Glioblastoma: Epidemiology and Imaging-Based Review

JOSEPH MADOUR, BS; JUSTIN BESSETTE, BS; JOEY Z. GU, MD; ERIKA L. THAYER, DO; HEINRICH ELINZANO, MD; ALESSANDRA J. SAX, MD

ABSTRACT

Glioblastoma (GBM) is an aggressive brain tumor, commonly occurring in the frontal and temporal lobes. GBM is characterized by low survival rates, high recurrence rates, and unclear risk factors, making management a significant challenge. Anatomic magnetic resonance imaging (MRI), including T1-weighted, T2-weighted, and fluid-attenuated inversion recovery (FLAIR), is the gold standard for diagnosis of GBM. These techniques have lower accuracy in evaluating treatment response, as pseudoprogression and radionecrosis can mimic true tumor progression (TrTP). Advanced imaging options that offer physiologic information, such as diffusion-weighted imaging, MR perfusion, MR spectroscopy, and Positron Emission Tomography (PET), have shown promise in aiding diagnosis and treatment response monitoring. The first-line treatment for GBM is maximal safe neurosurgical resection, followed by adjuvant radiotherapy and temozolomide, an oral DNA alkylating agent. Current research is focused on optimizing imaging to evaluate TrTP and developing novel treatments to increase survival rates.

KEYWORDS: Glioblastoma; imaging; MRI; CT; pseudoprogression

EPIDEMIOLOGY

Glioblastoma (GBM) is a rapidly progressing and fatal malignancy, with a five-year survival rate of only 7.1%.[1] It accounts for 51.5% of all primary central nervous system malignant tumors. While GBM tumors most typically present in the frontal and temporal lobes, they can also occur in other cortical and subcortical structures.[2] These tumors rarely metastasize, but they are inherently invasive, making surgical resection with clear margins infeasible. By definition, GBM is a grade IV glioma without a mutation in *isocitrate dehydrogenase* (*IDH*), also known as *IDH-wildtype*.[3] GBM is conventionally differentiated from other gliomas by classic histological features, such as microvascular proliferation or necrosis. However, the 2021 WHO classification introduced new molecular criteria that can be used to upgrade a tumor to GBM in the absence of the typical histological features. One of three molecular markers must be present: *telomerase reverse transcriptase* (*TERT)* promoter mutation, *epidermal growth factor receptor (EGFR)* amplification, or combined gain of whole chromosome 7 and loss of whole chromosome 10 (+7/–10).[3] Molecular sequencing is routinely employed in characterizing newly diagnosed brain tumors to detect actionable mutations and holds promise in changing GBM treatment. For example, tumors with *BRAF-V600E* or *NTRK* mutations can be treated with targeted therapy.[4] Additionally, immunotherapy can potentially be used to treat hypermutated phenotypes of GBM with high tumor burden, which are caused by mutated DNA mismatch repair genes or DNA polymerase complex.[5]

In Rhode Island (RI), the age-adjusted incidence of GBM has remained relatively steady, slightly increasing from 3.8 per 100,000 from 1995–1999 to 3.9 per 100,000 from 2015–2019 [**Table 1**].[6] These rates are higher than the national rate, which has hovered around 3.2 per 100,000 over that same time period.[7] Nationally, GBM incidence is markedly higher in males than in females, with 2020 incidence rates of 4.1 and 2.5 per 100,000, respectively. In addition, GBM incidence greatly increases with age, with 13.3 cases per 100,000 in the 65+ age group.[8] Both of these national trends were observed at the state level from 1995–2019, as the mean age of RI GBM patients was 64.8 years old, with males representing 55.1% of those patients. Lastly, 97.4% of RI GBM patients over this time period were White.

The clearest modifier of GBM survival is age, with patients in the 65+ age group exhibiting the lowest five-year survival rate of all examined age groups at 3%, according to national data from 2016.[8] Besides differences in age and sex, risk factors for developing GBM are not well-established. A recent

Table 1. Demographics and age-adjusted incidence rate of glioblastoma (ICD-O-3 9440/3) in RI (1995–2019)

Demographics	Mean Age (years)		Male (%)		White (%)
	64.8 ± 14.0		55.1		97.4
Incidence	**1995–1999**	**2000–2004**	**2005–2009**	**2010–2014**	**2015–2019**
Age-adjusted incidence rate, per 100,000 individuals	3.8	3.8	3.2	3.6	3.9

meta-analysis showed no increase in GBM risk with variables such as increased BMI, type 2 diabetes mellitus, alcohol consumption, NSAID use, or magnetic field exposure.[9] Another study found a 17% increased incidence of GBM in the highest socioeconomic status counties, compared with the lowest socioeconomic counties, though researchers struggled to identify specific risk factors to support this association.[10]

Clinical presentations for GBM patients vary based on the brain regions impacted by the tumor itself or the tumor's mass effect, with symptoms ranging from focal deficits, such as motor weakness, visual disturbance and focal seizures, to global impairments, including headaches, syncope and generalized convulsions.[11] Following diagnosis, the typical goals of care focus on slowing the progression of GBM while preserving normal brain function. Specific tumor characteristics have been identified that aid in predicting how efficacious certain treatments will be for patients. For example, tumors with a methylated *O-6-methylguanine-DNA methyltransferase* (*MGMT*) gene are more likely to respond favorably to temozolomide (TMZ), the first-line chemotherapeutic in GBM treatment regimens, than those with an unmethylated *MGMT*.[12] With further establishment of trends relating tumor characteristics to responsiveness to treatment, care plans for GBM patients will continue to evolve to maximize treatment efficacy.

IMAGING

CT

Before the introduction of MRI, computed tomography (CT) was the neuroimaging gold standard for diagnosing GBM. Given its accessibility, CT is usually the first imaging modality in a patient's work-up for a suspected brain lesion. On CT, the tumor can have a hypodense necrotic center with irregular, slightly hyperattenuating margins due to high cellularity, which can give a ring enhancement appearance on non-contrast imaging.[13] Due to the infiltrative nature of the tumor, it may cross the midline, extending to the contralateral hemisphere via the genu, body, and the splenium of the corpus callosum. Typically, CT also shows calcification, hemorrhage, mass effect, and vasogenic edema surrounding the tumor (**Figure 1**). Additionally, GBM's high vascularity lends itself well to visualization via perfusion CT imaging, which highlights the brain microcirculation and usually demonstrates increased tumor blood flow, cerebral blood volume (CBV), and vascular permeability.[14] These factors may help to distinguish GBM from grade 3 gliomas and other tumors, such as primary CNS lymphoma and metastatic brain tumors.[14,15] However, once a brain tumor is suspected, MRI is the neuroimaging gold standard due to its high specificity and sensitivity for GBM evaluation.[16]

MRI

The gold standard for GBM imaging includes pre- and post-gadolinium (Gd) contrast-enhanced T1 weighted imaging (T1WI) (**Figure 2A,B**), T2 weighted imaging (T2WI), and fluid-attenuated inversion recovery (FLAIR) MRI (**Figure 2C**).[17] Compared to CT, which uses density differences to distinguish tumor from normal tissue, MRI indirectly estimates tumor size by visualizing the gadolinium contrast that extravasates through the disrupted tumor vasculature. On T1WI, CSF appears hypointense (dark) and white matter tissue hyperintense (light), while the inverse is true on T2WI. FLAIR is similar to T2WI, except it attenuates normal CSF fluid, allowing easier detection of abnormal tissue. On pre-contrast T1WI, GBM appears as a hypointense or isointense mass with a central heterogeneous signal if

Figure 1. Non-contrast CT of the brain demonstrates an isodense lesion in the right frontotemporal brain associated with vasogenic edema and mass effect on the right lateral ventricle.

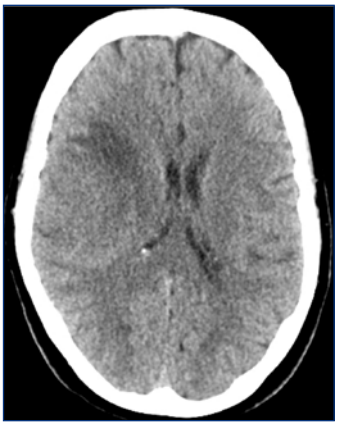
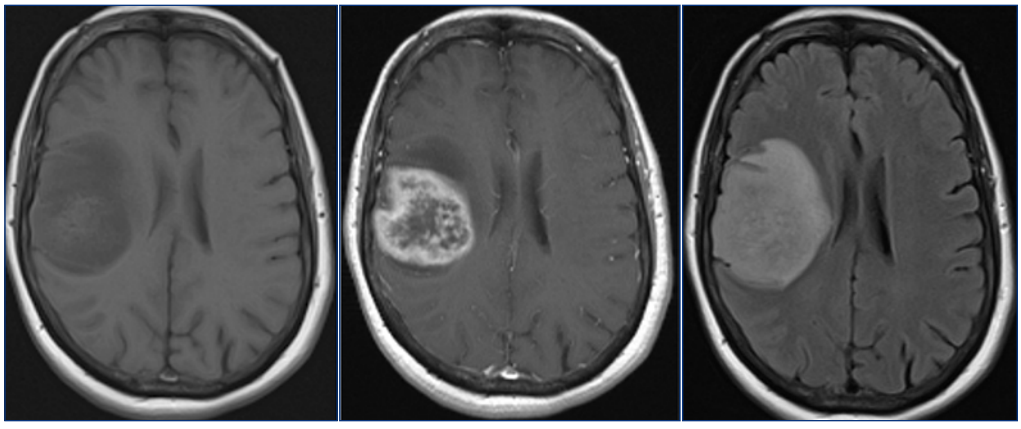


Figure 2. [**A**] Non-contrast enhanced T1-weighted imaging of the brain demonstrates a hypointense lesion in the right frontotemporal brain. [**B**] Post-contrast T1-weighted imaging demonstrates predominantly peripheral enhancement of the right frontotemporal lesion. [**C**] Axial T2-weighted fluid-attenuated inversion recovery imaging (FLAIR) demonstrates hyperintense signal associated with right frontotemporal lesion with mass effect resulting in right to left midline shift and effacement of the right lateral ventricle.



hemorrhage or necrosis is present.[18] Post-contrast T1WI illustrates the vascularity of the brain and detects any breakdown in the blood-brain barrier (BBB) due to tumors, abscesses, and other pathologies. On post-contrast T1WI, the area of necrosis appears hypointense while regions of viable tumor demonstrate hyperintense enhancement. Even though contrast enhancement is a common feature of high-grade gliomas (HGGs), including GBM, around 9% of HGG tumors do not enhance.[19] Additionally, it is difficult to determine the histologic grade of glioma on post-contrast T1WI.[20] GBM's highly infiltrative nature can help distinguish it from other gliomas, as it can extend into the contralateral hemisphere and deep nuclei of the cortex. Intratumoral hemorrhage and satellite lesions can also be highly suggestive of this malignancy. On T2WI/FLAIR, GBM appears as a hyperintense mass surrounded by vasogenic edema.

Although MR imaging is imperfect, it is necessary not only to guide the biopsy and confirmation of GBM but also to monitor treatment response. Post-contrast T1WI has conventionally been used for treatment response assessment but not without limitations. For example, a change in enhancement on imaging correlates with the breakdown of the blood-brain barrier (BBB), and, therefore, is not a direct measure of the tumor.[21] Increased enhancement occurs with both true tumor progression (TrTP) and pseudoprogression (PsP), posing a challenge to clinicians. It is important to recognize PsP on imaging since it does not represent TrTP and should not alter treatment course (**Figure 3**). PsP typically occurs within the first six months post-radiotherapy (RT), especially in the first three months, and usually improves without any intervention. The exact mechanisms behind PsP are unknown, with one hypothesis that radiotherapy causes increased vascular permeability and edema due to endothelial cell death.[22] A meta-analysis of HGGs showed that 36% of patients with MRI progression had PsP, 60% had TrTP, and 4% had an unknown outcome.[23]

Given the clinical importance of distinguishing TrTP from PsP on imaging, standardized guidelines to differentiate the two are essential. The Response Assessment in Neuro-Oncology (RANO) criteria provide an objective measure of treatment response in gliomas, which helps guide management.[24]

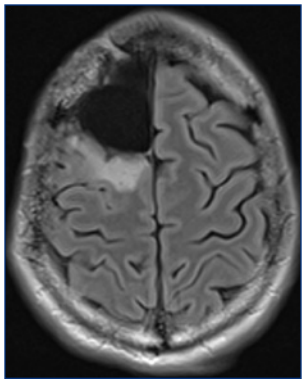


Figure 3. Axial T2-weighted fluid-attenuated inversion recovery imaging (FLAIR) demonstrates hyperintense signal posterior to right frontal resection cavity. This signal was not associated with post-contrast enhancement or elevated relative cerebral blood volume (rCBV).

The criteria take into account imaging factors like tumor size and presence of new lesions on MRI, as well as patient factors like clinical status and use of corticosteroids. The postradiotherapy MRI is used as the baseline for comparison with future scans. Depending on these factors, the treatment response is classified into complete response, partial response, stable disease, or progressive disease. Given the high incidence of PsP in the three months after radiotherapy, TrTP can only be confirmed by progression on repeat MRI during this period or with tissue sampling.

Radionecrosis is another treatment response that occurs due to radiation-induced damage of brain tissue and can mimic TrTP on imaging. In contrast to PsP, radionecrosis can occur six months to years after treatment and is usually irreversible.[25] Proposed mechanisms of radionecrosis include demyelination of white matter tracts, vascular endothelial damage, and changes in the fibrinolytic enzyme system. On MRI, findings of radionecrosis are most often seen at the tumor site, where the highest dose of radiation is delivered. On T2WI, this typically presents as an enhancing mass with a hyperintense necrotic center and surrounding edema. Given the similarity of the findings on MRI, it can be difficult to discern PsP and radionecrosis from TrTP. A meta-analysis looking at the diagnostic accuracy of MRI in evaluating treatment response in HGG patients found that anatomical MRI showed a pooled sensitivity of 68% and specificity of 77%.[26]

Given the limitations of conventional MRI, more advanced imaging techniques have been implemented in the clinical management of HGG patients. Diffusion-weighted imaging (DWI) measures the random movement of water molecules in tissue, which is affected by tissue cellularity. To quantify the extent of water diffusion, an apparent diffusion coefficient (ADC) is calculated, where lower scores correspond to lower (more restricted) diffusion. In the context of tumors, ADC is impacted by the tumor size and the extracellular matrix complexity, making it an indirect measure of tumor cellularity.[27] Typically, non-enhancing cystic and necrotic areas have high ADC values, whereas the solid portion of GBM has lower ADC values (comparable to white matter regions). By showing the heterogeneity of diffusion in the brain, ADC mapping provides valuable insight into the type of lesion present, helping differentiate grade 3 gliomas from GBMs.[28] A meta-analysis found that pooled ADC maps were 71% sensitive and 87% specific in evaluating treatment response in HGG, showing higher accuracy than conventional anatomic MRI.[26]

MR Perfusion

MR perfusion is another imaging modality that has shown promise in characterizing GBM physiology. This imaging can be done using three techniques: dynamic susceptibility contrast (DSC), dynamic contrast-enhanced (DCE), and arterial spin labeling (ASL) MR perfusion. DSC-MR perfusion,

or perfusion-weighted imaging (PWI), is the most widely used MR perfusion technique because it provides informative metrics such as CBV and cerebral blood flow.[27] This method relies on signal loss on T2 or T2* weighted images caused by the susceptibility effect from the Gd-based contrast agent passing through blood vessels. Studies have shown that GBM has an elevated CBV compared to lower-grade tumors and normal tissue, and that elevated CBV negatively correlates with prognosis.[29] DCE-MR perfusion, or "permeability" MRI, captures serial T1WI before, during, and after contrast to plot signal intensity over time in more detail than conventional T1WI. A useful metric derived from this technique is K-trans, which reflects the permeability of brain tissue and tumor angiogenesis.[27] A meta-analysis found that DSC- and DCE-perfusion have sensitivities of 87% and 92%, respectively, and specificities of 86% and 85%, respectively, making them more accurate than conventional MRI.[26] Lastly, ASL MR perfusion uses magnetically labeled water as a tracer and can be used to derive CBV. This technique is less widely used, potentially due to its lower signal-to-noise ratio and longer scanning time.[27] A recent meta-analysis found that DWI was slightly better than PWI (or DSC-MR perfusion) in terms of sensitivity (88% vs. 85%, respectively) and specificity (85% vs. 79%, respectively) in differentiating TrTP from PsP.[30] However, there was no significant difference in the area under the curve values between the two modalities (0.9156 for DWI and 0.9072 for PWI). These metrics highlight the strong performance of these modalities in treatment response evaluation of GBM, compared to conventional anatomic MRI. As seen, these methods not only help diagnose GBM but also show promise in evaluating treatment response and offering prognostic information.

MR Spectroscopy

Lastly, MR spectroscopy (MRS) is a useful technique for detecting metabolites present in brain tissue by using 1H (proton) and phosphorus 31 resonances. In GBM, MRS typically reveals increased choline (indicating increased membrane turnover), lactate (indicating hypoxia and necrosis), and lipids (indicating necrosis).[27] Additionally, the tumor demonstrates decreased *N*-acetyl aspartate (indicating impaired neuron mitochondrial integrity) and myoinositol (indicating disruption of the BBB and osmotic equilibrium).[27,31] A recent meta-analysis showed that elevated choline to *N*-acetyl aspartate ratio has high sensitivity and specificity for detecting TrTP.[32] MRS has demonstrated a sensitivity of 91% and a specificity of 95% in evaluating treatment response in HGG.[26] Thus, this technique not only shows promise in distinguishing GBM from other tumors but also in differentiating TrTP from PsP and radionecrosis.

Positron Emission Tomography

Although not universally used for tumor monitoring, Positron Emission Tomography (PET) may provide additional benefits in diagnosing GBM and monitoring its progression. [^{18}F]Fluoro-2-deoxy-D-glucose has traditionally been used as a surrogate for metabolic activity, which may be useful in differentiating metabolically active tumor from treatment-related changes. However, the brain's high glucose utilization at baseline decreases this radiotracer's specificity and limits its utility.[33] An amino acid tracer, 11C-methyl-2-methionine, has been used for guiding tumor biopsies due to its elevated uptake in tumor tissue. While it may have additional benefits relative to the glucose tracer, it is less accurate than MR perfusion for monitoring tumors in the posttreatment setting.[33] Alternatively, 18F-fluoromisonidazole, a marker of hypoxia, shows higher uptake in GBM tumors than in other non-GBM gliomas, making this tool useful in the initial GBM workup.[34] An increase in this radiotracer's signal also correlates with early tumor recurrence, while a decreased signal is seen in those receiving bevacizumab therapy.[35] An additional radiotracer, 18F-fluorothymidine, is a marker of cell proliferation and helps differentiate low- and high-grade gliomas.[33] While different radiotracers each have specific applications in GBM workup, the use of PET for GBM is still largely investigational and remains an active area of research. There are logistical barriers to routinely using PET in a clinical setting, and the additional benefits of PET compared to the validated tools of MR perfusion/spectroscopy remain unproven.

TREATMENT

Given the complexity of GBM, the current standard is a multimodal treatment consisting of surgery followed by adjuvant radiotherapy (RT) and TMZ, an oral DNA alkylating agent.[36] For patients who qualify for surgery, the gold standard is maximal safe resection of the contrast-enhancing tumor, and those who underwent gross total resection (GTR) have shown improved survival.[37] However, despite extensive resection, many patients experience tumor recurrence near the prior surgical site.[38] Several studies have explored the supramaximal resection (SMR) of GBM as an alternative, which involves the removal of tissue beyond the contrast-enhancing region. A recent meta-analysis showed that, relative to GTR, SMR results in a significant reduction of disease progression and an increase in survival time.[39] Notably, SMR is mainly performed on non-eloquent brain tissue, which could explain the favorable complication rates in the literature. Currently, there are no established guidelines on the optimal extent of resection in SMR, as increasing resection margins without potentially impacting neurological function and prognosis proves challenging.[40]

Surgical candidacy is determined after extensive imaging of the tumor and assessment of the patient's overall health.

Poor performance status and tumors that are multifocal, midline, or in deep brain areas are some factors that can preclude patients from resection.[41] Although the number of patients with inoperable GBMs is not well cited, it is estimated to be between 35 and 40%.[41] These patients usually undergo a stereotactic biopsy, which provides insight into tumor pathology and helps guide the treatment plan. Laser interstitial thermal therapy (LITT) has emerged as a new treatment modality for patients with unresectable GBMs.[42] A laser is guided through a catheter using advanced intraoperative imaging to ablate the tumor area with high temperatures. A recent study showed that patients who underwent LITT had a median progression-free survival of four months and a median overall survival of 11 months.[43]

After surgery, corticosteroids are added to treat the tumor-associated edema. Dexamethasone is the preferred medication due to its long half-life, high potency, and low mineralocorticoid activity.[44] Typically, the starting dose ranges from 2 to 16 mg depending on symptom severity, and it is administered for the shortest time possible, as prolonged dexamethasone use is detrimental to GBM patients.[45,46] If the patient is unresponsive or intolerant to corticosteroids, bevacizumab, a VEGF-A monoclonal antibody, can be used instead to treat cerebral edema symptoms.[47]

Typically, three to six weeks after surgery, patients receive radiation (30 fractions of 2 Gy over a six-week period for a total of 60 Gy) in addition to daily administration of oral TMZ.[46] Four weeks after the end of radiation, six 28-day cycles of adjuvant TMZ are done, where TMZ is administered for five consecutive days in each monthly cycle. This multimodal treatment was the result of the influential 2005 EORTC–NCIC phase III clinical trial, which demonstrated a median survival of 14.6 months for adjuvant TMZ and RT, significantly higher than the previous standard of care of adjuvant RT alone.[46] Although conventionally fractionated radiation is the gold standard if tolerated, hypofractionated radiation therapy is preferred in older patients or those with poor performance status.[47]

In addition to the standard of care, two adjuvant treatments have been approved by the Food and Drug Administration (FDA): Gliadel® in 1996 and tumor-treating fields (TTF) in 2015.[49,50] Although TMZ is the gold standard, only 20% of the drug in the plasma accumulates in the brain after oral intake, indicating inefficient delivery.[52] Gliadel® is an implantable biodegradable wafer that delivers carmustine at the GBM resection cavity.[53] It has been shown to increase median survival to 18.2 months when combined with RT and TMZ, 3.6 months higher than RT and TMZ alone. However, its use remains limited due to its rigid structure, rapid release, and high cost. The TTF device has transducer arrays consisting of electrodes that are placed on the patient's scalp to deliver low-intensity alternating electric fields.[54] It has been shown to inhibit the proliferation of tumor cells and improve survival outcomes when combined with maintenance TMZ relative to TMZ alone. Despite its demonstrated benefits in various trials, TTF adoption in clinical practice is still limited.

There have been several studies using immunotherapy in addition to RT and TMZ to treat GBM. However, most trials have failed to show survival benefits in patients, such as those using nivolumab and dendritic cell (DC) vaccines.[55,56] A recent phase I trial pulsed an autologous DC vaccine with lysate from GBM stem cells, which was safe, well tolerated, and showed improved survival outcomes.[56] A phase III randomized controlled trial (the DCVax-L trial) showed that adding a DC vaccine to the standard of care showed increased overall survival for both newly diagnosed and recurrent GBM, but the study did not meet its target endpoints.[57] The BBB poses a significant challenge to chemotherapy administration, as it largely prevents the passage of drugs.[58] Intra-arterial chemotherapy can increase drug concentration in tumor areas despite the BBB limitation,[59] but late-phase trials are lacking. More recently, a phase I trial demonstrated that MR-guided focused ultrasound, which transiently disrupts the BBB, is safe when delivering systemic chemotherapy to glioma patients.[60] Lastly, injectable drug delivery systems that could bypass the BBB altogether, such as nanoparticles and hydrogels, have been a focus of recent research.[61]

CONCLUSION

GBM remains a significant clinical challenge due to its complexity and aggressiveness. Several advanced imaging modalities have shown promise when used in conjunction with conventional MRI for diagnosis and evaluation of treatment response. Tumor heterogeneity and the limitation of the BBB pose significant challenges to current and potential treatment options. Future research is focused on personalizing multimodal treatment based on tumor profile, disrupting the BBB to deliver chemotherapies, and developing novel drug delivery systems.

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[Email corresponding author for complete reference list]

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Authors

Joseph Madour, BS, Warren Alpert Medical School of Brown University, Providence, RI.

Justin Bessette, BS, Warren Alpert Medical School of Brown University, Providence, RI.

Joey Z. Gu, MD, Department of Diagnostic Imaging, Warren Alpert Medical School of Brown University, Providence, RI.

Erika L. Thayer, DO, Department of Diagnostic Imaging, Warren Alpert Medical School of Brown University, Providence, RI.

Heinrich Elinzano, MD, Department of Neuro-oncology, Warren Alpert Medical School of Brown University, Providence, RI.

Alessandra J. Sax, MD, Department of Diagnostic Imaging, Warren Alpert Medical School of Brown University, Providence, RI.

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Correspondence

Joseph Madour, BS
joseph_madour@brown.edu