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Reply to Letter to the Editor

Response to Letter to Editor

We appreciate the interest, careful reading, and expressed questions of our Brain Tumor Imaging Protocol–Brain Metastasis (BTIP-BM) article[1] by Drs Arana and Arribas. They raise several points around the impact of 3T versus 1.5T in the setting of radiosurgery, on clinical outcomes, and on response assessment.

The primary goal of the BTIP-BM consensus recommendations was to give clinical investigators an imaging protocol(s) as a guiding starting point for their brain metastases clinical trials. This was motivated by many stakeholders in the development of therapeutics for brain metastases (including the FDA, pharmaceutical and biotech companies, and clinical trials cooperative groups) that desired standardized, accurate, and reproducible imaging means for the evaluation of new therapeutics or for comparative effectiveness evaluation. Therefore, radiotherapy treatment planning is also outside the context of the BTIP-BM protocols. The BTIP-BM protocols are specifically intended for diagnosis and response assessment, not radiotherapy planning, which usually requires a very specific and limited MRI scan with other considerations such as limiting geometric distortion and, frequently, compatibility with metal head frames.

As we fully accept that no multicenter clinical trial will be able to demand the use of 3T only, we included a 1.5T protocol that we have considered fully acceptable. However, it would be misleading to state that the 2 field strengths are equivalent, as the greater field strength at 3T produces greater signal-to-noise and contrast-to-noise ratios, allowing 3T systems to be pushed to higher physical resolution if desired. For the purposes of detecting small metastases, there will always be at least a theoretical advantage of 3T over 1.5T. Drs Arana and Arribas referenced the systematic review by Wardlaw et al[2] to claim that 3T is not superior to 1.5T on clinical grounds. However, this review evaluated 150 papers that included a variety of CNS pathologies, and from our review (eTable 1), these included only 2 papers[3,4] that studied anatomic imaging for brain metastases specifically. Both of these papers found "better detection" or "higher contrast" at 3T.

Although Drs Arana and Arribas correctly point out that small (<5 mm) brain metastases are not considered measurable disease according to Response Assessment in Neuro-Oncology–Brain Metastases (RANO-BM) guidelines, this criterion was generated to allow for the inclusion of imaging studies that used slice thickness up to 5 mm,[5] appreciating that RANO-BM guidelines were created to apply across a wide variety of scanner capabilities and implementations. Given the emergence of stereotactic radiosurgery as a prime treatment modality, it is likely that detection of small lesions will matter in upcoming years. Our BTIP-BM recommendations provide further guidance in an attempt to improve the consistency and quality of imaging data acquired in brain metastases trials moving forward.

With regard to the comments on response assessment, particularly the differentiation of radionecrosis versus tumor progression in asymptomatic patients, while we agree that this is a challenging diagnostic problem that requires clinical input, clinical imaging interpretation is well beyond the scope of the BTIP-BM paper. Furthermore, while many "advanced" imaging techniques, including dynamic contrast-enhanced MRI and some types of PET imaging, show promise, they generally lack multicenter trial validation and/or are not readily available across all centers participating in clinical trials. We encouraged the use of dynamic susceptibility contrast, while not making it part of a core protocol due to its lack of multicenter trial validation, largely based on its ease of use, wide availability, and extent of work already performed on its standardization.[6] We very much welcome further research and validation of some of these other advanced imaging techniques.

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References

1. Kaufmann TJ, Smits M, Boxerman J, et al. Consensus recommendations for a standardized brain tumor imaging protocol for clinical trials in brain metastases. *Neuro Oncol.* 2020;22(6):757–772.
2. Wardlaw JM, Brindle W, Casado AM, et al; SINAPSE Collaborative Group. A systematic review of the utility of 1.5 versus 3 tesla magnetic resonance brain imaging in clinical practice and research. *Eur Radiol.* 2012;22(11):2295–2303.
3. Nöbauer-Huhmann IM, Ba-Ssalamah A, Mlynarik V, et al. Magnetic resonance imaging contrast enhancement of brain tumors at 3 tesla versus 1.5 tesla. *Invest Radiol.* 2002;37(3):114–119.
4. Ba-Ssalamah A, Nöbauer-Huhmann IM, Pinker K, et al. Effect of contrast dose and field strength in the magnetic resonance detection of brain metastases. *Invest Radiol.* 2003;38(7):415–422.
5. Lin NU, Lee EQ, Aoyama H, et al; Response Assessment in Neuro-Oncology (RANO) group. Response assessment criteria for brain metastases: proposal from the RANO group. *Lancet Oncol.* 2015;16(6):e270–e278.
6. Boxerman JL, Quarles CC, Hu LS, et al. Consensus recommendations for a dynamic susceptibility contrast MRI protocol for use in high-grade gliomas. *Neuro Oncol.* 2020.