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# Imaging biomarkers for brain metastases: more than meets the eye

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See the article by Bhatia and Berger et al. in this issue, pp. 1578–1586.

Brain metastases are the most common malignancy of the central nervous system and affect upward of 30–40% of all cancer patients.[1] Historically, the primary treatment for patients with multiple brain metastases was whole brain radiation therapy, which was associated with adverse cognitive side effects and limited efficacy. Outcomes have recently improved due to the emergence of stereotactic radiosurgery, a less morbid radiation treatment option, and a growing number of systemic agents producing durable responses in the brain. Notably, immune checkpoint inhibitors have been associated with high response rates in brain metastases that approach those of systemic disease. Given the number of new treatment options that exist for patients with brain metastases, there is an emerging need for biomarkers to aid clinicians in individualizing treatment options for patients.

Although traditional biomarkers derived from tissue and serum have led to significant improvements in the personalization of cancer treatments for a number of malignancies, they have had less utility for patients with brain metastases. Imaging biomarkers represent a promising method to personalize therapy for patients with brain metastases and have several advantages compared with traditional biomarkers. First, unlike traditional biomarkers, which require additional potentially invasive testing, imaging biomarkers can be generated using diagnostic imaging that is collected in routine clinical practice. Additionally, tissue derived biomarkers are often extrapolated from biopsy of another site of disease and can exhibit discordant molecular features compared with brain metastasis.[2] In contrast, imaging biomarkers derive a risk estimate based on the brain metastases of interest. Lastly, unlike traditional tissue and serum biomarkers, which may require that samples be sent to a specialized facility for testing, imaging biomarkers utilize software that can be more easily scaled across a variety of clinical settings, including resource-limited environments.

Previous attempts at leveraging imaging findings for prognosis have been ineffective because of observer bias and intraobserver variability among radiologists. More recently, however, the rise of digitally stored imaging information coupled with advances in machine learning techniques has renewed interest in quantitative imaging biomarkers. In the field of radiomics, diagnostic imaging is converted to minable high-dimensional data, which are thought to reflect the underlying pathophysiology of a tumor. Radiomic imaging biomarkers have proven to be effective in identifying reproducible and accurate biomarkers for numerous cancer types.[3]

In this issue, Bhatia et al[4] show that radiomic features derived from pretreatment MRI are associated with improved overall survival for melanoma brain metastases treated with immune checkpoint inhibitors. Given recent evidence in both melanoma and non–small cell lung cancer that immune checkpoint inhibitors may provide durable responses in subsets of patients,[5] there is a clear need for biomarkers which can delineate patients who would benefit from immune checkpoint inhibitor therapy from those who require local radiation therapy.

Neuro-oncology is a field that is well positioned to benefit from advances in the field of radiomics. For one, advances in the types of sequences generated from MRI have increased the potentially minable data that can be used to generate prognostic signatures. Secondly, tissue diagnoses of brain metastases are often not practical, and non-invasive imaging biomarkers serve as a useful alternative. Lastly, assessing treatment response based on imaging is a well-documented clinical challenge within neuro-oncology, and radiomic features may represent an objective reproducible quantitative method to measure treatment response.

Radiomic analysis of MRI has been effective in multiple areas of neuro-oncology. Specifically, radiomic features have been used to non-invasively diagnose brain tumor histology and commonly tested molecular markers.[6,7] Additionally, evidence suggests that using radiomic imaging biomarkers in conjunction with molecular markers may provide the greatest

prognostic accuracy for brain tumors and represent a potential synergistic opportunity between imaging and traditional biomarkers.[2,8]

Although there is significant promise in the area of quantitative imaging, there are numerous challenges that prevent effective integration of imaging biomarkers into clinical practice. To be safe and effective, imaging biomarkers must be proven accurate and reproducible across a variety of clinical settings. Although the literature of unique imaging biomarkers is increasing, there is a paucity of externally validated signatures tested across different MRI protocols and diverse patient populations. Testing the generalizability of radiomic features is an ongoing area of investigation. Additionally, radiomic approaches are often used in concert with emerging machine learning techniques which require significant amounts of imaging data. Collaboration and data sharing among research groups are necessary to generate large minable datasets. Efforts for data sharing are administratively difficult given concerns regarding patient privacy and institutional barriers. Continued investment in public initiatives like the National Cancer Institute–sponsored Cancer Imaging Archive is necessary to provide venues for groups to share imaging data and collaborate.[9] Lastly, the relative lack of interpretability of radiomic biomarkers limits their utility for further scientific investigation. Unlike molecular biomarkers that can be explored to derive potential therapeutic targets, our current understanding of radiomic imaging biomarkers do not offer an easy pathway for therapeutic intervention or for untangling the biological determinants of the observed outcomes. Bhatia et al's study is highly illustrative of this limitation, magnified by the choice of survival as the endpoint of interest, rather than radiographic response. Multiple factors likely affect overall survival in patients with brain metastases, including systemic disease response, salvage treatments, and comorbidities. Biologically, brain metastases are influenced by tumor microenvironment as well as immune system and host factors. The biological meaning of correlated radiomic features remains obscure and merits further investigation. While of practical value in clinical management, this particular study does not offer novel biological insights into how factors detected in the radiomic analysis may actually point to mechanisms driving progression or response of these tumors.

Imaging biomarkers represent a promising area of research well suited for clinical neuro-oncology. As the utility of radiomic imaging biomarkers continues to emerge, integration with existing risk-stratification methods will translate to more personalized treatments. Integration of imaging biomarkers in future investigational protocols will be necessary to best leverage this emerging technology for patients, coupled with continuous efforts to understand the links between radiomics, tumor biology, and patient characteristics.

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