Commentary: Peritumoral Edema/Tumor Volume Ratio: A Strong Survival Predictor for Posterior Fossa Metastases

Brain peritumoral edema is a complex phenomenon, whose prognostic value is still debated with conflicting results both among the studies considering brain metastases and between the studies addressing primary brain cancers, such as high-grade gliomas (HGG).

The current series specifically evaluated the effect of peritumoral edema on the survival of a subset of patients affected with posterior fossa metastases treated with surgical resection. The main finding of the study was that a higher edema volume to tumor volume ratio was associated with a significantly lower overall survival compared with those with a lower edema volume to tumor volume ratio.

In general, the prognostic value of peritumoral edema of brain metastases is controversial. Spanberger et al demonstrated that large peritumoral edema is associated with better survival than small peritumoral edema. This conclusion might be due to smaller peritumoral edema being associated with higher propensity for brain-invasive growth, despite less angiogenesis and HIF1a expression. The survival benefit of large peritumoral edema was independent of the primary tumor type, although the role of molecular subtyping was not evaluated in the study. Kerschbaumer et al, however, found no correlation between extent of peritumoral edema and overall survival, but noted that edema is often responsible for the patients’ symptoms.

In the case of glioblastoma (GBM), Lacroix et al found, in a large retrospective series of 416 patients, that while the degree of enhancement and tumor necrosis on preoperative magnetic resonance imaging (MRI) correlated with poorer survival, extent of peritumoral edema did not. Conversely, Schoenegger et al showed that patients affected with GBM with severe edema had shorter survival than patients with minor edema. The difference between the 2 studies may in part be accounted for by the different methods in determining the degree of peritumoral edema, with the former group using a volumetric approach and the latter group using a simpler 2-dimensional metric. Additionally, the prognostic value of peritumoral edema might depend upon the molecular profiling of the tumor itself. As an example, peritumoral edema has a clear prognostic role for GBMs only in the setting of O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation, while GBMs with unmethylated MGMT have poor outcomes, regardless of the extent of edema.

What are the reasons for the contradicting prognostic value of peritumoral edema between studies addressing brain metastases alone and with respect to studies addressing primary brain tumors such as HGG?

First, the anatomical location of the tumors plays a pivotal role in determining the clinical relevance of peritumoral edema. The present series analyzes infratentorial metastases that can cause compression of functional and/or vital structures sooner than the supratentorial metastases at a given tumor and peritumoral edema volume. Thus, because of a merely mechanical consideration, the present series is more likely to find a negative prognostic value of peritumoral edema, regardless of the tumor histology, with respect to series including both supratentorial and infratentorial tumors.

In the second instance, although the peritumoral brain edema associated with primary glial tumors, primary non-glial tumors, and metastatic tumors has a similar radiological appearance, the physiopathological basis can be different: the edema associated with meningiomas and well-encapsulated metastases is mainly vasogenic, whereas the edema associated with HGG involves a combination of vasogenic edema and tumor cell infiltration. Thus, the conclusions about the prognostic value of peritumoral edema of brain metastases might be not valid in the

ABBREVIATIONS: GBM, glioblastoma; HGG, high-grade gliomas; MGMT, O6-methylguanine-DNA methyltransferase; MRI, magnetic resonance imaging
case of primary brain tumors, and vice versa. All of the studies mentioned above used 1.5 or 3-T MRI scans and defined peritumoral edema as T2 or FLAIR hyperintense regions. These regions may contain variable proportions of vasogenic edema, cytotoxic edema, and tumor cell infiltration. Therefore, better methods of distinguishing types of peritumoral edema may be useful in determining its effect on overall survival. Artzi et al applied machine learning algorithms to parse out subtle differences in the nonenhancing lesions surrounding the enhancing tumor in patients with HGG with respect to patients with brain metastases. A training dataset included “tumoral” regions (defined as the peritumoral lesion surrounding HGG) and “nontumoral” regions (defined as the peritumoral lesion surrounding brain metastases). “Tumoral” regions had significantly higher dynamic-contrast-enhanced plasma-volume (\(V_p\)) and volume-transfer-constant (\(k_{trans}\)) values than “nontumoral” regions. The application of the algorithm to patients affected with HGG treated with bevacizumab revealed a greater decrease in the “nontumoral” component of the peritumoral edema than the “tumoral” component. While this study is limited by the assumption that peritumoral edema of HGG and of brain metastases reflects the “tumoral” and “nontumoral” components, respectively, it presents an intriguing method for potentially distinguishing between tumor infiltration and pure vasogenic edema. Further development of such MRI processing algorithms and their wider application to brain tumor imaging will hopefully help neurosurgeons to formulate prognosis based on the imaging characteristics of the edema. Additionally, even using the current MRI sequences, different authors measured the peritumoral edema with different methods such as volumetric analysis and bidimensional assessment, which might, at least in part account for the conflicting results.

In the third instance, from a histological and clinical viewpoint, brain metastases represent a heterogeneous disease especially when compared to primary brain cancers, in terms of primary tumor histology and molecular profiling, extension of extracranial disease, and treatment algorithms (including different combinations of surgery, radiation, chemotherapy, and targeted agents). Thus, overall survival is widely variable depending on the aforementioned factors. Certainly, a detailed analysis and standardization of these parameters might, at least in part, solve the disagreement between the studies. Indeed, the present series includes only patients underwent surgical resection of brain metastases, while there is international consensus about the role of stereotactic radiosurgery as the first-line treatment for brain metastases with few exceptions, such as large posterior fossa metastases, metastases causing obstructive hydrocephalus and symptomatic metastases.

Disclosure
The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

REFERENCES