ACR Appropriateness Criteria® Brain Tumors

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Abstract

Brain tumors represent a complex and clinically diverse disease group, whose management is particularly dependent on neuroimaging given the wide range of differential diagnostic considerations and clinical scenarios. The introduction of advanced brain imaging tools into clinical practice makes it paramount for all treating physicians to recognize the range and understand the appropriate application of various conventional and advanced imaging modalities. The imaging recommendations for neuro-oncologic clinical scenarios involving screening in patients with increased genetic risk, screening in patients with systemic malignancy, pretreatment evaluation in patients with intra- and extraaxial brain tumors, posttreatment-surveillance in patients with known brain tumors after completion of therapy, and subsequent workup in the context of suspected radiographic progression are encompassed by this document.

The American College of Radiology Appropriateness Criteria are evidence-based guidelines for specific clinical conditions that are reviewed annually by a multidisciplinary expert panel. The guideline development and revision process support the systematic analysis of the medical literature from peer reviewed journals. Established methodology principles such as Grading of Recommendations Assessment, Development, and Evaluation or GRADE are adapted to evaluate the evidence. The RAND/UCLA Appropriateness Method User Manual provides the methodology to determine the appropriateness of imaging and treatment procedures for specific clinical scenarios. In those instances where peer reviewed literature is lacking or equivocal, experts may be the primary evidentiary source available to formulate a recommendation.

Key Words: Appropriateness Criteria, appropriate use criteria, AUC, brain metastases, glioma, meningioma, MRI, PET

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ACR Appropriateness Criteria® Brain Tumors. Variants 1 to 6 and Table 1 and 2.

Variant 1. Adult. Primary brain tumor screening. Genetic risk factors.

Procedure	Appropriateness Category	Relative Radiation Level
MRI head without and with IV contrast	Usually Appropriate	O
MRI complete spine without and with IV contrast	May Be Appropriate	O
MRI head without IV contrast	May Be Appropriate	O
MR spectroscopy head without IV contrast	Usually Not Appropriate	O
MRI complete spine with IV contrast	Usually Not Appropriate	O
MRI complete spine without IV contrast	Usually Not Appropriate	O
MRI functional (fMRI) head without IV contrast	Usually Not Appropriate	O
MRI head perfusion with IV contrast	Usually Not Appropriate	O
MRI head perfusion without IV contrast	Usually Not Appropriate	O
MRI head with IV contrast	Usually Not Appropriate	O
MRI head without IV contrast with DTI	Usually Not Appropriate	O
CT head with IV contrast	Usually Not Appropriate	☢☢☢
CT head without and with IV contrast	Usually Not Appropriate	☢☢☢
CT head without IV contrast	Usually Not Appropriate	☢☢☢
DOTATATE PET/CT brain	Usually Not Appropriate	☢☢☢
DOTATATE PET/MRI brain	Usually Not Appropriate	☢☢☢
FDG-PET/CT brain	Usually Not Appropriate	☢☢☢
FDG-PET/MRI brain	Usually Not Appropriate	☢☢☢
Fluciclovine PET/MRI brain	Usually Not Appropriate	☢☢☢
Fluciclovine PET/CT brain	Usually Not Appropriate	☢☢☢☢

Variant 2. Adult. Secondary or metastatic brain tumor screening. Extracranial malignancy.

Procedure	Appropriateness Category	Relative Radiation Level
MRI head without and with IV contrast	Usually Appropriate	O
MRI complete spine without and with IV contrast	May Be Appropriate	O
MRI head without IV contrast	May Be Appropriate	O
MR spectroscopy head without IV contrast	Usually Not Appropriate	O
MRI complete spine with IV contrast	Usually Not Appropriate	O
MRI complete spine without IV contrast	Usually Not Appropriate	O
MRI functional (fMRI) head without IV contrast	Usually Not Appropriate	O
MRI head perfusion with IV contrast	Usually Not Appropriate	O
MRI head perfusion without IV contrast	Usually Not Appropriate	O
MRI head with IV contrast	Usually Not Appropriate	O
MRI head without IV contrast with DTI	Usually Not Appropriate	O
CT head with IV contrast	Usually Not Appropriate	☢☢☢
CT head without and with IV contrast	Usually Not Appropriate	☢☢☢
CT head without IV contrast	Usually Not Appropriate	☢☢☢
DOTATATE PET/CT brain	Usually Not Appropriate	☢☢☢
DOTATATE PET/MRI brain	Usually Not Appropriate	☢☢☢
FDG-PET/CT brain	Usually Not Appropriate	☢☢☢
FDG-PET/MRI brain	Usually Not Appropriate	☢☢☢
Fluciclovine PET/MRI brain	Usually Not Appropriate	☢☢☢
Fluciclovine PET/CT brain	Usually Not Appropriate	☢☢☢☢

Variant 3. Adult. Suspected intraaxial brain tumor based on prior imaging. Pretreatment evaluation.

Procedure	Appropriateness Category	Relative Radiation Level
MRI head perfusion with IV contrast	Usually Appropriate	O
MRI head without and with IV contrast	Usually Appropriate	O
MR spectroscopy head without IV contrast	May Be Appropriate	O
MRI complete spine without and with IV contrast	May Be Appropriate	O
MRI functional (fMRI) head without IV contrast	May Be Appropriate	O
MRI head perfusion without IV contrast	May Be Appropriate	O
MRI head without IV contrast	May Be Appropriate	O
MRI head without IV contrast with DTI	May Be Appropriate	O
Fluciclovine PET/MRI brain	May Be Appropriate	☢☢☢
Fluciclovine PET/CT brain	May Be Appropriate	☢☢☢☢
MRI complete spine with IV contrast	Usually Not Appropriate	O
MRI complete spine without IV contrast	Usually Not Appropriate	O
MRI head with IV contrast	Usually Not Appropriate	O
CT head with IV contrast	Usually Not Appropriate	☢☢☢
CT head without and with IV contrast	Usually Not Appropriate	☢☢☢
CT head without IV contrast	Usually Not Appropriate	☢☢☢
DOTATATE PET/CT brain	Usually Not Appropriate	☢☢☢
DOTATATE PET/MRI brain	Usually Not Appropriate	☢☢☢
FDG-PET/CT brain	Usually Not Appropriate	☢☢☢
FDG-PET/MRI brain	Usually Not Appropriate	☢☢☢

Variant 4. Adult. Suspected extraaxial brain tumor based on prior imaging. Pretreatment evaluation.

Procedure	Appropriateness Category	Relative Radiation Level
MRI head without and with IV contrast	Usually Appropriate	O
MRI complete spine without and with IV contrast	May Be Appropriate	O
MRI functional (fMRI) head without IV contrast	May Be Appropriate	O
MRI head without IV contrast	May Be Appropriate	O
DOTATATE PET/CT brain	May Be Appropriate	☢☢☢
DOTATATE PET/MRI brain	May Be Appropriate	☢☢☢
MR spectroscopy head without IV contrast	Usually Not Appropriate	O
MRI complete spine with IV contrast	Usually Not Appropriate	O
MRI complete spine without IV contrast	Usually Not Appropriate	O
MRI head perfusion with IV contrast	Usually Not Appropriate	O
MRI head perfusion without IV contrast	Usually Not Appropriate	O
MRI head with IV contrast	Usually Not Appropriate	O
MRI head without IV contrast with DTI	Usually Not Appropriate	O
CT head with IV contrast	Usually Not Appropriate	☢☢☢
CT head without and with IV contrast	Usually Not Appropriate	☢☢☢
CT head without IV contrast	Usually Not Appropriate	☢☢☢
FDG-PET/CT brain	Usually Not Appropriate	☢☢☢
FDG-PET/MRI brain	Usually Not Appropriate	☢☢☢
Fluciclovine PET/MRI brain	Usually Not Appropriate	☢☢☢
Fluciclovine PET/CT brain	Usually Not Appropriate	☢☢☢☢

Variant 5. Adult. Known history of brain tumor. Posttreatment surveillance.

Procedure	Appropriateness Category	Relative Radiation Level
MRI head perfusion with IV contrast	Usually Appropriate	O
MRI head without and with IV contrast	Usually Appropriate	O
MRI complete spine without and with IV contrast	May Be Appropriate	O
MRI head perfusion without IV contrast	May Be Appropriate	O
MRI head without IV contrast	May Be Appropriate (Disagreement)	O
MR spectroscopy head without IV contrast	Usually Not Appropriate	O
MRI complete spine with IV contrast	Usually Not Appropriate	O
MRI complete spine without IV contrast	Usually Not Appropriate	O
MRI functional (fMRI) head without IV contrast	Usually Not Appropriate	O
MRI head with IV contrast	Usually Not Appropriate	O
MRI head without IV contrast with DTI	Usually Not Appropriate	O
CT head with IV contrast	Usually Not Appropriate	☢☢☢
CT head without and with IV contrast	Usually Not Appropriate	☢☢☢
CT head without IV contrast	Usually Not Appropriate	☢☢☢
DOTATATE PET/CT brain	Usually Not Appropriate	☢☢☢
DOTATATE PET/MRI brain	Usually Not Appropriate	☢☢☢
FDG-PET/CT brain	Usually Not Appropriate	☢☢☢
FDG-PET/MRI brain	Usually Not Appropriate	☢☢☢
Fluciclovine PET/MRI brain	Usually Not Appropriate	☢☢☢
Fluciclovine PET/CT brain	Usually Not Appropriate	☢☢☢☢

Variant 6. Adult. Known history of brain tumor. New or enlarging lesion on posttreatment surveillance. Next imaging study.

Procedure	Appropriateness Category	Relative Radiation Level
MRI head perfusion with IV contrast	Usually Appropriate	O
MRI head perfusion without IV contrast	Usually Appropriate	O
MRI head without and with IV contrast	Usually Appropriate	O
MR spectroscopy head without IV contrast	May Be Appropriate	O
MRI head without IV contrast	May Be Appropriate	O
MRI head without IV contrast with DTI	May Be Appropriate	O
DOTATATE PET/CT brain	May Be Appropriate	☢☢☢
DOTATATE PET/MRI brain	May Be Appropriate	☢☢☢
FDG-PET/CT brain	May Be Appropriate	☢☢☢
FDG-PET/MRI brain	May Be Appropriate	☢☢☢
MRI complete spine with IV contrast	Usually Not Appropriate	O
MRI complete spine without and with IV contrast	Usually Not Appropriate	O
MRI complete spine without IV contrast	Usually Not Appropriate	O
MRI functional (fMRI) head without IV contrast	Usually Not Appropriate	O
MRI head with IV contrast	Usually Not Appropriate	O
CT head with IV contrast	Usually Not Appropriate	☢☢☢
CT head without and with IV contrast	Usually Not Appropriate	☢☢☢
CT head without IV contrast	Usually Not Appropriate	☢☢☢
Fluciclovine PET/MRI brain	Usually Not Appropriate	☢☢☢
Fluciclovine PET/CT brain	Usually Not Appropriate	☢☢☢☢

Table 1. Appropriateness category names and definitions

Appropriateness Category Name	Appropriateness Rating	Appropriateness Category Definition
Usually Appropriate	7, 8, or 9	The imaging procedure or treatment is indicated in the specified clinical scenarios at a favorable risk-benefit ratio for patients.
May Be Appropriate	4, 5, or 6	The imaging procedure or treatment may be indicated in the specified clinical scenarios as an alternative to imaging procedures or treatments with a more favorable risk-benefit ratio, or the risk-benefit ratio for patients is equivocal.
May Be Appropriate (Disagreement)	5	The individual ratings are too dispersed from the panel median. The different label provides transparency regarding the panel's recommendation. "May be appropriate" is the rating category and a rating of 5 is assigned.
Usually Not Appropriate	1, 2, or 3	The imaging procedure or treatment is unlikely to be indicated in the specified clinical scenarios, or the risk-benefit ratio for patients is likely to be unfavorable.

Table 2. Relative radiation level designations

RRL	Adult Effective Dose Estimate Range (mSv)	Pediatric Effective Dose Estimate Range (mSv)
O	0	0
☢	<0.1	<0.03
☢☢	0.1-1	0.03-0.3
☢☢☢	1-10	0.3-3
☢☢☢☢	10-30	3-10
☢☢☢☢☢	30-100	10-30

Note: Relative radiation level (RRL) assignments for some of the examinations cannot be made, because the actual patient doses in these procedures vary as a function of a number of factors (eg, region of the body exposed to ionizing radiation, the imaging guidance that is used). The RRLs for these examinations are designated as "varies."

SUMMARY OF LITERATURE REVIEW

Introduction/Background

Brain tumors represent a complex and clinically diverse disease group whose management is particularly dependent on neuroimaging given the wide range of differential diagnostic considerations and clinical scenarios. The introduction of advanced brain imaging tools into clinical practice makes it paramount for all treating physicians to recognize the range of available diagnostic modalities and understand the appropriate application of various advanced imaging modalities including perfusion MRI, MR spectroscopy (MRS), and PET.

In patients with certain genetic syndromes, screening of asymptomatic individuals is appropriate given high risk for specific central nervous system (CNS) neoplasms. Although this scenario (Variant 1) is uncommon, screening primarily involves MRI, although intervals may vary by condition.

A common clinical scenario involves patients with known systemic malignancy in whom screening for brain metastases may be indicated (Variant 2). Screening interval recommendations exist for selected primary tumors such as lung cancer and melanoma; screening for brain metastases may also be appropriate in patients with other types of cancer such as breast cancer and lymphoproliferative neoplasms. MRI offers anatomical screening, and other advanced imaging tools can be useful for lesion characterization.

Pretreatment evaluation for patients with suspected or known brain tumors can be stratified into intraaxial (Variant 3) and extraaxial (Variant 4) tumors. MRI is most useful for anatomical imaging; depending on tumor location, vascular imaging may be useful to delineate tumor relationship to arterial or venous vessels. Advanced imaging using perfusion MRI and MRS provides additional characterization, particularly for intraaxial tumors. Diffusion tensor imaging (DTI) and functional MRI (fMRI) may be helpful for surgical planning in cases in which tumor involves eloquent brain regions. Although fluorine-18-2-fluoro-2-deoxy-D-glucose (FDG)-PET is commonly available, amino acid PET and DOTATATE PET are emerging tools used for

diagnosis and treatment planning for glioblastoma and meningioma, respectively.

Posttreatment surveillance in patients with known brain tumors (Variant 5) includes both conventional MRI for brain tumor given excellent anatomic resolution [1] and perfusion MRI to evaluate tumor vascularity and/or blood–brain barrier permeability. For patients who completed treatment and demonstrate new MRI findings (Variant 6), protocols incorporate advanced perfusion MRI to map the extent of viable tumor, and FDG-PET or DOTATATE PET to aid in differentiating suspected radiation necrosis and tumor recurrence for intraaxial and extraaxial neoplasms, respectively.

SPECIAL IMAGING CONSIDERATIONS

DTI measures water diffusion properties of brain tissue and can be used to visualize functionally relevant white matter tracts using DTI-based tractography, which helps to safely resect tumors while maximizing resection extent, which has been shown to be critical for clinical outcomes in patients with brain tumors [2], and has improved outcomes by reducing risk of postoperative neurologic deficits [3].

fMRI is a valuable preoperative planning tool in patients with brain tumors. A systematic review and meta-analysis found that the use of preoperative fMRI was associated with lower rates of postoperative morbidities and higher Karnofsky performance scores [4].

MRS detects metabolites via nuclear MR while taking advantage of the excellent spatial resolution of MRI. MRS-based studies have shown specific profiles for high-grade and low-grade gliomas, as well as for radiation necrosis [5].

For the purposes of this document, perfusion MRI (arterial spin labeling [ASL], dynamic susceptibility contrast-enhanced [DSC] and dynamic contrast-enhanced [DCE]) imaging techniques have been combined, although the type of perfusion MRI acquisition for which the literature evidence is available will be presented when relevant for individual clinical variants. ASL uses endogenous water as contrast, whereas DSC and DCE require gadolinium-based contrast administration. DSC is based on T2* effects and generates leakage corrected relative cerebral blood volume (rCBV) as the main output parameter. Consensus recommendations for DSC-MRI protocol for use in high-grade gliomas have been put forward that are compatible with the standardized brain tumor imaging protocol (BTIP) for high-grade gliomas, the recommended protocol for the national clinical trials network [6]. DCE is based on T1-relaxivity and generates parameters such as the fractional plasma volume and volumetric transfer constant.

FDG-PET can demonstrate progressive or recurrent neoplasm with robust sensitivity and specificity [7], however, has important limitations, including 1) heterogeneity of FDG-avidity among different primary and secondary brain neoplasm subtypes, and 2) high physiologic FDG-avidity of normal cortex and deep gray nuclei resulting in partial volume averaging effects.

Amino-acid targeted (AA)-PET has demonstrated superior diagnostic accuracy (compared with FDG-PET and contrast-enhanced MRI) in numerous academic trials for differentiating progression from radiation-related changes in both primary and secondary brain neoplasms. Fluciclovine and fluorodopa (FDOPA) are AA-PET radiotracers currently approved in the United States (primarily used in prostate cancer and Parkinsonian syndromes, respectively) and are included in this discussion given recent studies demonstrating clinical usefulness in glioblastoma [8] and brain metastases [9]. Given this emerging evidence, with more prospective studies currently underway, it is likely that fluciclovine PET will play a larger role in clinical brain tumor management in the near future. [F18]-fluoro-ethyl-tyrosine (FET) is an extensively studied AA-PET tracer for brain tumors [10] but is presently not yet approved in the United States.

Somatostatin receptor (SSTR)-targeted PET/CT and PET/MRI with [Ga68] DOTATATE (and the recently approved [Cu64] DOTATATE) represent a valuable adjunct to conventional brain MRI in patients with meningioma and other SSTR-positive brain and skull base neoplasms [11], with established usefulness and cost-effectiveness in the context of postoperative radiotherapy planning [12-17].

Other targeted PET radiotracers with potential for future clinical translation include fluoromisonidazole, which visualizes hypoxia and has demonstrated promise in the delineation of recurrent tumor from radiation necrosis in the posttreatment/postimmunotherapy setting in glioblastoma [18]. Emerging evidence further suggests clinical applications for [Ga68] and [F18] prostate specific membrane antigen-targeted PET in glioblastoma [19]. Another example is [F18] fluoroestradiol PET, a clinically approved radiotracer used in patients with metastatic estrogen-receptor positive breast cancer that has recently been applied to dedicated brain PET for posttreatment evaluation of breast cancer brain metastases and for which further studies will be needed to determine clinical impact on a population level [20].

DISCUSSION OF PROCEDURES BY VARIANT

Variant 1: Adult. Primary brain tumor screening. Genetic risk factors

The most common genetic conditions associated with primary CNS tumors are Lynch syndrome, neurofibromatosis (NF) type 1, Li-Fraumeni syndrome, tuberous sclerosis, familial adenomatous polyposis, retinoblastoma, multiple endocrine neoplasia type 1, von Hippel-Lindau syndrome

(VHL), Gorlin syndrome, schwannomatosis (including NF2-related schwannomatosis), ataxia-telangiectasia, Cowden syndrome, and melanoma-astrocytoma syndrome. Although these conditions are overall rare, Lynch syndrome is the most common with an estimated frequency of 1 in 300. Presenting factors raising concern for an underlying genetic condition in a patient presenting with brain tumor include family history (multiple family members with cancer), personal history of prior cancer, age at diagnosis younger than expected in the general population, rare histology that is difficult to categorize, and skin abnormalities. Screening typically involves MRI of the neuraxis, with a frequency of 1 to 3 years [21]. For VHL, biannual MRI of the brain and spine is recommended starting at age 10 years to screen for hemangioblastoma, whereas annual MRI of the brain is recommended for Li-Fraumeni syndrome and tuberous sclerosis. DOTATATE PET/CT may have usefulness in evaluating certain syndromes associated with tumors overexpressing SSTR2; however, it is usually not useful in the context of screening.

CT Head With IV Contrast. There is no relevant literature to support the use of CT head with intravenous (IV) contrast for screening in patients with genetic syndromes predisposing to brain tumors. Because the goal of screening is early detection of disease, CT is usually not performed given the relatively lower spatial resolution and tissue contrast compared to MRI.

CT Head Without and With IV Contrast. There is no relevant literature to support the use of CT head without and with IV contrast for screening in patients with genetic syndromes predisposing to brain tumors.

CT Head Without IV Contrast. There is no relevant literature to support the use of CT head without IV contrast for screening in patients with genetic syndromes predisposing to brain tumors.

DOTATATE PET/CT Brain. There is no relevant literature to support the use of DOTATATE PET/CT brain for screening for brain neoplasms in patients with predisposing genetic conditions. In patients with selected genetic syndromes increasing the risk for SSTR2-overexpressing tumors, such as MEN1 and hereditary paraganglioma-pheochromocytoma syndrome, evaluation with DOTATATE PET/CT may have specific usefulness. In patients with NF2-related schwannomatosis and suspected meningioma based on MRI without and with IV contrast, somatostatin analog PET/CT or PET/MRI may be used to confirm the suspected diagnosis as well as for treatment planning purposes [22]. In patients with VHL disease, DOTATATE PET/CT has shown usefulness in the detection of hemangioblastomas as well as other VHL-associated non–CNS neoplasms [23].

DOTATATE PET/MRI Brain. There is no relevant literature to support the use of DOTATATE PET/MRI brain for screening for brain neoplasms in patients with predisposing genetic conditions. In patients with selected genetic syndromes increasing the risk for SSTR2-overexpressing tumors, such as MEN1 and hereditary paraganglioma-pheochromocytoma syndrome, evaluation with DOTATATE PET/MRI may have specific usefulness. In patients with NF2-related schwannomatosis and suspected meningioma based on MRI without and with IV contrast, somatostatin analog PET/CT or PET/MRI may be used to confirm the suspected diagnosis as well as for treatment planning purposes [22]. In patients with VHL disease, DOTATATE PET/CT has shown usefulness in the detection of hemangioblastomas as well as other VHL-associated non–CNS neoplasms [23].

FDG-PET/CT Brain. There is no relevant literature to support the use of FDG-PET/CT brain for screening for brain neoplasms in patients with predisposing genetic conditions.

FDG-PET/MRI Brain. There is no relevant literature to support the use of FDG-PET/MRI brain for screening for brain neoplasms in patients with predisposing genetic conditions.

Fluciclovine PET/CT Brain. There is no relevant literature to support the use of fluciclovine PET/CT brain for screening for brain neoplasms in patients with predisposing genetic conditions.

Fluciclovine PET/MRI Brain. There is no relevant literature to support the use of fluciclovine PET/MRI for screening for brain neoplasms in patients with predisposing genetic conditions.

MR Spectroscopy Head Without IV Contrast. There is no relevant literature to support the use of MRS for screening for brain neoplasms in patients with predisposing genetic conditions.

MRI Complete Spine With IV Contrast. There is no relevant literature to support the use of MRI total spine with IV contrast for screening for brain neoplasms in patients with predisposing genetic conditions.

MRI Complete Spine Without and With IV Contrast. MRI total spine without and with IV contrast is a useful tool for screening for neoplasms in patients with predisposing genetic conditions when MRI of the neuraxis is recommended, typically with a frequency of 1 to 3 years [21]. For example, in NF2-related schwannomatosis, spinal nerve sheath tumors, meningiomas, and ependymomas can all occur, which justify surveillance spinal MRI without and with IV contrast every 2 to 3

years beginning at age 10 years (with option to begin at an earlier age in patients with high-risk genotypes) [24]. The superior soft tissue resolution of MRI and added detail from IV contrast justify its use for spinal screening in the appropriate clinical context.

MRI Complete Spine Without IV Contrast. There is no relevant literature to support the use of MRI total spine without IV contrast for screening for neoplasms in patients with predisposing genetic conditions, given the preference for IV gadolinium-based contrast to characterize spinal neoplasms.

MRI Functional (fMRI) Head Without IV Contrast. There is no relevant literature to support the use of fMRI for screening for brain neoplasms in patients with predisposing genetic conditions.

MRI Head Perfusion With IV Contrast. There is no relevant literature to support the use of MR perfusion with IV contrast for screening for brain neoplasms in patients with predisposing genetic conditions.

MRI Head Perfusion Without IV Contrast. There is no relevant literature to support the use of MR perfusion without IV contrast for screening for brain neoplasms in patients with predisposing genetic conditions.

MRI Head With IV Contrast. There is no relevant literature to support the use of MRI head with IV contrast for screening for brain neoplasms in patients with predisposing genetic conditions.

MRI Head Without and With IV Contrast. MRI brain without and with IV contrast is an appropriate means of screening for neoplasms in patients with predisposing genetic conditions, particularly at the time of initial diagnosis. Follow-up intervals are determined by syndrome specific guidelines; thus, for Li-Fraumeni syndrome, annual screening is recommended [25]. For NF2-related schwannomatosis, IV contrast is helpful for delineation of meningiomas, schwannomas, and ependymomas. In patients with known NF2-related schwannomatosis, surveillance MRI of the brain without and with IV contrast is recommended annually, starting at age 10 years (earlier in patients with high-risk genotypes), with the option to reduce frequency to every 2 to 3 years in the absence of characteristic sites of involvement at baseline [24].

MRI Head Without IV Contrast. When screening for primary brain tumor in asymptomatic patient with genetic risk factors, MRI remains the most sensitive modality. IV contrast administration is preferred for optimal tumor sensitivity, particularly at the time of initial diagnosis; subsequent annual screening MRI can be performed without IV contrast as long as there are no new abnormalities [25,26]. For certain syndromes, characteristic lesions can be visualized without IV contrast, such as neurofibromas, osseous dysplasias such as sphenoid wing dysplasia, and enlargement of neural foramina in the case of NF1. However, IV contrast is recommended for screening for primary glial neoplasms.

MRI Head Without IV Contrast With DTI. There is no relevant literature to support the use of DTI MRI for screening for brain neoplasms in patients with predisposing genetic conditions.

Variant 2: Adult. Secondary or metastatic brain tumor screening. Extracranial malignancy

Patients with primary systemic malignancies are at risk for brain metastases. Treatment of brain metastases depends on number and size of individual lesions, in addition to location and systemic disease burden; thus, early diagnosis of brain metastases is paramount. The National Comprehensive Cancer Network consensus guidelines recommend screening with MRI of the brain (without and with IV contrast) for patients with stage II-IV non–small-cell lung cancer, small-cell lung cancer of any stage, and stage IIIC-IV melanoma, given the propensity of these neoplasms to metastasize to the brain [27]. Although there is no specific consensus recommendation for patients with breast cancer, screening with MRI may also be useful in this population. MRI without and with IV contrast is the overall study of choice in this clinical scenario, with both FDG and amino acid PET exhibiting significant limitations with regard to specificity and resolution [28].

CT Head With IV Contrast. There is no relevant literature to support the use of CT head with IV contrast for screening for brain metastases in asymptomatic patients with extracranial malignancy.

CT Head Without and With IV Contrast. There is no relevant literature to support the use of CT head without and with IV contrast for screening for brain metastases in asymptomatic patients with extracranial malignancy.

CT Head Without IV Contrast. There is no relevant literature to support the use of CT head without IV contrast for screening for brain metastases in asymptomatic patients with extracranial malignancy. CT without and with IV contrast may be considered.

DOTATATE PET/CT Brain. DOTATATE PET/CT brain is usually not useful for screening for brain metastases in asymptomatic patients with extracranial malignancy. Should a dural-based enhancing mass be identified on screening MRI without and with IV contrast, and

differential considerations include meningioma versus dural-based metastasis, further evaluation with somatostatin analog PET/CT or PET/MRI may be useful to increase diagnostic certainty. Furthermore, somatostatin analog PET/CT or PET/MRI can be helpful in disease extent evaluation and planning of radionuclide therapy in patients with intracranial metastases from SSTR2-positive tumors such as esthesioneuroblastoma [11].

DOTATATE PET/MRI Brain. Somatostatin analog PET/MRI is usually not useful for screening for brain metastases in asymptomatic patients with extracranial malignancy. Should a dural-based enhancing mass be identified on screening MRI without and with IV contrast, and differential considerations include meningioma versus dural-based metastasis, further evaluation with somatostatin analog PET/CT or PET/MRI may be useful to increase diagnostic certainty. Furthermore, somatostatin analog PET/CT or PET/MRI can be helpful in disease extent evaluation and planning of radionuclide therapy in patients with intracranial metastases from SSTR2-positive tumors such as esthesioneuroblastoma [11].

FDG-PET/CT Brain. There is no relevant literature to support the use of FDG-PET/CT for screening for brain metastases in asymptomatic patients with extracranial malignancy.

FDG-PET/MRI Brain. There is no relevant literature to support the use of FDG-PET/MRI for screening for brain metastases in asymptomatic patients with extracranial malignancy.

Fluciclovine PET/CT Brain. There is no relevant literature to support the use of fluciclovine PET/CT brain for screening for brain metastases in asymptomatic patients with extracranial malignancy.

Fluciclovine PET/MRI Brain. There is no relevant literature to support the use of fluciclovine PET/MRI brain for screening for brain metastases in asymptomatic patients with extracranial malignancy.

MR Spectroscopy Head Without IV Contrast. There is no relevant literature to support the use of MRS for screening for brain metastases in asymptomatic patients with extracranial malignancy.

MRI Complete Spine With IV Contrast. MRI complete spine with IV contrast is usually not useful for screening for brain metastases in asymptomatic patients with extracranial malignancy.

MRI Complete Spine Without and With IV Contrast. MRI total spine without and with IV contrast is a useful tool used in screening for metastases along the neuraxis in patients with known diagnosis of extracranial malignancy. The superior soft tissue resolution of MRI and added detail from IV contrast justify its use for spinal screening in the appropriate clinical context.

MRI Complete Spine Without IV Contrast. There is no relevant literature to support the use of MRI complete spine without IV contrast for screening for metastases in asymptomatic patients with extracranial malignancy.

MRI Functional (fMRI) Head Without IV Contrast. fMRI is usually not useful for screening for brain metastases in asymptomatic patients with extracranial malignancy.

MRI Head Perfusion With IV Contrast. MRI head perfusion with IV contrast is usually not useful for screening for brain metastases in asymptomatic patients with extracranial malignancy.

MRI Head Perfusion Without IV Contrast. MRI head perfusion without IV contrast is usually not useful for screening for brain metastases in asymptomatic patients with extracranial malignancy.

MRI Head With IV Contrast. MRI head with IV contrast is usually not useful for screening for brain metastases in asymptomatic patients with extracranial malignancy.

MRI Head Without and With IV Contrast. MRI brain without and with IV contrast is a sensitive tool for screening for brain metastases in asymptomatic patients with extracranial malignancy [29,30]. Three-dimensional high-resolution pre- and postcontrast T1 and postcontrast T2 fluid-attenuated inversion recovery (FLAIR) imaging is important to facilitate early detection of small parenchymal, dural-based, and leptomeningeal metastases and can ensure optimized management including stereotactic radiosurgery as well as careful selection of appropriate systemic therapies [31]. Parenchymal metastases are most common and characteristically occur at the gray–white matter junction. Approximately 80% of brain metastases occur in the supratentorial brain [30]. The posterior fossa is more commonly involved in cases of metastases from gynecological and gastrointestinal primary malignancy [32]. Brain metastases can also involve the skull, dura and leptomeninges, pituitary gland and stalk, and the choroid plexus [29].

MRI Head Without IV Contrast. MRI brain without IV contrast may demonstrate vasogenic edema and mass effect often associated with metastases [29,30]. Whereas discrete lesions can often be directly visualized, IV contrast is typically preferred for improved delineation of intraaxial and extraaxial (leptomeningeal and/or dural-based) lesions [29,30].

MRI Head Without IV Contrast With DTI. DTI MRI is usually not useful for screening for screening for brain metastases in asymptomatic patients with extracranial malignancy.

Variant 3: Adult. Suspected intraaxial brain tumor based on prior imaging. Pretreatment evaluation

Intraaxial brain tumors include primary neoplasms and metastatic disease. Glioblastoma is the most common primary malignant brain neoplasm and portends a poor prognosis. Optimized imaging at diagnosis is critical, particularly because the clinical presentation is variable depending on tumor location and size and because of the importance of imaging in maximizing diagnostic accuracy in differentiating intraaxial brain tumor from other etiologies such as ischemia and inflammatory/infectious processes. Patients may initially present with stroke-like symptoms, seizures, or cognitive impairment and may thus undergo noncontrast CT as their initial evaluation. MRI offers excellent spatial resolution and tissue contrast and is critical at the time of diagnosis to ensure accurate delineation of tumor extent, extent of tissue involvement, and associated mass effect, as well as for preoperative stratification into high- versus low-grade glioma (noting that contrast enhancement does not have to correlate with World Health Organization (WHO) grade because high-grade tumors can show minimal enhancement and certain low-grade tumors can be avidly enhancing) [33]. Vascular imaging may be appropriate to better delineate tumor relationship to arterial and/or venous vessels (for example, invasion of dural venous sinuses by meningioma represents a common surgical planning challenge). Advanced imaging using perfusion MRI and MRS may help narrowing the differential diagnosis in the preoperative setting for intraaxial tumors. DTI and fMRI may be helpful for surgical planning in cases in which tumor involves eloquent brain regions. Although FDG-PET is of limited usefulness in pretreatment planning for intraaxial brain tumors, it can be helpful in the posttreatment evaluation of residual or recurrent tumor (Variant 6). AA-PET and DOTATATE PET are emerging tools used for diagnosis and treatment planning for glioblastoma and meningioma, respectively. AA-PET radiotracers have shown promise in the evaluation of primary and secondary intraaxial tumors in the posttreatment setting; however, at present are not clinically applied at the time of initial diagnosis. For the purposes of this clinical scenario, patients already may have some form of prior imaging (eg, CT performed at initial presentation due to neurologic deficits or other clinical symptoms based on lesion location). The below discussion reviews the usefulness of different imaging modalities in the preoperative/pretreatment setting for optimization of further management.

CT Head With IV Contrast. There is no relevant literature to support the use of CT head with IV contrast for pretreatment evaluation for suspected intraaxial brain tumor based on prior imaging. CT without and with IV contrast may be considered for this clinical scenario.

CT Head Without and With IV Contrast. There is no relevant literature to support the use of CT head without and with IV contrast for pretreatment evaluation for suspected intraaxial brain tumor based on prior imaging.

CT Head Without IV Contrast. There is no relevant literature to support the use of CT head without IV contrast for pretreatment evaluation for suspected intraaxial brain tumor based on prior imaging. CT without and with IV contrast may also be considered.

DOTATATE PET/CT Brain. Somatostatin analog PET/CT has no specific application in the pretreatment evaluation for suspected intraaxial brain tumor. Should a mass with MRI features suggestive of hemangioblastoma or medulloblastoma be identified, further evaluation with somatostatin analog PET/CT or PET/MRI may increase diagnostic certainty, although no systematic studies have been performed evaluating the usefulness of DOTATATE PET in these patient populations [34].

DOTATATE PET/MRI Brain. Somatostatin analog PET/MRI has no specific application in the pretreatment evaluation for suspected intraaxial brain tumor. Should a mass with MRI features suggestive of hemangioblastoma or medulloblastoma be identified, further evaluation with somatostatin analog PET/CT or PET/MRI may increase diagnostic certainty, although no systematic studies have been performed evaluating the usefulness of DOTATATE PET in these patient populations [34].

FDG-PET/CT Brain. FDG-PET/CT has significant limitations particularly in the pretreatment evaluation for suspected intraaxial brain tumor based on prior imaging, given high physiologic FDG-avidity in the cortex and deep gray nuclei. There are at present no definite diagnostic thresholds available for accurate differentiation of tumor grade by FDG-PET—typically, low-grade gliomas—have uptake similar to or less than normal white matter (although some low-grade gliomas such as pilocytic astrocytomas have high FDG-avidity), whereas grade 3 and 4 gliomas typically have FDG uptake greater than that of normal white matter; furthermore, many nonneoplastic conditions such as acute inflammatory or infectious processes can result in increased FDG-avidity [35]. An emerging research avenue that may increase diagnostic accuracy of preoperative FDG-PET in the future is PET radiomics analysis, in which a recent study demonstrated the potential of FDG-PET radiomics

signatures to predict methyltransferase (MGMT) promoter methylation status in glioma [36].

FDG-PET/MRI Brain. FDG-PET/MRI has significant limitations particularly in the pretreatment evaluation for suspected intraaxial brain tumor based on prior imaging, given high physiologic FDG-avidity in the cortex and deep gray nuclei. There are at present no definite diagnostic thresholds available for accurate differentiation of tumor grade by FDG-PET—typically, low-grade gliomas—have uptake similar to or less than normal white matter (although some low-grade gliomas such as pilocytic astrocytomas have high FDG-avidity), whereas grade 3 and 4 gliomas typically have FDG uptake greater than that of normal white matter; furthermore, many nonneoplastic conditions such as acute inflammatory or infectious processes can result in increased FDG-avidity [35]. An emerging research avenue that may increase diagnostic accuracy of preoperative FDG-PET in the future is PET radiomics analysis, in which a recent study demonstrated the potential of FDG-PET radiomics signatures to predict MGMT promoter methylation status in glioma [36].

Fluciclovine PET/CT Brain. AA-PET/CT has a specific application at primary diagnosis in guiding operative planning. Per most recent European Association of Nuclear Medicine (EANM), the Society of Nuclear Medicine and Molecular Imaging (SNMMI), the European Association of Neuro-oncology (EANO), and the working group for Response Assessment in Neurooncology with PET (PET-RANO) practice guideline, a negative F18-fluoroethyltyrosine (FET)/C11-methionine (MET)/FDOPA PET at diagnosis (uptake in the background range or slightly above) exclude a WHO grade 3 and 4 glioma, lymphoma, and metastasis with high probability, although a low-grade glioma cannot be definitively excluded [35]. FET-PET has shown usefulness in delineating nonenhancing tumor component for radiation planning purposes in patients with glioblastoma [37]. Although at present fluciclovine and FDOPA are clinically approved in the United States, emerging data demonstrating clinical usefulness of fluciclovine in the postsurgical/postradiation setting raise the possibility of an indication expansion in the near future [8,9].

Fluciclovine PET/MRI Brain. AA-PET/MRI has a specific application at primary diagnosis in guiding operative planning. Per most recent EANM/EANO/SNMMI/RANO practice guideline, a negative FET/MET/FDOPA PET at diagnosis (uptake in the background range or slightly above) exclude a WHO grade 3 and 4 glioma, lymphoma, and metastasis with high probability, although a low-grade glioma cannot be definitively excluded [35]. FET-PET has shown usefulness in delineating nonenhancing tumor component for radiation planning purposes in patients with glioblastoma [37]. Although at present fluciclovine and FDOPA are clinically approved in the United States, emerging data demonstrating clinical usefulness of fluciclovine in the postsurgical/postradiation setting raise the possibility of an indication expansion in the near future [8,9].

MR Spectroscopy Head Without IV Contrast. Hydrogen (proton) MRS can noninvasively visualize the biochemical tissue composition in vivo and has been applied to help identify and diagnose intracranial tumors [38]. Therefore, MRS is an adjunct tool in the pretreatment evaluation for suspected intraaxial brain tumor. Significant heterogeneity in protocols across institutions exists. MRS allows measurement of brain metabolite levels, including N-Acetyl-aspartate (NAA), a marker of neuronal integrity, total choline, a marker of neoplastic proliferation, total creatine, an energy metabolite that may vary based on tumor type and grade, lactate, the end-product of glycolytic metabolism, and lipid, a marker of necrosis. MRS may increase diagnostic certainty in cases in which low-grade glioma is a differential diagnostic consideration along with nonneoplastic conditions such as chronic inflammatory demyelination. Ratios of metabolite peak areas are typically reported, and gliomas have shown increased total Cho/NAA and total Cho/Cr ratios compared with contralateral control [39]. This approach allows differentiating high- and low-grade glioma with an accuracy of 87% according to a meta-analysis incorporating 30 publications [40].

More recently, 2-hydroxyglutarate-MRS has shown promise as a noninvasive means of determining isocitrate dehydrogenase (IDH) status; however, more evidence is needed to facilitate wider clinical translation; furthermore, the complex postprocessing involved may limit more widespread availability in the near term [41].

MRI Complete Spine With IV Contrast. MRI complete spine with IV contrast is usually not useful for pretreatment evaluation for suspected intraaxial brain tumor based on prior imaging.

MRI Complete Spine Without and With IV Contrast. MRI total spine without and with IV contrast is a useful tool in specific scenarios such as suspected primary neoplasm with ependymal or leptomeningeal involvement. The superior soft tissue resolution of MRI and added detail from IV contrast justify its use for spinal screening in the appropriate clinical context.

MRI Complete Spine Without IV Contrast. MRI complete spine without IV contrast is usually not useful for pretreatment evaluation for suspected intraaxial brain tumor based on prior imaging.

MRI Functional (fMRI) Head Without IV Contrast. fMRI is an adjunct tool in the pretreatment evaluation for suspected intraaxial brain tumor and can be performed as task-based fMRI, in which paradigms are applied to generate activation of specific networks in the brain, and resting-state fMRI, which does not depend on patient performance and can be performed while the patient is under anesthesia [42]. Clinical scenarios in which fMRI may be particularly useful include the need to map expressive language task based on tumor location, in which the highest specificity was found [43]. A recent meta-analysis pooling 10 studies with a total of 214 patients found a sensitivity of 44% and specificity of 80% (validated with direct cortical stimulation) [43]. A systematic review focused on language mapping found sensitivity and specificity of 44% and 80%, respectively, on a per-patient basis [43]. Overall accuracy of fMRI is thus moderate, and there is considerable heterogeneity in protocols across institutions. Another recent systematic review and meta-analysis found that patients in whom preoperative fMRI was used had higher postoperative Karnofsky performance scores and were less likely to experience postoperative morbidities [4].

MRI Head Perfusion With IV Contrast. MR perfusion is an adjunct tool in the pretreatment evaluation for suspected intraaxial brain tumor based on prior imaging, often used to increase diagnostic certainty prior to obtaining pathology confirmation. For example, one study combined ASL and DCE MRI to differentiate primary CNS lymphoma from high-grade glioma and brain metastases [44]. Another study demonstrated usefulness of percentage signal recovery, a DSC-MRI derived metric, in differentiating glioblastoma, lymphoma, metastasis, and meningioma [45]. In the pediatric population, preoperative DSC-MRI demonstrated a sensitivity of 100% in differentiating high-grade and low-grade gliomas, superior to that of conventional MRI alone [46]. Similarly, in adult gliomas, preoperative DSC-MRI was useful in survival prediction and optimization of biopsy targeting [47]. Moreover, DSC-MRI–derived rCBV predicted improved overall survival in patients with newly diagnosed glioblastoma who were treated with bevacizumab on the Radiation Therapy Oncology Group (RTOG) 0825 trial (a phase III trial of standard therapy with bevacizumab or without [placebo] in newly diagnosed glioblastoma) and evaluated with perfusion MRI on the American College of Radiology Imaging Network (ACRIN) trial 6686 [48]. A recent study in 216 adult patients with diffusion glioma found that, in combination with apparent diffusion coefficient histogram analysis and MRS, DSC-MRI had a high diagnostic accuracy in predicting key molecular markers such as IDH mutation and 1p19q deletion status [49]. In secondary brain neoplasms, perfusion imaging also may support prediction of key tumor biomarkers; for example, a DSC-MRI–based study found that rCBV can help preoperatively determine HER2 status in patients with suspected breast cancer brain metastases [50]. There is further emerging evidence that deep-learning assisted approaches can be translated to allow MR perfusion-based survival prediction in glioblastoma [51].

MRI Head Perfusion Without IV Contrast. MR perfusion is an adjunct tool in the pretreatment evaluation for suspected intraaxial brain tumor based on prior imaging, often used to increase diagnostic certainty prior to obtaining pathology confirmation. For example, one study combined ASL and DCE MRI to differentiate primary CNS lymphoma from high-grade glioma and brain metastases [44]. Another study demonstrated usefulness of percentage signal recovery, a DSC-MRI–derived metric, in differentiating glioblastoma, lymphoma, metastasis, and meningioma [45]. In the pediatric population, preoperative DSC-MRI demonstrated a sensitivity of 100% in differentiating high-grade and low-grade gliomas, superior to that of conventional MRI alone [46]. Similarly, in adult gliomas, preoperative DSC-MRI was useful in survival prediction and optimization of biopsy targeting [47]. Moreover, DSC-MRI–derived rCBV predicted improved overall survival in patients with newly diagnosed glioblastoma who were treated with bevacizumab on the RTOG 0825 trial (a phase III trial of standard therapy with bevacizumab or without [placebo] in newly diagnosed glioblastoma) and evaluated with perfusion MRI on the ACRIN trial 6686 [48]. A recent study in 216 adult patients with diffusion glioma found that, in combination with apparent diffusion coefficient histogram analysis and MRS, DSC-MRI had high diagnostic accuracy in predicting key molecular markers such as IDH mutation and 1p19q deletion status [49]. In secondary brain neoplasms, perfusion imaging also may support prediction of key tumor biomarkers; for example, a DSC-MRI–based study found that rCBV can help preoperatively determine HER2 status in patients with suspected breast cancer brain metastases [50]. There is further emerging evidence that deep-learning assisted approaches can be translated to allow MR perfusion-based survival prediction in glioblastoma [51].

MRI Head With IV Contrast. MRI head with IV contrast is usually not useful for pretreatment evaluation for suspected intraaxial brain tumor based on prior imaging.

MRI Head Without and With IV Contrast. MRI brain without and with IV contrast is the standard of care for pretreatment evaluation for suspected intraaxial brain tumor based on prior imaging, demonstrating higher sensitivity and specificity compared with noncontrast CT [52]. MRI brain

without and with IV contrast is critical for surgical and radiation treatment planning due to its excellent soft tissue contrast and high spatial resolution [53]. Contrast enhancement in an intraaxial brain tumor indicates breakdown of the blood–brain barrier, and in conjunction with the tumor location and enhancement pattern can provide important insights into the differential diagnosis [33]. Standardization for MRI acquisition protocols is critical, especially for enrollment in multicenter clinical trials. Consensus recommendations for a standardized BTIP have been put forth, which include high-resolution 3D T1 pre- and postcontrast imaging, axial 2D T2 FLAIR, axial diffusion-weighted imaging, axial susceptibility-weighted imaging (SWI), and axial T2 [54]. Postcontrast 3D T2 FLAIR imaging can aid in the delineation of leptomeningeal metastases, a rare but important occurrence in adult gliomas with implications for subsequent management and overall survival [55]. Building on the aforementioned BTIP, an analogous standardized MRI acquisition protocol for brain metastases has been proposed, again emphasizing the importance of standardization for enrollment in multicenter clinical trials [56].

MRI Head Without IV Contrast. MRI brain with IV contrast administration is preferred for optimal tumor delineation, both for improved delineation of intraaxial and extraaxial (leptomeningeal and/or dural-based) lesions. Noncontrast MRI sequences are helpful in this clinical context (pretreatment evaluation for suspected intraaxial brain tumor) and include DWI, which can provide an assessment of tumor cellularity, as well as tumor-associated hypoxia [33]. SWI can provide information regarding presence of intratumoral blood products and mineralization [33]. In suspected low-grade gliomas, noncontrast MRI allows for assessment of the T2-FLAIR mismatch sign, an imaging biomarker of IDH-mutant, 1p/19q non–co-deleted low-grade glioma [57,58]. Although the T2-FLAIR mismatch can be a helpful biomarker, considerable heterogeneity exists in its diagnostic performance across studies [57]. Notably, a recent consortium study evaluating WHO grade 4 gliomas demonstrated significant association between partial T2-FLAIR mismatch and presence of IDH mutation [59].

MRI Head Without IV Contrast With DTI. DTI MRI is an adjunct tool in the pretreatment evaluation for suspected intraaxial brain tumor based on prior imaging, particularly in cases of tumor involving, or in close proximity to, eloquent brain regions [3]. A systematic review assessing the effectiveness of preoperative DTI in brain tumor resection surgery has found that incorporation of DTI in preoperative planning improved postoperative neurologic deficit rate, increased resection yield (including increased rates of gross total resection), and shortened operative time [60]. Of note, advanced DTI metrics such as fractional anisotropy, kurtosis anisotropy, and restriction fraction have recently been shown to correlate with IDH genotype in gliomas and may have additional value as an adjunct modality [61]. Limitations of DTI include its limited ability to resolve multiple fibers and its susceptibility to partial volume effects [2].

Variant 4: Adult. Suspected extraaxial brain tumor based on prior imaging. Pretreatment evaluation

Meningiomas are by far the most common primary extraaxial brain tumors, with important differential diagnostic considerations including hemangiopericytomas, lymphomas, and schwannomas, as well as dural-based metastases in patients with systemic malignancies [62]. Lesion location is very important in the differential diagnosis of extraaxial tumors for lesions in the cerebellopontine angle, primary differential considerations include schwannoma, meningioma, and metastasis; along the cerebral convexities, primary considerations are meningioma, metastases, hemangiopericytoma, and lymphoma; in the pineal region, pineal tumors, germ cell tumors, metastases, and glial tumors have to be considered; differential diagnosis for intraventricular masses includes ependymoma, subependymoma, meningioma, central neurocytoma, and giant cell astrocytoma; for sellar and suprasellar masses, key differential considerations are pituitary neuroendocrine tumor, meningioma, and craniopharyngioma [63]. The possibility of dural-based or leptomeningeal metastases from unknown primary has to be considered especially in older patients [64]. For the purposes of this clinical scenario, patients already may have some form of prior imaging (eg, CT performed at initial presentation because of neurologic deficits or other clinical symptoms based on lesion location). The following discussion reviews the usefulness of different imaging modalities in the preoperative/pretreatment setting for optimization of further management.

CT Head With IV Contrast. There is no relevant literature to support the use of CT head with IV contrast for pretreatment evaluation for suspected extraaxial brain tumor based on prior imaging.

CT Head Without and With IV Contrast. There is no relevant literature to support the use of CT head without and with IV contrast for pretreatment evaluation for suspected extraaxial brain tumor based on prior imaging.

CT Head Without IV Contrast. There is no relevant literature to support the use of CT head without IV contrast for pretreatment evaluation for suspected extraaxial brain tumor based on prior imaging. However, if not previously performed, CT may be helpful in surgical planning and

differential diagnosis to determine presence of associated osseous findings such as erosion and hyperostosis. For tumors with characteristic osseous findings (such as osteolytic changes in chordomas), CT head without IV contrast provides relevant diagnostic information [63]. Presence of osseous erosions is uncommon in meningiomas should raise the possibility of alternative differential diagnostic considerations [62].

DOTATATE PET/CT Brain. Somatostatin analog PET/CT may be useful in the pretreatment evaluation for suspected extraaxial brain tumor based on prior imaging [65]. SSTR2 expression is a hallmark of meningioma, the most common primary brain tumor [66]. Normal brain tissue, as well as normal dura, does not express SSTR2, resulting in very high target to background ratio in PET imaging of meningiomas. Somatostatin analog PET/CT or PET/MRI may be helpful in the preoperative setting to confirm suspected diagnosis and for surgical planning [66], particularly in determining presence and extent of osseous invasion [67,68]. Although rare, SSTR2-negative meningioma has been described, and thus caution must be taken to interpret somatostatin analog PET in the context of other available imaging and clinical data [69].

DOTATATE PET/MRI Brain. Somatostatin analog PET/MRI may be useful in the pretreatment evaluation for suspected extraaxial brain tumor based on prior imaging [65]. SSTR2 expression is a hallmark of meningioma, the most common primary brain tumor [66]. Normal brain tissue, as well as normal dura, does not express SSTR2, resulting in very high target to background ratio in PET imaging of meningiomas. Somatostatin analog PET/CT or PET/MRI may be helpful in the preoperative setting to confirm suspected diagnosis and for surgical planning [66], particularly in determining presence and extent of osseous invasion [67,68]. Although rare, SSTR2-negative meningioma has been described, and thus caution must be taken to interpret somatostatin analog PET in the context of other available imaging and clinical data [69].

FDG-PET/CT Brain. There is no relevant literature to support the use of FDG-PET/CT brain in the pretreatment evaluation for suspected extraaxial brain tumor based on prior imaging.

FDG-PET/MRI Brain. There is no relevant literature to support the use of FDG-PET/MRI brain in the pretreatment evaluation for suspected extraaxial brain tumor based on prior imaging.

Fluciclovine PET/CT Brain. There is no relevant literature to support the use of fluciclovine PET/CT brain in the pretreatment evaluation for suspected extraaxial brain tumor based on prior imaging.

Fluciclovine PET/MRI Brain. There is no relevant literature to support the use of fluciclovine PET/MRI brain in the pretreatment evaluation for suspected extraaxial brain tumor based on prior imaging.

MR Spectroscopy Head Without IV Contrast. There is no relevant literature to support the use of MRS for pretreatment evaluation for suspected extraaxial brain tumor based on prior imaging.

MRI Complete Spine With IV Contrast. There is no relevant literature to support the use of MRI complete spine with IV contrast for pretreatment evaluation for suspected extraaxial brain tumor based on prior imaging.

MRI Complete Spine Without and With IV Contrast. MRI total spine without and with IV contrast is a useful tool for screening purposes in this patient population due to superior soft tissue resolution and added detail from IV contrast, particularly for intraventricular and ependymal tumors, lymphoma in suspected genetic syndromes such as NF1 and NF2-related schwannomatosis, and if dural-based or leptomeningeal metastasis represents a possible differential diagnostic consideration [64]. However, total spine MRI may not be needed preoperatively for suspected isolated benign extraaxial tumors such as meningioma or schwannoma.

MRI Complete Spine Without IV Contrast. There is no relevant literature to support the use of MRI complete spine without IV contrast for pretreatment evaluation for suspected extraaxial brain tumor based on prior imaging.

MRI Functional (fMRI) Head Without IV Contrast. There is limited literature to support the use of fMRI for pretreatment evaluation for suspected extraaxial brain tumor based on prior imaging. However, both fMRI and DTI can be useful in specific clinical scenarios; for example, a study in 60 patients with lateral ventricular meningiomas found a higher rate of visual field preservation and fewer cases of transient postoperative aphasia in the study group compared with the control group [70].

MRI Head Perfusion With IV Contrast. MR perfusion may be useful as an adjunct tool for pretreatment evaluation for suspected extraaxial brain tumor based on prior imaging. Meningiomas are highly vascular tumors, and ASL MRI has shown potential usefulness in noninvasive meningioma grading [71]. DCE MRI characteristics were found to correlate with DOTATATE avidity in higher-grade meningioma, which may support use of DCE MRI in this population [72].

MRI Head Perfusion Without IV Contrast. MR perfusion may be useful as an adjunct tool for pretreatment evaluation for suspected extraaxial brain tumor based on prior imaging. Meningiomas are highly vascular tumors, and ASL MRI has shown potential usefulness in noninvasive meningioma grading [71]. DCE MRI characteristics were found to correlate with DOTATATE avidity in higher-grade meningioma, which may support use of DCE MRI in this population [72].

MRI Head With IV Contrast. There is no relevant literature to support the use of MRI head with IV contrast for pretreatment evaluation for suspected extraaxial brain tumor based on prior imaging.

MRI Head Without and With IV Contrast. MRI brain without and with IV contrast is a useful tool for pretreatment evaluation for suspected extraaxial brain tumor based on prior imaging. Typical MRI features of meningiomas are homogeneous dural-based enhancement, the presence of a dural tail (tapering extension along the adjacent dura mater), and the presence of a CSF cleft between tumor and brain; intratumoral calcifications can be present in meningiomas and are visualized with SWI [62,63]. Meningiomas can often demonstrate reduced diffusion though this finding is not specific. Vasogenic edema in subjacent parenchyma can occur and can be well delineated with T2 FLAIR MRI, and more commonly coincides with specific histologic subtypes (such as angiomatous and secretory meningiomas) although does not reliably predict WHO grade [62,63]. MRI findings that should alert the interpreting radiologist to the possibility of a meningioma mimic include marked T2-hypo- or hyperintensity, absence of a dural tail, and a dural displacement sign [62,63].

MRI Head Without IV Contrast. MRI brain with IV contrast administration is preferred for optimal tumor delineation, both for improved delineation of intraaxial and extraaxial (leptomeningeal and/or dural-based) lesions. Noncontrast MRI sequences helpful in this clinical context (pretreatment evaluation for suspected extraaxial brain tumor) include DWI, which can provide an assessment of tumor cellularity, as well as tumor-associated hypoxia [33,62,63]. SWI can provide information regarding presence of intratumoral blood products and mineralization [33,62,63]. T2 FLAIR imaging can assist in determining extraaxial location by demonstrating a CSF cleft and can further demonstrate the presence of any subjacent parenchymal edema [62,63].

MRI Head Without IV Contrast With DTI. There is limited literature to support the use of DTI MRI for pretreatment evaluation for suspected extraaxial brain tumor based on prior imaging. However, both fMRI and DTI can be useful in specific clinical scenarios; for example, a study in 60 patients with lateral ventricular meningiomas found a higher rate of visual field preservation and fewer cases of transient postoperative aphasia in the study group compared to the control group [70].

Variant 5: Adult. Known history of brain tumor. Posttreatment surveillance

Posttreatment surveillance in patients with known brain tumors primarily relies on conventional MRI, the reference standard in brain tumor surveillance imaging. However, conventional MRI lacks specificity despite excellent anatomic resolution [1]. Perfusion MRI adds detail regarding tumor vascularity and blood brain barrier permeability. Incorporation of perfusion MRI in surveillance protocols has demonstrated clinical usefulness despite considerable heterogeneity among perfusion MRI acquisition and analysis protocols [6,45,48]. For glioblastomas and other high-grade gliomas, the Response Assessment in Neuro-Oncology (RANO) working group recently re-evaluated recommended surveillance intervals in relation to progression-free and overall survival in more than 1,000 patients with newly diagnosed and recurrent glioblastoma and found that a postradiotherapy MRI should serve as the baseline (rather than comparing preradiotherapy to postradiotherapy MRI). The same study found that extent of T2 FLAIR abnormalities did not correlate with outcomes and should thus not be used for response assessment [73]. The recently updated RANO Criteria for High- and Low-Grade Gliomas emphasize the importance of the postradiotherapy MRI as the "new baseline" rather than the postsurgical MRI [74]. For low-grade gliomas, surveillance with MRI without and with IV contrast (with perfusion MRI representing a helpful adjunct modality) is appropriate at longer time intervals. MRI without and with IV contrast is also useful in posttreatment surveillance in patients with brain metastases, with the interval depending on the primary neoplasm and the type of treatment the patient is receiving (systemic chemotherapy, radiation therapy, combination therapy, immunotherapy, and others). For patients with meningioma undergoing postoperative surveillance, MRI without and with IV contrast is useful and the surveillance interval depends on the WHO grade (as determined histologically based on number of mitotic figures per 10 high-power fields), as well as molecular features and postoperative management. For purposes of postoperative management, WHO grade 1 tumors typically are followed with MRI without and with IV contrast every 6 to 12 months (noting the usefulness of combined histologic and molecular profiling in optimizing the frequency of imaging follow-up), whereas WHO grade 2 and 3

tumors necessitate more frequent follow-up, especially after postoperative radiation therapy.

CT Head With IV Contrast. There is no relevant literature to support the use of CT head with IV contrast for posttreatment surveillance in patient with known history of brain tumor. CT without and with IV contrast may be considered.

CT Head Without and With IV Contrast. There is no relevant literature to support the use of CT head without and with IV contrast for posttreatment surveillance in patient with known history of brain tumor.

CT Head Without IV Contrast. There is no relevant literature to support the use of CT head without IV contrast for posttreatment surveillance in patient with known history of brain tumor. CT without and with IV contrast may be considered.

DOTATATE PET/CT Brain. DOTATATE PET/CT is usually not useful in posttreatment surveillance in patients with a known history of brain tumor. There is emerging evidence that somatostatin analog PET/CT and PET/MRI provides a more accurate delineation of resection extent and thus is a useful adjunct modality in the postoperative management of meningioma, particularly WHO grade 2 and 3 tumors, including assessment of response to radiotherapy [75]. Once gross total resection has been determined, somatostatin analog PET should be reserved for the clinical scenario of new findings on surveillance MRI (Variant 6).

DOTATATE PET/MRI Brain. DOTATATE PET/MRI is usually not useful in posttreatment surveillance in a patient with a known history of brain tumor. There is emerging evidence that somatostatin analog PET/CT and PET/MRI provides a more accurate delineation of resection extent and thus is a useful adjunct modality in the postoperative management of meningioma, particularly WHO grade 2 and 3 tumors, including assessment of response to radiotherapy [75]. Once gross total resection has been determined, somatostatin analog PET should be reserved for the clinical scenario of new findings on surveillance MRI (Variant 6).

FDG-PET/CT Brain. FDG-PET/CT is usually not useful in routine posttreatment surveillance in a patient with a known history of brain tumor. In the presence of new findings on conventional MRI (Variant 6) in patients with gliomas and brain metastases, FDG-PET/CT or FDG-PET/MRI could be considered, particularly in the postradiation setting and the presence of new or enlarging enhancement, with the purpose of differentiating disease progression from pseudoprogression and radiation necrosis, as discussed below (Variant 6).

FDG-PET/MRI Brain. FDG-PET/MRI is usually not useful in routine posttreatment surveillance in a patient with a known history of brain tumor. In the presence of new findings on conventional MRI (Variant 6) in patients with gliomas and brain metastases, FDG-PET/CT or FDG-PET/MRI could be considered, particularly in the postradiation setting and the presence of new or enlarging enhancement, with the purpose of differentiating disease progression from pseudoprogression and radiation necrosis, as discussed below (Variant 6).

Fluciclovine PET/CT Brain. Fluciclovine PET/CT brain is usually not useful in posttreatment surveillance in patients with a known history of brain tumor. In the presence of new findings on conventional MRI (Variant 6) in patients with gliomas and brain metastases, AA-PET/CT or PET/MRI, including with fluciclovine, may be considered, particularly in the postradiation setting and the presence of new or enlarging enhancement, with the purpose of differentiating disease progression from pseudoprogression and radiation necrosis, as discussed below (Variant 6).

Fluciclovine PET/MRI Brain. Fluciclovine PET/MRI brain is usually not useful in posttreatment surveillance in patients with a known history of brain tumor. In the presence of new findings on conventional MRI (Variant 6) in patients with gliomas and brain metastases, AA-PET/CT or PET/MRI, including with fluciclovine, may be considered, particularly in the postradiation setting and the presence of new or enlarging enhancement, with the purpose of differentiating disease progression from pseudoprogression and radiation necrosis, as discussed below (Variant 6).

MR Spectroscopy Head Without IV Contrast. There is no relevant literature to support the use of MRS for posttreatment surveillance in patient with known history of brain tumor.

MRI Complete Spine With IV Contrast. There is no relevant literature to support the use of MRI complete spine with IV contrast for posttreatment surveillance in patients with a known history of brain tumor.

MRI Complete Spine Without and With IV Contrast. MRI total spine without and with IV contrast may be useful for screening purposes in this patient population, if not previously completed. Total spine MRI is not needed in asymptomatic patients with resected benign extraaxial tumors such as meningioma or schwannoma. In rare cases of clinically suspected leptomeningeal dissemination from primary glial neoplasms, MRI total spine without and with IV

contrast may be helpful in evaluating for leptomeningeal disease.

MRI Complete Spine Without IV Contrast. There is no relevant literature to support the use of MRI complete spine without IV contrast for posttreatment surveillance in patient with known history of brain tumor.

MRI Functional (fMRI) Head Without IV Contrast. There is no relevant literature to support the use of fMRI for posttreatment surveillance in patients with known history of brain tumor.

MRI Head Perfusion With IV Contrast. MR perfusion may be useful as an adjunct tool for posttreatment surveillance in patients with known history of brain tumor. The standardized BTIP for both gliomas and brain metastases includes recommended MR perfusion (DSC) parameters [54,56]. Although perfusion MRI is most helpful in the presence of new findings on conventional MRI (Variant 6), the integration of perfusion MRI in posttreatment surveillance MRI protocols avoids the need to have to repeat imaging should new findings emerge on conventional surveillance imaging. For both gliomas and brain metastases, both DCE and DSC-MRI parameters have demonstrated clinical usefulness in the posttreatment surveillance setting. A meta-analysis found pooled overall sensitivity and specificity of DSC in differentiating true progression from pseudoprogression to be 90% and 88%, respectively; for DCE, pooled overall sensitivity and specificity were 89% and 85%, respectively. However, there was significant heterogeneity bias and publication bias reported in the same meta-analysis [76]. Notably, bevacizumab therapy affects DSC-MRI–derived rCBV values, which has to be considered in patients undergoing bevacizumab therapy [48].

Meningiomas are highly vascular tumors, and DCE MRI characteristics correlate with DOTATATE avidity in higher-grade meningioma, which may support the use of DCE MRI in this population [72]. ASL MRI has further shown promise in noninvasive meningioma grading [71].

MRI Head Perfusion Without IV Contrast. MR perfusion may be useful as an adjunct tool for posttreatment surveillance in patients with a known history of brain tumor. The standardized BTIP for both gliomas and brain metastases includes recommended MR perfusion (DSC) parameters [54,56]. Although perfusion MRI is most helpful in the presence of new findings on conventional MRI (Variant 6), the integration of perfusion MRI in posttreatment surveillance MRI protocols avoids the need to have to repeat imaging should new finding emerge on conventional surveillance imaging. For both gliomas and brain metastases, both DCE and DSC-MRI parameters have demonstrated clinical usefulness in the posttreatment surveillance setting. A meta-analysis found pooled overall sensitivity and specificity of DSC in differentiating true progression from pseudoprogression to be 90% and 88%, respectively; for DCE, pooled overall sensitivity and specificity were 89% and 85%, respectively. However, there was significant heterogeneity bias and publication bias reported in the same meta-analysis [76]. Notably, bevacizumab therapy affects DSC-MRI–derived rCBV values, which has to be considered in patients undergoing bevacizumab therapy [48].

Meningiomas are highly vascular tumors, and DCE MRI characteristics correlate with DOTATATE avidity in higher-grade meningioma, which may support use of DCE MRI in this population [72]. ASL MRI has further shown promise in noninvasive meningioma grading [71].

MRI Head With IV Contrast. There is no relevant literature to support the use of MRI head with IV contrast for posttreatment surveillance in patient with known history of brain tumor.

MRI Head Without and With IV Contrast. MRI brain without and with IV contrast is a useful means of posttreatment surveillance in patients with known history of brain tumor and is the modality of choice due to its excellent soft tissue contrast and high spatial resolution [53]. Contrast enhancement in an intraaxial brain tumor indicates breakdown of the blood–brain-barrier, and in conjunction with the tumor location and enhancement pattern, can provide important insights into the differential diagnosis [33]. Standardization for MRI acquisition protocols is critical especially for enrollment in multicenter clinical trials. Consensus recommendations for a standardized BTIP have been put forth, which include high-resolution 3D T1 pre- and postcontrast imaging, axial 2D T2 FLAIR, axial diffusion-weighted imaging, axial SWI, and axial T2 [54]. Postcontrast 3D T2 FLAIR imaging can aid in the delineation of leptomeningeal metastases, a rare but important occurrence in adult gliomas with implications for subsequent management and overall survival [55]. Building on the aforementioned BTIP, an analogous standardized MRI acquisition protocol for brain metastases has been proposed, again emphasizing the importance of standardization for enrollment in multicenter clinical trials [56]. For extraaxial tumors, typical MRI features of meningiomas are homogeneous dural-based enhancement, the presence of a dural tail (tapering extension along the adjacent dura matter), and the presence of a CSF cleft between tumor and brain; intratumoral calcifications can be present in meningiomas and are visualized with SWI [62,63]. Meningiomas

can often demonstrate reduced diffusion though this finding is not specific. Vasogenic edema in subjacent parenchyma can occur and can be well delineated with T2/FLAIR MRI, and more commonly coincides with specific histologic subtypes (such as angiomatous and secretory meningiomas) although does not reliably predict WHO grade [62,63]. MRI findings that should alert the interpreting radiologist to the possibility of a meningioma mimic include marked T2-hypo- or hyperintensity, absence of a dural tail, and a dural displacement sign [62,63].

MRI Head Without IV Contrast. MRI brain with IV contrast administration is preferred for optimal tumor delineation, both for improved delineation of intraaxial and extraaxial (leptomeningeal and/or dural-based) lesions. Noncontrast MRI sequences are helpful in this clinical context (posttreatment surveillance in patient with known history of brain tumor) include DWI, which can provide an assessment of tumor cellularity [54,56,62,63]. SWI can provide information regarding presence of intratumoral blood products and mineralization [62,63]. T2/FLAIR imaging in extraaxial tumors can assist in determining extraaxial location by demonstrating a CSF cleft and can further demonstrate the presence of any subjacent parenchymal edema [62,63].

MRI Head Without IV Contrast With DTI. There is no relevant literature to support the use of DTI MRI for posttreatment surveillance in patient with known history of brain tumor.

Variant 6: Adult. Known history of brain tumor. New or enlarging lesion on posttreatment surveillance. Next imaging study

MRI without and with IV contrast is the reference standard in neuro-oncologic imaging, including in the clinical context of new or enlarging lesion on posttreatment surveillance imaging. MRI can help with anatomic lesion localization and can demonstrate associated findings such as the presence of acute or chronic intralesional blood products, associated edema, and mass effect. However, diagnostic accuracy of MRI is limited in the posttreatment setting, when differentiation between progressive disease, pseudoprogression, and radiation necrosis is of paramount clinical importance.

In gliomas, progressive disease is defined as a >25% increase in size, and satisfying other RANO criteria, or a new measurable lesion (confirmed on subsequent short-interval [4 weeks]) follow-up, or clinical deterioration. Typical findings on conventional MRI without and with IV contrast include enhancing lesions crossing the midline, or localizing to outside the radiotherapy field, solid enhancement, and mass effect. Overall, sensitivity and specificity of conventional MRI is modest (68% and 77%, respectively). In the context of bevacizumab therapy, enhancement is not a reliable metric. Pseudoprogression is characterized as increasing or new enhancement occurring within 3 to 6 months following completion of radiotherapy; patients typically are doing well clinically, and MRI findings typically resolve or improve on short-interval follow-up imaging. Pathophysiologically, pseudoprogression is thought to reflect transient endothelial injury and associated inflammation. Pseudoprogression overall conveys better prognosis. The incidence of pseudoprogression is highest 12 weeks after radiotherapy completion. The recently updated RANO Criteria for High- and Low-Grade Gliomas emphasize the importance of the postradiotherapy MRI as the "new baseline" rather than the postsurgical MRI [74]. Radiation necrosis typically occurs after 6 to 12 months following radiotherapy completion (although it can occur at any time postradiotherapy) and conveys a worse prognosis. Typically, new enhancement is visualized within the radiation field, often in a periventricular distribution. In contrast to progressive disease, radiation necrosis is typically associated with heterogeneous or "frond-like" enhancement, with a central necrotic component, which typically demonstrates high T2 signal and can demonstrate restricted diffusion.

FDG-PET/CT and FDG-PET/MRI can be helpful in increasing diagnostic certainty when evaluating new or enlarging enhancing lesions in patients with glioma in the posttreatment setting. Limitations of FDG-PET include the high physiologic FDG-avidity of gray matter resulting in suboptimal target-to-background ratio, as well as the potential of increased FDG avidity in nonneoplastic etiologies such as inflammation and infection. FDG-PET demonstrated a pooled sensitivity and specificity of 77% and 78%, respectively, with a higher sensitivity and specificity in PET/MRI due to improved spatial resolution and co-registration [7]. There is a lack of standardization with regard to standardized uptake value diagnostic thresholds, with both white matter– and gray matter–specific reference thresholds having been proposed in the literature.

AA-PET radiotracers fluciclovine and FDOPA are clinically approved in the United States. There is emerging clinical evidence for usefulness of fluciclovine in the postsurgical/postradiation setting, raising the possibility of an indication expansion in the near future [8,9].

CT Head With IV Contrast. There is no relevant literature to support the use of CT head with IV contrast for the clinical scenario of a new or enlarging lesion on posttreatment surveillance in patient with known history of brain tumor.

CT Head Without and With IV Contrast. There is no relevant literature to support the use of CT head without and with IV contrast for the clinical scenario of a new or enlarging lesion on posttreatment surveillance in patient with known history of brain tumor.

CT Head Without IV Contrast. There is no relevant literature to support the use of CT head without IV contrast for the clinical scenario of a new or enlarging lesion on posttreatment surveillance in patient with known history of brain tumor. CT without and with IV contrast may be considered.

DOTATATE PET/CT Brain. Somatostatin analog PET/CT may have usefulness in the clinical scenario of a new or enlarging lesion on posttreatment surveillance in patient with known history of brain tumor, if the pathology of the original tumor was consistent with a SSTR2-positive neoplasm, the most common of which is meningioma [66]. Normal brain tissue, as well as normal dura, does not express SSTR2, resulting in very high target to background ratio in PET imaging of meningiomas. DOTATATE PET/MRI has excellent diagnostic accuracy in differentiating viable meningioma from postsurgical and post-RT change [15]. Although rare, the possibility of SSTR2-negative meningioma has to be considered, particularly if conventional MRI findings are suspicious for recurrence, thus caution must be taken to interpret somatostatin analog PET in the context of other available imaging and clinical data [69].

Other SSTR2-expressing tumors where somatostatin analog PET/CT or PET/MRI may be appropriate to differentiate progression from postradiation change include pituitary neuroendocrine tumors (pitNET, also known as pituitary adenoma), which can present a diagnostic challenge at the time of recurrence, particularly in the context of extrasellar extension, though few studies focused on this subject have been published [77]. Furthermore, there is considerable heterogeneity of reported SSTR subtype expression profiles in the literature [78]. Both medulloblastoma and hemangioblastoma express SSTR2, and further research on usefulness of somatostatin analog PET/CT or PET/MRI in these patient populations is warranted. Somatostatin analog PET/CT or PET/MRI has shown clinical usefulness in the posttreatment evaluation of SSTR2-positive skull base neoplasms such as paraganglioma and esthesioneuroblastoma [11].

DOTATATE PET/MRI Brain. Somatostatin analog PET/MRI may have usefulness in the clinical scenario of a new or enlarging lesion on posttreatment surveillance in patient with known history of brain tumor, if the pathology of the original tumor was consistent with a SSTR2-positive neoplasm, the most common of which is meningioma [66]. Normal brain tissue, as well as normal dura, does not express SSTR2, resulting in very high target to background ratio in PET imaging of meningiomas. DOTATATE PET/MRI has excellent diagnostic accuracy in differentiating viable meningioma from postsurgical and post-RT change [15]. Although rare, the possibility of SSTR2-negative meningioma has to be considered, particularly if conventional MRI findings are suspicious for recurrence, thus caution must be taken to interpret somatostatin analog PET in the context of other available imaging and clinical data [69].

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FDG-PET/CT Brain. FDG-PET/CT may be useful in this clinical scenario of a new or enlarging lesion on posttreatment surveillance in patient with known history of brain tumor. FDG-PET can demonstrate progressive or recurrent neoplasm; however, limitations include heterogeneity of FDG-avidity among different primary and secondary brain neoplasm subtypes and high physiologic FDG-avidity of normal cortex and deep gray nuclei resulting in partial volume averaging effects. Nevertheless, FDG-PET/CT was shown to have pooled sensitivity and specificity of 77% and 78%, respectively [76], with a higher sensitivity and specificity in PET/MRI because of improved spatial resolution and co-registration [7]. There are at present no definite diagnostic thresholds available for accurate differentiation of tumor grade by FDG-PET; typically, low-grade gliomas have uptake similar to or less than normal white matter (although some low-grade gliomas such as pilocytic astrocytomas typically have high FDG-avidity), whereas grade 3/4 gliomas typically have FDG uptake greater than that of normal white matter; furthermore, many nonneoplastic conditions such as acute inflammatory or infectious processes can result in increased FDG-avidity [35].

FDG-PET/MRI Brain. FDG-PET/MRI may be useful in this clinical scenario of a new or enlarging lesion on

posttreatment surveillance in patients with a known history of brain tumor. FDG-PET can demonstrate progressive or recurrent neoplasm; however, limitations include heterogeneity of FDG-avidity among different primary and secondary brain neoplasm subtypes and high physiologic FDG-avidity of normal cortex and deep gray nuclei resulting in partial volume averaging effects. Nevertheless, FDG-PET/CT was shown to have a pooled sensitivity and specificity of 77% and 78%, respectively [76], with a higher sensitivity and specificity in PET/MRI due to improved spatial resolution and co-registration [7]. There are at present no definite diagnostic thresholds available for accurate differentiation of tumor grade by FDG-PET; typically, low-grade gliomas have uptake similar to or less than normal white matter (although some low-grade gliomas such as pilocytic astrocytomas typically have high FDG-avidity), whereas grade 3/4 gliomas typically have FDG uptake greater than that of normal white matter; furthermore, many nonneoplastic conditions such as acute inflammatory or infectious processes can result in increased FDG-avidity [35].

Fluciclovine PET/CT Brain. AA-PET/CT, for example, with fluciclovine, may have usefulness in the clinical scenario of a new or enlarging lesion on posttreatment surveillance in patients with a known history of brain tumor. FET-PET has shown promise in differentiating progression from pseudoprogression in high-grade glioma and is in wide clinical use in Europe, though not currently clinically approved in the United States. Fluciclovine is approved in the United States for use in metastatic prostate cancer and has shown promise in the evaluation of primary brain neoplasms, including both high- and low-grade gliomas [10]. Caveats include the possibility of mild amino acid tracer activity related to nonneoplastic conditions such as acute/subacute ischemia, inflammatory/infectious process, or status epilepticus [10]. Additionally, up to 30% of IDH-mutated low-grade gliomas do not demonstrate significant AA-PET avidity [79].

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MR Spectroscopy Head Without IV Contrast. MRS may be useful in the clinical scenario of a new or enlarging lesion on posttreatment surveillance in a patient with a known history of brain tumor. A systematic review and meta-analysis demonstrated high sensitivity and specificity of MRS in this clinical context, 91% (95% confidence interval [CI], 79%-97%) and 95% (95% CI, 65%-99%), respectively, which was highest in this study compared to other advanced MRI based modalities [1].

MRI Complete Spine With IV Contrast. There is no relevant literature to support the use of MRI complete spine with IV contrast in the clinical scenario of a new or enlarging lesion on posttreatment surveillance in a patient with a known history of brain tumor.

MRI Complete Spine Without and With IV Contrast. There is no relevant literature to support the use of MRI complete spine without and with IV contrast in the clinical scenario of a new or enlarging lesion on posttreatment surveillance in a patient with a known history of brain tumor.

MRI Complete Spine Without IV Contrast. There is no relevant literature to support the use of MRI complete spine without IV contrast in the clinical scenario of a new or enlarging lesion on posttreatment surveillance in a patient with a known history of brain tumor.

MRI Functional (fMRI) Head Without IV Contrast. There is no relevant literature to support the use of fMRI for the clinical scenario of a new or enlarging lesion on posttreatment surveillance in a patient with a known history of brain tumor.

MRI Head Perfusion With IV Contrast. MR perfusion is an important adjunctive tool in the clinical scenario of a new or enlarging lesion on posttreatment surveillance in patients with a known history of brain tumor. Despite challenges of heterogeneity in acquisition protocols and in diagnostic accuracy data, a 2016 survey of almost 200 academic and private practice institutions in the United States found that 87% of survey respondents included perfusion MRI in their brain tumor MRI protocol, with DSC-MRI being the most commonly performed method of perfusion MRI, compared with DCE and ASL MRI, and with only about half of responding institutions incorporating quantitative analysis [80]. In a systematic review and meta-analysis evaluating advanced MRI technique for treatment response evaluation in high-grade glioma, DSC-MRI was found to have a sensitivity of 87% and specificity of 86% across 18 studies with 708 patients, whereas DCE MRI was found to have a sensitivity of

92% and specificity of 85% across 5 studies with 207 patients [1]. A separate meta-analysis found pooled overall sensitivity and specificity of DSC in differentiating true progression from pseudoprogression to be 90% and 88%, respectively; for DCE, pooled overall sensitivity and specificity were 89% and 85%, respectively. However, there was significant heterogeneity bias and publication bias reported in the same meta-analysis [76].

MRI Head Perfusion Without IV Contrast. MR perfusion is an important adjunctive tool in the clinical scenario of a new or enlarging lesion on posttreatment surveillance in patients with a known history of brain tumor. Despite challenges of heterogeneity in acquisition protocols and in diagnostic accuracy data, a 2016 survey of almost 200 academic and private practice institutions in the United States found that 87% of survey respondents included perfusion MRI in their brain tumor MRI protocol, with DSC-MRI being the most commonly performed method of perfusion MRI, compared with DCE and ASL MRI, and only about half of responding institutions incorporating quantitative analysis [80]. In a systematic review and meta-analysis evaluating advanced MRI technique for treatment response evaluation in high-grade glioma, DSC-MRI was found to have a sensitivity of 87% and specificity of 86% across 18 studies with 708 patients, whereas DCE MRI was found to have a sensitivity of 92% and specificity of 85% across 5 studies with 207 patients [1]. A separate meta-analysis found pooled overall sensitivity and specificity of DSC in differentiating true progression from pseudoprogression to be 90% and 88%, respectively; for DCE, pooled overall sensitivity and specificity were 89% and 85%, respectively. However, there was significant heterogeneity bias and publication bias reported in the same meta-analysis [76].

MRI Head With IV Contrast. There is no relevant literature to support the use of MRI head with IV contrast in the clinical scenario of a new or enlarging lesion on posttreatment surveillance in a patient with a known history of brain tumor.

MRI Head Without and With IV Contrast. MRI brain without and with IV contrast is a useful modality for the clinical scenario of a new or enlarging lesion on posttreatment surveillance in a patient with known history of brain tumor. Typical findings on conventional MRI without and with IV contrast include enhancing lesions crossing the midline, or localizing to outside the radiotherapy field, solid enhancement, and mass effect. Overall, sensitivity and specificity of conventional MRI is modest (68% and 77%, respectively). In the context of bevacizumab therapy, enhancement is not a reliable metric. Pseudoprogression is characterized as increasing or new enhancement occurring within 3 to 6 months following completion of radiotherapy; patients typically are doing well clinically, and MRI findings typically resolve or improve on short-interval follow-up imaging. Pathophysiologically, pseudoprogression is thought to reflect transient endothelial injury and associated inflammation. Pseudoprogression overall conveys better prognosis [74]. Radiation necrosis typically occurs after 6 to 12 months following radiotherapy completion and conveys a worse prognosis. Typically, new enhancement is visualized within the radiation field, often in a periventricular distribution. In contrast to progressive disease, radiation necrosis is typically associated with heterogeneous or "frond-like" enhancement, with a central necrotic component, which typically demonstrates high T2 signal and can demonstrate restricted diffusion.

MRI Head Without IV Contrast. MRI brain without IV contrast can demonstrate hypercellularity, intralesional hemorrhage, and infiltrative T2 hyperintense component, and thus the standardized BTIP includes precontrast T1, T2, DWI, and SWI series, all of which could be obtained on MRI brain without IV contrast. However, MRI brain without IV contrast is insufficient to adequately delineate residual or recurrent enhancing tumor. Both primary and metastatic brain tumors often recur with enhancing disease due to leaky vasculature, which is best demonstrated on postcontrast T1 imaging [54,56].

MRI Head Without IV Contrast With DTI. Literature regarding the use of DTI MRI in the clinical scenario of a new or enlarging lesion on posttreatment surveillance in patients with a known history of brain tumor is heterogeneous; therefore, at present there is insufficient data to support DTI MRI in this clinical context. Although some studies showed no change in fractional anisotropy between progressive disease and pseudoprogression [81], others showed increased fractional anisotropy in progressive disease [40].

SUMMARY OF HIGHLIGHTS

This is a summary of the key recommendations from the variant tables. Refer to the complete narrative document for more information.

- Variant 1: For primary brain tumor screening in patients with genetic risk factors, MRI of the brain without and with IV contrast is the preferred screening modality. Screening of the spine using MRI without and with IV contrast may also be appropriate depending on the clinical context.
- Variant 2: For secondary screening for brain metastases in patients with systemic malignancy, MRI of the brain without and with IV contrast is recommended. Screening of the spine using MRI without and with

IV contrast may also be appropriate depending on the clinical context.

- Variant 3: For pretreatment evaluation in patients with suspected intraaxial brain tumor based on prior imaging, MRI of the brain without and with IV contrast is recommended due to excellent spatial resolution and tissue contrast, to ensure accurate delineation of tumor extent, extent of tissue or vascular involvement and associated mass effect, as well as for preoperative differential diagnosis. For initial pretreatment evaluation, MRI head perfusion with IV contrast is also usually appropriate and MR spectroscopy may also aid in differential diagnosis. fMRI may be helpful for surgical planning in cases in which tumor involves eloquent brain regions. FDG-PET is of limited usefulness in pretreatment planning for intraaxial brain tumors. Amino acid PET (ie, fluciclovine) is an emerging tool used for diagnosis and treatment planning for glioblastoma and may be appropriate.
- Variant 4: For pretreatment evaluation in patients with suspected extraaxial brain tumor based on prior imaging, MRI without and with IV contrast is recommended. Somatostatin-analog PET (DOTATATE) may be useful in the preoperative setting to better characterize suspected meningioma before surgery or radiotherapy.
- Variant 5: Posttreatment surveillance in patients with known brain tumors relies primarily on conventional MRI, therefore MRI head without and with IV contrast and perfusion MRI with IV contrast adds detail regarding tumor vascularity and blood–brain barrier permeability and is usually appropriate. MRI total spine without and with IV contrast may be useful for screening purposes in this patient population, particularly if not previously completed. Total spine MRI is usually not appropriate in asymptomatic patients with resected benign extraaxial tumors such as meningioma or schwannoma.
- Variant 6: In patients with a known history of brain tumor and new and enlarging lesion on posttreatment surveillance imaging, MRI without and with IV contrast can help with anatomic lesion localization and can demonstrate associated findings such as the presence of acute or chronic intralesional blood products, associated edema, and mass effect. However, because the diagnostic accuracy of MRI is limited in the posttreatment setting for differentiating between progressive disease, pseudoprogression, and radiation necrosis, the addition of MRI perfusion imaging can aid in specificity. FDG-PET/CT and FDG-PET/MRI and MR spectroscopy can be helpful in increasing diagnostic certainty when evaluating new or enlarging enhancing lesions in patients with glioma in the posttreatment setting. Somatostatin analog PET/CT (DOTATATE) may have usefulness in the clinical scenario of a new or enlarging lesion on posttreatment surveillance in patients with a known history of brain tumor if the pathology of the original tumor was consistent with a SSTR2-positive neoplasm, most commonly meningioma. Amino acid PET/CT (ie, fluciclovine) is an emerging tool for differentiating progression from pseudoprogression in high-grade glioma but is not currently clinically approved in the United States for this indication.

SUPPORTING DOCUMENTS

The evidence table, literature search, and appendix for this topic are available at https://acsearch.acr.org/list. The appendix includes the strength of evidence assessment and the final rating round tabulations for each recommendation.

For additional information on the Appropriateness Criteria methodology and other supporting documents go to https://www.acr.org/Clinical-Resources/Clinical-Tools-and-Reference/Appropriateness-Criteria.

GENDER EQUALITY AND INCLUSIVITY CLAUSE

The ACR acknowledges the limitations in applying inclusive language when citing research studies that predates the use of the current understanding of language inclusive of diversity in sex, intersex, gender and gender-diverse people. The data variables regarding sex and gender used in the cited literature will not be changed. However, this guideline will use the terminology and definitions as proposed by the National Institutes of Health [82].

RELATIVE RADIATION LEVEL INFORMATION

Potential adverse health effects associated with radiation exposure are an important factor to consider when selecting the appropriate imaging procedure. Because there is a wide range of radiation exposures associated with different diagnostic procedures, a relative radiation level (RRL) indication has been included for each imaging examination. The RRLs are based on effective dose, which is a radiation dose quantity that is used to estimate population total radiation risk associated with an imaging procedure. Patients in the pediatric age group are at inherently higher risk from exposure, because of both organ sensitivity and longer life expectancy (relevant to the long latency that appears to accompany radiation exposure). For these reasons, the RRL dose estimate ranges for pediatric

examinations are lower as compared with those specified for adults (see Table 2). Additional information regarding radiation dose assessment for imaging examinations can be found in the ACR Appropriateness Criteria® Radiation Dose Assessment Introduction document [83].

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