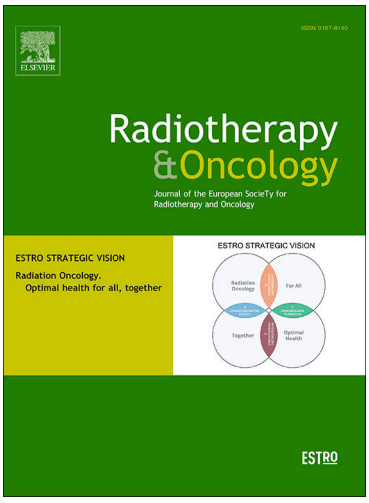
Journal Pre-proofs



Letter to the Editor

Response to commentary on "Improving risk assessment of local failure in brain metastases patients using vision transformers − A multicentric development and validation study" by Zhang et al

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Response to commentary on “Improving risk assessment of local failure in brain metastases patients using vision transformers − A multicentric development and validation study” by Zhang et al.

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We appreciate the thoughtful and constructive remarks on our manuscript [1] by Dr. Xiaowei Zhang et al. in their commentary titled “Personalizing Brain Metastasis Radiotherapy with AI: Can Vision Transformers Bridge the Gap?”. The authors raise several valid and insightful points. We would like to emphasize first that our study, in its current form, is not intended for immediate clinical adoption and indeed requires further validation. In the following, we address the relevant limitations.

As also discussed in our article, the collection of the data before the definition of the BM RANO criteria was indeed a non-standardized local failure (LF) assessment among centers, which could introduce subjectiveness and noise in the endpoint. By validation using multiple independent external test cohorts with potentially inconsistent LF definitions, we could show that reproducibility is possible. Nevertheless, prior to clinical application validation with LF defined with BM RANO, ideally in a prospective setting, is needed.

To define what patients classified as being at “high-risk” for LF would mean for an oncologist, such patients could benefit from risk-adapted treatment and follow-up strategies. These may involve dose escalation of SRT or the use of broader CTV margins, both of

which have been shown to improve local control [2]. Additionally, systemic agents capable of crossing the blood–brain barrier may be considered as adjunct therapy. Closer follow-up intervals could further support the early detection of LF.

The observed variation in model performance across subgroups defined by primary cancer location is valid but largely unavoidable given the underlying data distribution. Subgroups that were well represented in the training data, such as breast cancer, non-small cell lung cancer, and melanoma, and had at least minimal representation in the test cohort, exhibited consistent predictive performance. In contrast, the “Other” category, which aggregates multiple underrepresented subgroups, lacked sufficient data to enable reliable validation.

Finally, as noted, a portion of the model’s attention extended beyond the gross tumor volume in the saliency visualizations. These maps were generated using the *Beyond Attention* method [3], which propagates relevance across transformer layers and multi-head attention blocks to identify regions that most strongly contribute to the model’s output. Since each attention head and layer can emphasize different aspects of the input, the final saliency map represents one possible aggregation of these distributed attention patterns. Such post hoc interpretability methods offer valuable qualitative insights but do not provide a causal explanation of the model’s reasoning. Therefore, not all of the activations should be overinterpreted as biologically meaningful, as the true causal basis of model decision-making remains an open challenge in explainable deep learning.
We intended to use these maps to provide qualitative reassurance of the tumor focus in learning rather than definitive mechanistic insights.

In conclusion, we thank Dr. Zhang et al. for their valuable insights. Their comments help clarify our study’s scope, limitations, and future directions, and we hope our responses contribute constructively to the ongoing scientific discussion.

References

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Declaration of Interest

The authors declare no conflicts of interest regarding this letter.

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