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A 34-gene expression biomarker predicts meningioma outcomes and radiotherapy responses

David R. Raleigh and Matthias Preusser

Departments of Radiation Oncology, Neurological Surgery, and Pathology, University of California San Francisco, San Francisco, California, USA (D.R.R.); Division of Oncology, Department of Medicine I, Medical University of Vienna, Vienna, Austria (M.P.)

Corresponding Author: David R. Raleigh, MD, PhD, Departments of Radiation Oncology, Neurological Surgery, and Pathology, University of California San Francisco, Helen Diller Family Cancer Research Building, 1450 3rd Street, HD481, San Francisco, CA 94158, USA (david.raleigh@ucsf.edu)

Surgery is the mainstay of treatment for meningiomas, which are the most common primary intracranial tumors.[1] Radiotherapy is often used for definitive or postoperative meningioma treatments,[2] but biomarkers that distinguish meningiomas benefitting from radiotherapy versus meningiomas where radiotherapy may not improve long-term clinical outcomes are lacking. Although most CNS WHO grade 1 meningiomas can be effectively treated with surgery or radiotherapy, some WHO grade 1 meningiomas develop recurrences that cannot be predicted from histological features and some WHO grade 2 or grade 3 meningiomas are unexpectedly well controlled with standard interventions. These data suggest that new biomarkers are needed to guide meningioma risk stratification and patient selection for radiotherapy. In the interim, the NRG BN-003 and EORTC 1308 (ROAM) phase 3 clinical trials randomize patients with primary WHO grade 2 meningiomas to postoperative surveillance or postoperative radiotherapy after gross total resection.[3] These studies and their phase 2 nonrandomized predecessors, RTOG 0539 and EORTC 22042-26042, were initiated before the development of biomarkers that could be used to predict meningioma outcomes or radiotherapy responses. A post hoc analysis of EORTC 22042-26042 reported independent prognostic impact of DNA methylation class and chromosome 1p loss in WHO grade 2 and 3 meningiomas undergoing high-dose radiotherapy but could not evaluate a predictive role of these biomarkers due to the nonrandomized trial design.[4]

A study published in *Nature Medicine*[5] reports a new biomarker that improves discrimination of meningioma outcomes in head-to-head comparison with 9 other systems for meningioma classification, including the current standard of care, CNS WHO 2021 grade. Using retrospective clinical and molecular data from 1856 meningiomas that were resected at 12 institutions across 3 continents, including 103 meningiomas from RTOG 0539, the study investigators show that expression of 34 genes reliably predicted postoperative local recurrence (AUC 0.81) and overall survival (AUC 0.80) from fresh-frozen or formalin-fixed/paraffin-embedded meningiomas. Moreover, they show that the gene expression biomarker distinguished meningiomas benefiting from postoperative radiotherapy (HR 0.54) versus meningiomas where radiotherapy did not improve long-term clinical outcomes. The biomarker was developed using 173 meningiomas from a single institution, and clinical and analytical validation was performed in independent meningiomas to generate the performance metrics reported here. Using a total of 4898 bioinformatic assays, the study investigators demonstrate that the gene expression biomarker predicted outcomes within strata of other meningioma classifications systems based on histological features (CNS WHO 2016), histological and molecular features (CNS WHO 2021), DNA methylation probes, groups, subgroups, or class, or based on gene expression types, integrated score, or integrated grade. Importantly, the gene expression biomarker remained independently predictive on multivariate analyses after incorporating each of the 9 other meningioma classification systems tested.

These data suggest that gene expression profiling could be used to refine postoperative management for 29.8% of patients with meningiomas compared to traditional clinical and histological features that are used as inclusion or stratification criteria on NRG BN-003, EORTC 1308 (ROAM), RTOG 0539, and EORTC 22042-26042. More broadly, the development of the first biomarker to predict benefit from the only established nonsurgical therapy for meningiomas provides a framework for molecularly guided trials of treatment escalation or de-escalation for patients. At present, many incidentally detected meningiomas are treated with radiotherapy in the absence of a histological diagnosis, but a majority of these tumors do not grow on long-term follow-up even without intervention.[6] Predictive biomarkers such as the one described in *Nature Medicine* may therefore enable a paradigm of pre-radiotherapy (or pre-resection) biopsy for patients with meningiomas, followed by close observation of asymptomatic tumors with reassuring molecular features. Such a paradigm may reduce unnecessary toxicity and healthcare costs by refining risk stratification.

These results and their implications for neuro-oncology practice should be interpreted in the context of their

limitations. Although the study investigators provide robust validation of the 34-gene expression biomarker in large multicenter external cohorts, these cohorts spanned multiple decades that were comprised of different paradigms in meningioma treatment and classification. The majority of clinical data were obtained retrospectively, but the study provides investigator-blinded, independent validation using meningiomas and clinical data that were prospectively collected from patients enrolled on RTOG 0539. Pathology and radiology reviews were performed independently at each institution, but the heterogeneity in clinical review across independent cohorts may better represent the heterogeneity intrinsic to routine clinical practice, and the meningiomas from RTOG 0539 that were included in this study underwent central pathology and radiology review.

Despite being large, the external validation cohorts in this study included only 210 patients who received postoperative radiotherapy. Thus, further external and prospective validation will likely be important for widespread translation of these discoveries to patients. Meningioma samples from NRG BN-003 and EORTC 1308 (ROAM), for instance, could provide additional validation of gene expression biomarker performance in the context of postoperative radiotherapy. Ultimately, randomized prospective studies of radiotherapy versus observation using the gene expression biomarker or other molecular classification systems as inclusion or stratification criteria may be necessary for adoption of molecularly guided care for patients with meningiomas. Incorporating the gene expression biomarker alongside approaches for unsupervised meningioma molecular grouping, which do not predict radiotherapy responses[7] but may predict susceptibility to molecular therapy,[8,9] may be necessary to optimize treatments for patients with meningiomas that are resistant to standard interventions. In the future, it will be important to evaluate the predictive value of the 34-gene expression biomarker described here not only for external beam radiotherapy, but also for emerging radioligand therapies such as ^{177}Lu-DOTATATE, which are under clinical development in meningiomas.[10] In sum, this new approach for meningioma risk stratification represents an important first step toward biomarker-guided treatments for patients with the most common primary intracranial tumors.

Conflict of Interest

D.R.R. has received honoraria for consultation or advisory board participation from the following for-profit companies: Tipping Point, Gamma Tile. M.P. has received honoraria for lectures, consultation, or advisory board participation from the following for-profit companies: Bayer, Bristol-Myers Squibb, Novartis, Gerson Lehrman Group (GLG), CMC Contrast, GlaxoSmithKline, Mundipharma, Roche, BMJ Journals, MedMedia, Astra Zeneca, AbbVie, Lilly, Medahead, Daiichi Sankyo, Sanofi, Merck Sharp & Dome, Tocagen, Adastra, Gan & Lee Pharmaceuticals, Janssen, Servier, Miltenyi, Böhringer-Ingelheim.

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