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Radiomics—A new age of presurgical assessment to improve outcomes in pediatric neuro-oncology

Santosh Valvi and Jordan R. Hansford

Department of Paediatric and Adolescent Oncology/Haematology, Perth Children's Hospital, Nedlands, West Australia, Australia (S.V.); Brain Tumour Research Laboratory, Telethon Kids Institute, Nedlands, West Australia, Australia (S.V.); Division of Paediatrics, University of Western Australia Medical School, Nedlands, West Australia, Australia (S.V.); Michael Rice Cancer Centre, Women's and Children's Hospital, North Adelaide, South Australia, Australia (J.R.H.); Australian Bragg Centre for Proton Radiotherapy, South Australia Health and Medical Research Institute, Adelaide, South Australia, Australia (J.R.H.); South Australian Immunogenomics Cancer Institute, Faculty of Health and Medical Sciences, The University of Adelaide, Adelaide, South Australia, Australia (J.R.H.)

Corresponding Author: Jordan R. Hansford, BScH, MSc, MBBS, FRACP, Michael Rice Cancer Centre, Women's and Children's Hospital, 72 King William Rd, North Adelaide, SA 5006, Australia (jordan.hansford@sa.gov.au).

Ependymoma (EP) is the third most common malignant brain tumor among children, most frequently arising in the posterior fossa (PF). Advances in understanding the disease through molecular analyses have led to the identification of EP molecular subgroups occurring at different locations along the neuraxis. PF EP has been classified into group A (PFA) and group B (PFB) subgroups with distinct molecular and clinical characteristics.[1] PFA occurs predominantly in infants and young children and has a poorer prognosis, whereas PFB is diagnosed in older children and adults with an excellent prognosis.[1,2] The extent of surgical resection is key in PF EP outcomes with studies confirming a better prognosis for patients undergoing a gross total resection (GTR). However, due to their proximity to vital structures including the basilar artery and cranial nerves, these tumors can carry a significant surgical risk of harm. These complications may require intensive rehabilitation therapies and are often permanent. Hence, the prediction of EP subgroup preoperatively may have immense long-term outcome benefits.

Radiomics is an evolving arm of radiology where large amounts of quantitative data from medical images are extracted and mathematical algorithms, including utilizing machine learning, are applied to the data to predict underlying features of the patient's lesion. These data can then be utilized to improve clinical decision making. This contrasts with radiogenomics, where imaging features are combined with genomic data to construct clinical prediction models through deep learning to stratify patients, guide therapeutic strategies, and evaluate clinical outcomes.[3] Radiogenomics can also be used interchangeably with radiation genomics and the variable response to radiation therapy (RT) based upon underlying genetic features.

In this issue of *Neuro-Oncology*, Zhang et al applied machine learning strategies to identify magnetic resonance imaging (MRI)-based biomarkers of high-risk EP and to differentiate PFA from PFB.[4] They conducted a multicenter, retrospective study comparing molecular analysis with radiomic signatures in 157 EP patients. PFA and PFB molecular subgroups were determined based on gene expression profiling using a NanoString-based assay. About 1800 quantitative radiomic features were extracted from presurgical T2-weighted (T2-MRI) and gadolinium-enhanced T1-weighted (T1-MRI) imaging. Survival analysis was performed on patients achieving a GTR regardless of molecular status. Patients in a presumed PFA cohort with either molecular confirmation of PFA or patients <10 years at diagnosis without a molecular subgroup confirmation had outcome analyses in both GTR/subtotal resection (STR) groups. Finally, a molecular classifier was developed for radiomic features. T2 radiomic features stratified patients into high- and low-risk subgroups. Similarly, T1-MRI features were able to differentiate PFA and PFB EP subgroups confirmed by molecular studies on the tumor samples. In the presumed PFA cohort, T1/T2 modeling was able to further identify high- and low-risk groups with significantly superior overall survival (OS) for the low-risk group. The survival benefit was retained for these patients with STR as well.

The clinical utility of this study is 2-fold. It is known that molecular subgroup is the most important prognostic biomarker for PF EP[1]; PFB EP patients having a far better outcome compared to PFA EP patients. Radiomic information can provide preoperative clarity for family discussion from a prognostic point of view. Secondly, although a GTR is always preferable, radiologic subgroup prediction, as shown by the authors, may help in reducing postoperative complications by risk-benefit profiling at the time of presurgical planning. PFA EP patients with an incomplete resection have a very poor outcome with 5-year progression-free survival (PFS) as low as 26.1% in

one cohort.[5] Therefore, by predicting PFA EP radiologically, this may subsequently help the surgeon to plan to achieve GTR. On the other hand, PFB EP patients may not need as aggressive surgery if there are significant risks of postoperative morbidity. This would be comparable to patients with a WNT subgroup medulloblastoma (MB) where there is no definite survival benefit to GTR. Small residual tumor removal is not recommended if there is a high risk of neurologic morbidity, given the excellent response to chemotherapy in these patients.[6] While the role of chemotherapy in EP remains unresolved, given the excellent outcomes for most PFB EP, surgery only approaches may be considered in the future. For those with residual tumors, RT approaches to the involved field can continue to be the standard of care. Prospective studies will be needed to confirm this treatment de-escalation approach.[7]

Interestingly, the authors were further able to stratify PFA EP patients into high- and low-risk groups. This is important as tumors with certain chromosomal imbalances have worse prognoses. In the Children's Oncology Group (COG) ACNS0121 trial, 5-year event-free survival (EFS) was 35.7% for PFA EP patients with 1q gain compared to 81.5% for those without.[8] This was confirmed in a recent study analyzing samples from 663 patients with PFA EP. In addition to poor prognosis conferred by chromosome 1q gain, chromosome 6q loss was identified as an ultra-high-risk PFA EP subgroup. Patients in this subgroup had a very poor prognosis with 5-year PFS of 7.3% for 6q loss only and 0% for both 1q gain and 6q loss.[9] In the current study by Zhang et al, the 5-year OS for high- and low-risk groups was like the ACNS0121 experience implying potential radiogenomic biomarkers to identify high-risk groups among PFA EP patients.

Machine learning strategies involving radiomics have been shown to predict MB subgroups and they are being investigated in various brain tumors.[10]This is the first study describing the role of MRI features to risk stratify EP as well as differentiate PFA and PFB radiologically. However, it will be useful to further investigate these radiomic features in the setting of prospective clinical trials to confirm their prognostic value. We suggest radiogenomic studies of EP will help to further clarify the importance of GTR for those with higher risk features already known in the PFA subgroup. This will provide more confidence for a personalized surgical approach in patients to potentially reduce the postoperative complications while not affecting survival. These techniques could be expanded to include risk stratification of diseases with subgroups where GTR is seemingly of less importance including WNT MB. Radiomic characteristics are not expected to replace molecular analysis; however, it will be complimentary providing useful information for surgical planning and informed consent discussions with families.

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