity and edema, and relative cerebral blood volume (rCBV) measurements from dynamic susceptibility contrast (DSC) perfusion-weighted imaging. Elevated rCBV values represent well-vascularized areas of the lesion that correlate with features characteristic of more aggressive phenotypes and have been used to distinguish recurrent tumor from the effects of treatment within new areas of enhancement; however, rCBV requires standardized acquisitions and post-processing software to correct for leakage in order to compare among sites.[6] Although ADC maps can now be generated automatically on most scanners and have revealed early changes during therapy, the interpretation of these values becomes more complex in the post-treatment setting when there is a heterogeneous mixture of tumor cells and treatment-induced edema within the same voxel.

In their article entitled "Multiparametric MRI for early identification of therapeutic response in recurrent glioblastoma treated with immune checkpoint inhibitors", Song et al.[7] retrospectively evaluated in patients with recurrent glioblastoma whether early changes in quantitative metrics derived from diffusion and perfusion MRI before and after the administration of an ICI can determine radiographic response at 6 months. By calculating the mean relative ADC (rADC) and multiple perfusion-weighted imaging-derived parameters within the contrast-enhancing lesion before and after ICI therapy, they found that only rADC showed promise as an early marker of subsequent response at 6 months. In their univariate analysis of pre- and post-ICI timepoints, a decrease in mean post-treatment rADC in the contrast-enhancing lesion was associated with significantly worse radiographic response 6 months later in the 19 patients studied (7 responders and 12 progressors). A second analysis of interval changes of values between pre- and post-ICI corroborated these findings, whereby an increase in post-ICI rADC values was associated with a favorable response after 6 months, whereas decreased rADC signified progression in all but two of the 19 patients. Perfusion metrics, however, revealed similar interval changes between time points for both response categories and were not individually associated with response at either time point.

Identifying early, quantitative changes after ICI therapy that are markers of subsequent response holds promise in identifying patients who will benefit from remaining on this type of therapy even when pseudo-progression is suspected.

Despite it being one of the larger studies on imaging response to ICIs to date, the findings presented will need to be replicated in a larger cohort, underscoring the need for pooling together these data across multiple institutions in order to ultimately elucidate their relationship to progression-free and overall survival. The influence of prior and concomitant therapies on these early response metrics, especially those that are anti-angiogenic in mechanism, should also be evaluated because of their widespread use in the recurrent setting and opposing effects on blood-brain barrier permeability and vascular normalization. As rADC has emerged as a marker of early response for various therapeutic strategies in patients with glioblastoma,[8] it is not surprising that it also demonstrates potential as an early marker of response to ICIs, despite nearly half of the patients who progressed by 6 months receiving concomitant bevacizumab therapy. Further analysis in a prospective, bevacizumab-naïve cohort is warranted, however, before the role of perfusion parameters can be negated as early markers of ICI response. Although the mean lesion-level analyses performed in this study are an important first step towards identifying markers of ICI response, voxel-level analyses that can capture the spatial heterogeneity of ADC changes within the lesion over time may prove advantageous in future analyses.

As the current landscape of emerging targeted therapies continues to interfere with our conventional markers of response based on traditional anatomical imaging, it has become increasingly important to formally incorporate other, well-established imaging metrics into existing response assessment criteria. Although there is no shortage of promising MRI-derived functional and metabolic imaging markers, ADC from diffusion-weighted MRI is advantageous in that it can reveal early changes reflective of response to various types of targeted therapy and is relatively simple to acquire using standardized protocols and post-processing automatically on clinical scanners. The next challenge on the horizon becomes how to best to incorporate ADC to improve the current definitions of response assessment and transform our current frameworks for clinical trial design to incorporate improved endpoints for response characterization in a way that maximizes therapeutic benefit for individual patients.

Keywords

ADC | diffusion MRI | glioma | immune checkpoint inhibitors | immunotherapy | response to therapy

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