Central Nervous System Cancers, Version 3.2020

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ABSTRACT

The NCCN Guidelines for Central Nervous System (CNS) Cancers focus on management of adult CNS cancers ranging from non-invasive and surgically curable pilocytic astrocytomas to metastatic brain disease. The involvement of an interdisciplinary team, including neurosurgeons, radiation therapists, oncologists, neurologists, and neuroradiologists, is a key factor in the appropriate management of CNS cancers. Integrated histopathologic and molecular characterization of brain tumors such as gliomas should be standard practice. This article describes NCCN Guidelines recommendations for WHO grade I, II, III, and IV gliomas. Treatment of brain metastases, the most common intracranial tumors in adults, is also described.

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NCCN CATEGORIES OF EVIDENCE AND CONSENSUS

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PLEASE NOTE

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

The complete NCCN Guidelines for Central Nervous System Cancers are not printed in this issue of *JNCCN* but can be accessed online at NCCN.org.

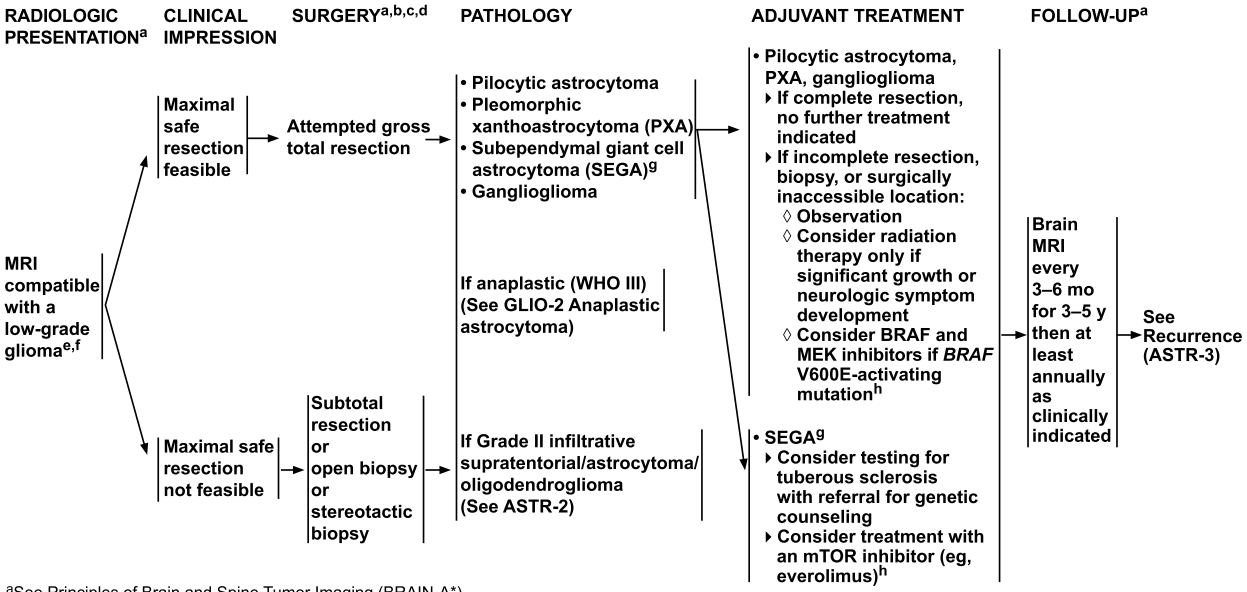
Disclosures for the NCCN Central Nervous System Cancers Panel

At the beginning of each NCCN Guidelines Panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Central Nervous System Cancers Panel members can be found on page 1570. (The most recent version of these guidelines and accompanying disclosures are available at NCCN.org.)

The complete and most recent version of these guidelines is available free of charge at NCCN.org.

Adult Low-Grade (WHO Grade I or II) Glioma/Pilocytic and Infiltrative Supratentorial Astrocytoma/Oligodendroglioma



[a]See Principles of Brain and Spine Tumor Imaging (BRAIN-A*).
[b]See Principles of Brain Tumor Surgery (BRAIN-B*).
[c]Recommended molecular diagnostics include 1p19q chromosomal status, IDH1/2 mutation status, and *BRAF* V600E mutation. See Principles of Brain Tumor Pathology (BRAIN-F*).
[d]Postoperative brain MRI within 48 hours after surgery.
[e]Consider a multidisciplinary review in treatment planning, especially once pathology is available. See Principles of Brain and Spine Tumor Management (BRAIN-E*).
[f]If radiographically the tumor appears to be a high-grade glioma, see GLIO-1.
[g]The need to treat SEGAs or other findings in the appropriate tuberous sclerosis patient population should be determined by the patient's symptoms and/or change on serial radiologic studies. Referral to a neurofibromatosis or specialty center is recommended.
[h]See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).

*Available online, in these guidelines, at NCCN.org.

ASTR-1

Overview

Primary brain tumors are a heterogeneous group of neoplasms with varied outcomes and management strategies. Primary malignant brain tumors range from pilocytic astrocytomas, which are very uncommon, noninvasive, and surgically curable, to glioblastoma, the most common malignant brain tumor in adults, which is highly invasive and virtually incurable. Likewise, patients with metastatic brain disease may have rapidly progressive systemic disease or no systemic cancer at all. These patients may have one or many brain metastases, and they may have a malignancy that is highly responsive or, alternatively, highly resistant to radiation therapy (RT) or chemotherapy. Because of this marked heterogeneity, the prognostic features and treatment options for primary and metastatic brain tumors must be carefully reviewed on an individual basis and sensitively communicated to each patient. In addition, central nervous system (CNS) tumors are associated with a range of symptoms such as seizures, fatigue, impaired short term memory, changes in cognition or behavior (particularly anxiety and depression), impaired mobility, impairment of speech and comprehension, and visual impairment, as well as complications such as intracerebral edema, infections, endocrinopathies, and venous thromboembolism that can seriously impact patients' quality of life.

Gliomas

The NCCN Guidelines for CNS Cancers include recommendations for management of the following gliomas[1]:

- Grade I: pilocytic astrocytoma, pleomorphic xanthoastrocytoma, ganglioglioma, subependymal giant cell astrocytoma
- Grade II: diffuse astrocytoma and oligodendroglioma
- Grade III: anaplastic astrocytoma and oligodendroglioma
- Grade IV: glioblastoma

Molecular Profiling for Gliomas

Integrated histopathologic and molecular characterization of gliomas should be standard practice. Molecular/genetic characterization complements standard histologic analysis, providing additional diagnostic and prognostic

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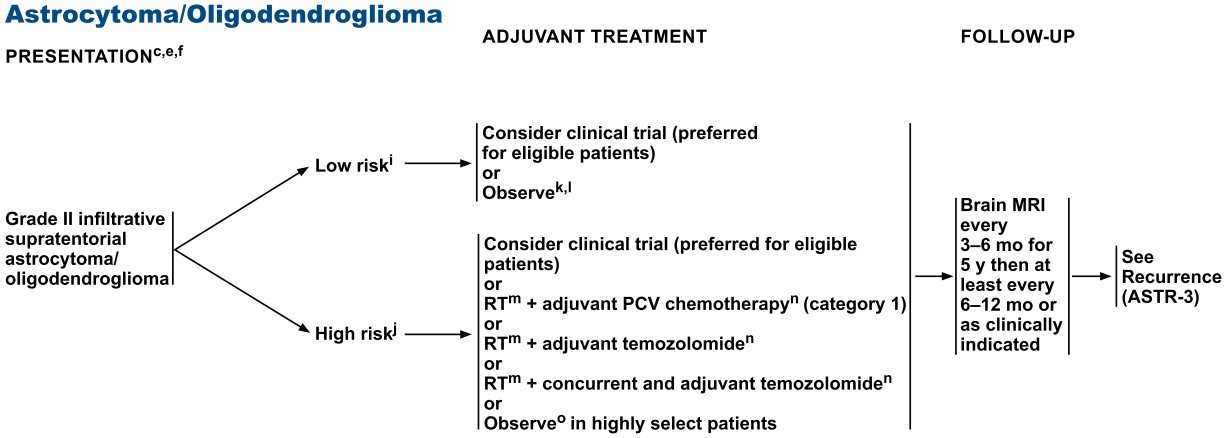

[c]Recommended molecular diagnostics include 1p19q chromosomal status, IDH1/2 mutation status, and *BRAF* V600E mutation. See Principles of Brain Tumor Pathology (BRAIN-F*).
[e]Consider a multidisciplinary review in treatment planning, especially once pathology is available. See Principles of Brain and Spine Tumor Management (BRAIN-E*).
[f]If radiographically the tumor appears to be a high-grade glioma, see GLIO-1.
[i]Low-risk features: ≤40 y and gross total resection (GTR).
[j]High-risk features: >40 y or subtotal resection (STR) or open or stereotactic biopsy. Other high-risk factors that are sometimes taken into consideration are tumor size, neurologic deficits, and presence of sequencing verified IDH wild type.
[k]Regular follow-up is essential for patients receiving observation alone after resection.
[l]In the event that other risk factors are considered and treatment is warranted, treat as high risk. There may also be rare circumstances in which treating a patient with fractionated external beam RT alone (category 2B) or chemotherapy alone (category 2B) may be considered. See Principles of Brain and Spinal Cord Tumor Radiation (BRAIN-C*) or Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).
[m]For low-grade gliomas, See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C*).
[n]See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).
[o]The results of RTOG 9802 showed that there was a significant improvement in median overall survival in high-risk low-grade glioma patients treated with RT followed by PCV x 6 cycles compared with RT alone after a tissue diagnosis was made. However, this important study did not address whether all of these patients should be treated right away. Observation after diagnosis may be a reasonable option for a high-risk low-grade glioma patient who is neurologically asymptomatic or stable. Close monitoring with brain MRIs is important.

*Available online, in these guidelines, at NCCN.org.

ASTR-2

information that improves diagnostic accuracy and aids in treatment selection.

Updated Classification of Gliomas Based on Histology and Molecular Features

In 2016, the WHO classification for grade II–III gliomas was revised as follows: (1) oligodendrogliomas are now defined as tumors that have 1p19q codeletion and *IDH* mutation (unless molecular data are not available and cannot be obtained, in which case designation can be based on histology with appropriate caveats); (2) anaplastic gliomas were further subdivided according to *IDH* mutation status; (3) oligoastrocytoma is no longer a valid designation unless molecular data (1p19q codeletion and *IDH* mutation status) are not available and cannot be obtained.[1] Such tumors should be described as "oligoastrocytoma, not otherwise specified (NOS)" to indicate that the characterization of the tumor is incomplete. Very rare cases of concurrent, spatially distinct oligodendroglioma (1p19q codeleted) and astrocytoma (1p19q intact) components in the same tumor may also be labeled oligoastrocytoma.[1] It is important to note that correlations between the molecularly defined 2016 WHO categories and the histology-based 2007 WHO categories are limited and vary across studies.[2–5] Thus, the change from 2007 WHO to 2016 WHO reclassified a significant proportion of gliomas.

Multiple independent studies on gliomas have conducted genome-wide analyses evaluating an array of molecular features (eg, DNA copy number, DNA methylation, protein expression) in large populations of patients with grade II–IV tumors.[4,6,7] Unsupervised clustering analyses, an unbiased method for identifying molecularly similar tumors, have been used to identify subgroups of gliomas with distinct molecular profiles.[4,6,7] Remarkably, further analysis has shown that these molecular subgroups could be distinguished based on only a handful of molecular features, including mutation of *IDH1/2* and 1p19q codeletion, biomarkers independently verified by many studies as hallmarks for distinguishing molecular subgroups in grade II–III gliomas.[2–5,7–13] Using these markers alone, the majority of grade II–III tumors can be divided into 3 molecular subtypes: (1) mutation of either

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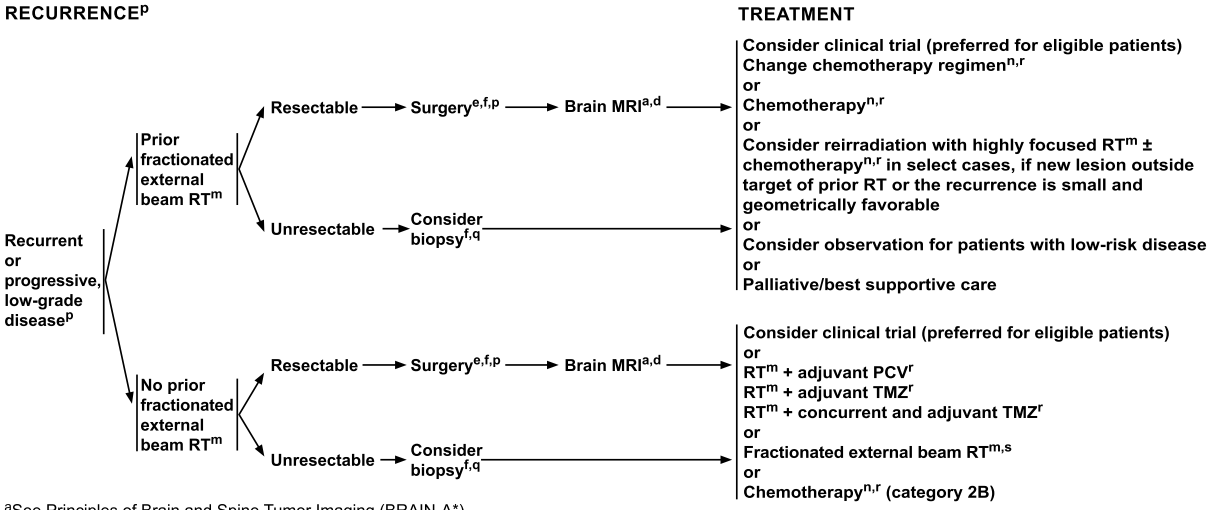


[a]See Principles of Brain and Spine Tumor Imaging (BRAIN-A*).
[d]Postoperative brain MRI within 48 hours after surgery.
[e]Consider a multidisciplinary review in treatment planning, especially once pathology is available. See Principles of Brain and Spine Tumor Management (BRAIN-E*).
[f]If radiographically the tumor appears to be a high-grade glioma, see GLIO-1.
[m]For low-grade gliomas, See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C*).
[n]See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).
[p]If GTR is achieved in a patient with low-risk disease, consider further observation.
[q]Recurrence on neuroimaging can be confounded by treatment effects. To confirm tumor recurrence and assess for possible transformation of tumor to higher grade, strongly consider tumor tissue sampling (biopsy at minimum) if there is a high index of suspicion of recurrence. Sixty percent or more of astrocytomas and 40%–50% of oligodendrogliomas will eventually undergo transformation to a higher grade. For treatment of patients with transformation to high-grade disease, see GLIO-1.
[r]Brain MRI every 2–3 months while on treatment, then every 6 months indefinitely, to assess disease recurrence/progression during treatment with chemotherapy. (See BRAIN-A*).
[s]RT alone is not encouraged, but may be appropriate for select cases (eg, poor performance status).

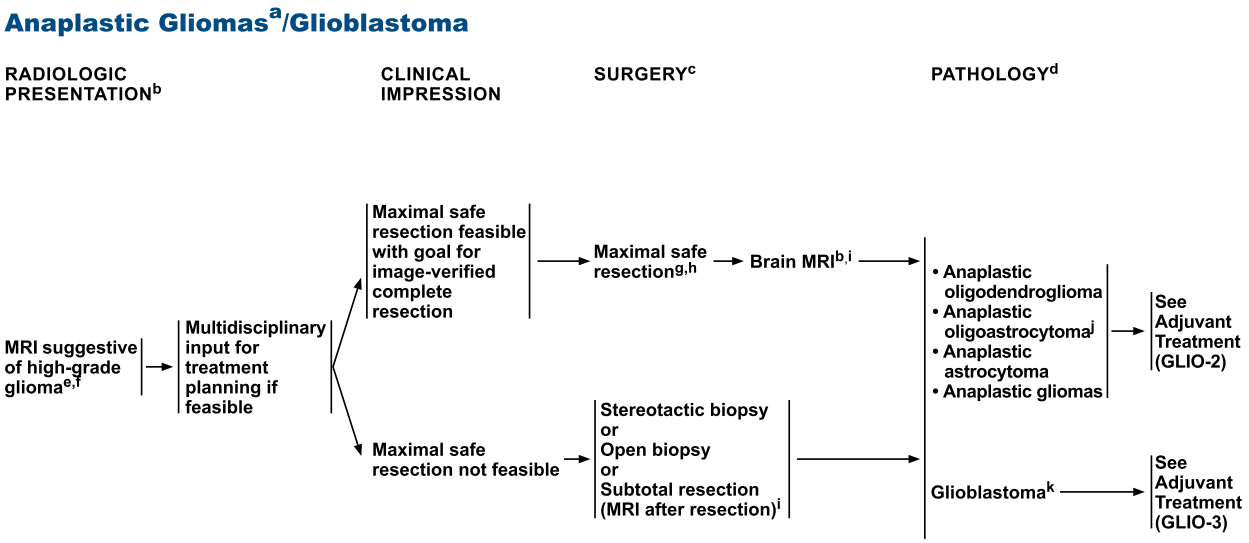
*Available online, in these guidelines, at NCCN.org.

ASTR-3

IDH1 or *IDH2* (*IDH*-mut) with 1p19q codeletion (1p19q codel); (2) *IDH*-mut with no 1p19q codeletion or with isolated deletion of 1p or 19q; and (3) no mutation of *IDH1* or *IDH2* (*IDH* wild type; *IDH*-wt).[4] Multiple studies have shown that the 1p19q codeletion is strongly associated with *IDH* mutations, such that true whole-arm 1p19q codeletion in *IDH*-wt tumors is extremely rare.[2,3,10,14,15] In a tumor that is equivocal, the presence of an *IDH* mutation indicates at least a grade II diffusely infiltrative glioma.[16] Grade I noninfiltrative gliomas do not have *IDH* mutations.[16]

Other mutations commonly detected in gliomas can have diagnostic and prognostic value, such as those involving the histone chaperone protein, ATRX, which are most often found in grade II–III gliomas and secondary glioblastomas.[17,18] *ATRX* mutation is robustly associated with *IDH* mutations, and this combination is strongly suggestive of astrocytoma.[19] In contrast, *ATRX* mutation is nearly always mutually exclusive with 1p19q codeletion. Therefore, a glioma that has loss of normal ATRX immunostaining is unlikely to be an oligodendroglioma. Mutations in the promoter region of the *telomerase reverse transcription* (*TERT*) gene occur frequently in glioblastomas and oligodendrogliomas.[20,21] *TERT* promoter mutations in gliomas are associated with 1p19q codeletion and *IDH* mutations in oligodendrogliomas.[22] Interestingly, they are also highly characteristic of *IDH*-wt, *ATRX* wild-type glioblastomas, especially those that contain amplification of epidermal growth factor receptor (EGFR).[20,21] *H3K27M* mutations in the histone-encoding *H3F3A* gene are mostly found in diffuse midline gliomas in both children and adults.[23] Patients with these *H3K27M* mutated gliomas tend to have a very poor prognosis regardless of histologic appearance, so they are classified as WHO grade IV.[22,23]

Analyses of large databases have also suggested a number of other molecular markers as being potential characteristic/prognostic features of specific subgroups.[3,5,7,10,14,19] Molecular features suggested as markers for subtyping grade II–III gliomas include mutations in *NOTCH1*, *CIC*, *FUBP1*; mutation in *TP53* and/or overexpression of aberrant *TP53*; *PTEN* loss or promoter methylation; amplification of *EGFR*; and chromosome 7 gain, chromosome 10 loss.[2,4,5,11,22] Due to



[a]This pathway includes the classification of mixed anaplastic oligoastrocytoma (AOA), anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), and other rare anaplastic gliomas.
[b]See Principles of Brain and Spine Tumor Imaging (BRAIN-A*).
[c]See Principles of Brain Tumor Surgery (BRAIN-B*).
[d]See Principles of Brain Tumor Pathology (BRAIN-F*).
[e]Biopsy prior to administration of steroids if MRI compatible with CNS lymphoma.
[f]Consider a multidisciplinary review in treatment planning, especially once pathology is available. See Principles of Brain and Spine Tumor Management (BRAIN-E*).
[g]If frozen section diagnosis supports high-grade glioma.
[h]Consider carmustine (BCNU) wafer implant during maximal safe resection (category 2B). Treatment with carmustine wafer may impact enrollment in adjuvant clinical trials.
[i]Postoperative brain MRI within 48 hours after surgery.
[j]The 2016 WHO Classification of Tumors of the CNS has deleted oligoastrocytoma as a category, although "anaplastic oligoastrocytoma, NOS" may continue to be used for 1) patients with mixed histology and no available molecular data (ie, no tissue available for analysis) for determining whether to classify as oligodendroglioma versus astrocytoma; or 2) rare instances in which the tumor has regions with histologic features of oligoastrocytoma with 1p19q-codeletion, and distinct regions with histologic features of astrocytoma without 1p19q-codeletion.
[k]This pathway also includes gliosarcoma.

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GLIO-1

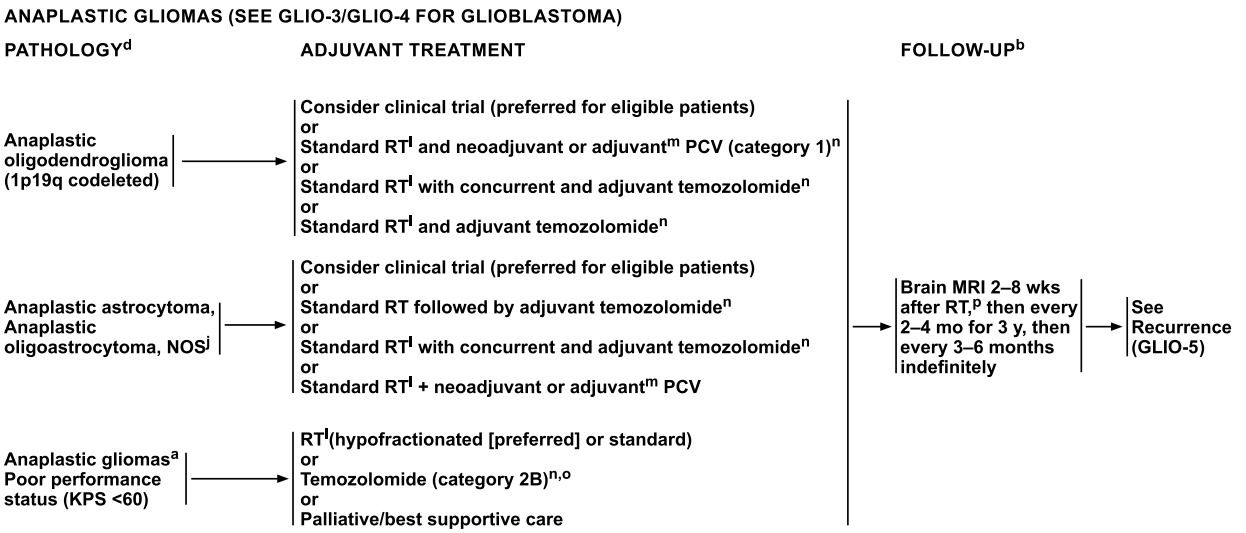
variability in results across studies, many of these molecular markers are not yet widely used to subclassify gliomas, although the 2020 version of the WHO classification of CNS tumors will include *CDKN2A/B* homozygous deletion as evidence of grade 4 status in *IDH* mutant astrocytomas, as indicated by a recent consensus statement.[24]

Prognostic Relevance of Molecular Subgroups in Glioma

Numerous large studies of patients with brain tumors have determined that, among grade II–III gliomas, 1p19q codeletion correlates with greatly improved progression-free survival (PFS) and overall survival (OS).[3,7,8,25–27] Likewise, the presence of an *IDH* mutation is a strong favorable prognostic marker for OS in grade II–III gliomas.[4] Analyses within single treatment arms showed that the *IDH* status is prognostic for outcome across a variety of postoperative adjuvant options. For example, in the NOA-04 phase III randomized trial in newly diagnosed anaplastic gliomas, *IDH* mutation was associated with improved PFS, longer time to treatment failure, and extended OS in each of the 3 treatment arms: standard RT (n=160); combination therapy with procarbazine, lomustine, and vincristine (PCV; RT upon progression; n=78); and temozolomide (TMZ; RT upon progression; n=80).[26]

Multiple independent studies have shown that subdividing gliomas by molecular subtype, especially *IDH1/2* and 1p19q status, yields greater prognostic separation than subdivision based on histology (as defined by WHO 2007). These include very large studies covering multiple grades and histology-based subtypes of gliomas,[4,7,25] as well as smaller studies limited to 1 or 2 grades or histologic subtypes.[3,28–30] Multiple studies have also shown that, among patients with grade II–III gliomas, the *IDH*-mut plus 1p19q-codeletion group has the best prognosis, followed by *IDH*-mut without 1p19q codeletion; the *IDH*-wt group has the worst prognosis.[3–5,25–27] Analyses within single treatment arms have confirmed this trend in prognosis across a variety of postoperative adjuvant treatment options.[3,26,27,30]

Anaplastic Gliomas[a]/Glioblastoma



[a]This pathway includes the classification of mixed AOA, AA, AO, and other rare anaplastic gliomas.
[b]See Principles of Brain and Spine Tumor Imaging (BRAIN-A*).
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[j]The 2016 WHO Classification of Tumors of the CNS has deleted oligoastrocytoma as a category, although "anaplastic oligoastrocytoma, NOS" may continue to be used for 1) patients with mixed histology and no available molecular data (ie, no tissue available for analysis) for determining whether to classify as oligodendroglioma versus astrocytoma; or 2) rare instances in which the tumor has regions with histologic features of oligoastrocytoma with 1p19q-codeletion, and distinct regions with histologic features of astrocytoma without 1p19q-codeletion.
[l]See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C*).
[m]The panel recommends that PCV be administered after RT (as per EORTC 26951) since the intensive PCV regimen given prior to RT (RTOG 9402) was not tolerated as well.
[n]See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).
[o]Consider temozolomide if tumor is MGMT promoter methylated.
[p]Within the first 3 months after completion of RT and concomitant temozolomide, diagnosis of recurrence can be indistinguishable from pseudoprogression on neuroimaging.

*Available online, in these guidelines, at NCCN.org.

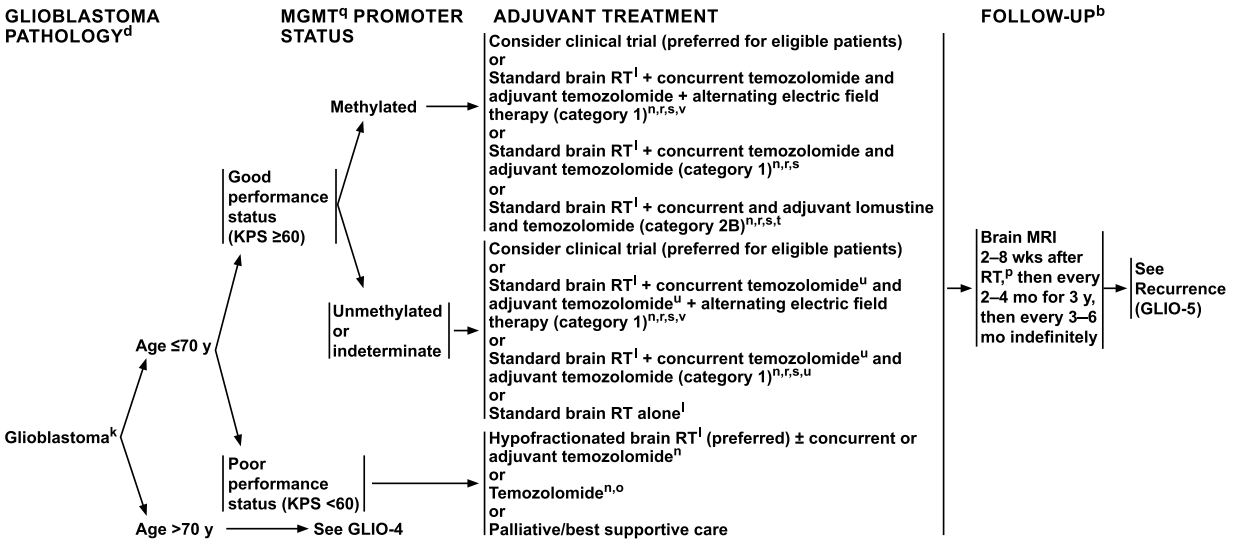
GLIO-2

TERT mutations in patients with high-grade *IDH*-wt glioma are associated with shorter OS, compared with *IDH*-wt tumors without a *TERT* mutation.[5,21,31] However, a multivariate analysis of data from 291 patients with *IDH*-mut+1p19q-codeleted oligodendrogliomas showed that absence of a *TERT* mutation was associated with worse OS, compared with patients with *TERT*-mut oligodendrogliomas (HR, 2.72; 95% CI, 1.05–7.04; P=.04).[32]

MGMT (*O*-6-methylguanine-DNA methyltransferase) is a DNA repair enzyme that can cause resistance to DNA-alkylating drugs.[33] *MGMT* promoter methylation is associated with better survival outcomes in patients with high-grade glioma and is a predictive factor for response to treatment with alkylating chemotherapy such as TMZ or lomustine,[22,34–36] even in older adult patients.[37,38] Tumors with *H3K27M* mutations are far less likely to be *MGMT* promoter methylated[23] and are associated with worse prognosis.[39,40] Patients whose glioblastomas contain *H3F3A* G34 mutations however, may have relatively higher rates of *MGMT* promoter methylation, and do not have a worse prognosis than other *IDH*-wt glioblastomas.[40,41]

Most pilocytic astrocytomas in pediatric patients contain *BRAF* fusions or, less commonly, *BRAF* V600E mutations, especially those arising in the posterior fossa; such tumors are rarely high grade.[42] *BRAF* fusion is associated with better prognosis in pediatric low-grade astrocytoma.[42–44] The likelihood of a *BRAF* fusion in a pilocytic astrocytoma decreases with age.[42] The *BRAF* V600E mutation is present in most pleomorphic xanthoastrocytomas, though it has also been found in some other pediatric low-grade gliomas, such as gangliogliomas and dysembryoplastic neuroepithelial tumors,[22,42,45] as well as a small proportion of glioblastomas (especially epithelioid glioblastoma).[46] Retrospective studies have shown that *BRAF* V600E may be associated with increased risk of progression in pediatric low-grade gliomas,[47] but one study found that this association was not quite statistically significant (n=198; P=.07).[44] Some have shown that tumors with a *BRAF* V600E mutation may respond to BRAF inhibitors such as vemurafenib,[48–50] but ongoing trials will

Anaplastic Gliomas[a]/Glioblastoma



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[k]This pathway also includes gliosarcoma.
[l]See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C*).
[n]See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).
[o]Consider temozolomide if tumor is MGMT promoter methylated.
[p]Within the first 3 months after completion of RT and concomitant temozolomide, diagnosis of recurrence can be indistinguishable from pseudoprogression on neuroimaging.
[q]MGMT= O6-methylguanine-DNA methyltransferase.
[r]Combination of modalities may lead to increased toxicity or radiographic changes.
[s]Benefit of treatment with temozolomide for glioblastomas beyond 6 months is unknown.
[t]Moderate to significant myelosuppression was observed, but the toxicity profile for this regimen is not yet fully defined.
[u]Clinical benefit from temozolomide is likely to be lower in patients whose tumors lack MGMT promoter methylation.
[v]Alternating electric field therapy is only an option for patients with supratentorial disease.

*Available online, in these guidelines, at NCCN.org.

GLIO-3

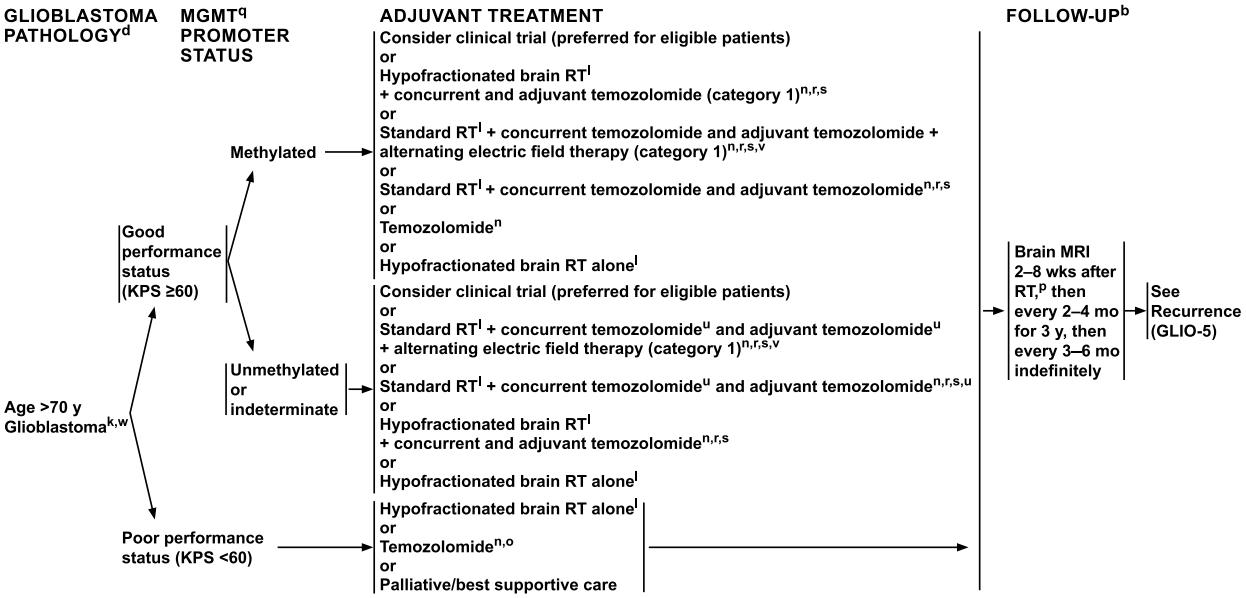
further clarify targeted treatment options in the presence of a *BRAF* fusion or V600E mutation (eg, NCT03224767, NCT03430947). *BRAF* fusion and/or mutation testing are clinically indicated in patients with low-grade glioma.

NCCN Molecular Testing Recommendations for Glioma

Recommendations for molecular testing of glioma tumors are provided in the "Principles of Brain Tumor Pathology" section (Brain-F, available online, in these guidelines, at NCCN.org). Based on studies showing that *IDH* status is associated with better prognosis in patients with grade II–III glioma,[14,25,26,51] the panel recommends *IDH* mutation testing in patients with glioma. Immunohistochemistry can detect the most common *IDH* mutation, which is *IDH1* R132H. However, sequencing must be done to detect the less common *IDH1* mutations (eg, *IDH1* R132C) and *IDH2*. This sequencing should be done in the proper clinical context (eg, younger patients with nonenhancing gliomas). Patients with oligodendroglioma should also undergo 1p19q testing. However, since 1p19q codeletion is strongly associated with *IDH* mutation,[14,15,52] 1p19q testing is not necessary in tumors that are definitely *IDH*-wt, and tumors without an *IDH* mutation should not be regarded as 1p19q codeleted, even when results suggest otherwise. Mutation testing for *ATRX* and *TERT* are also recommended, given the diagnostic value of these mutations.[17,19–21] Screening for *H3K27M* mutations (*H3F3A* and *HIST1H3B* sequencing preferred) and *BRAF* fusion and/or mutation testing may be carried out as clinically indicated.

Grade III–IV gliomas should undergo testing for *MGMT* promoter methylation status, since *MGMT* promoter methylated tumors typically respond better to alkylating chemotherapy, compared with unmethylated tumors.[34,37,38,53] To date, there are no targeted agents that have shown improvement in OS in the treatment of glioblastoma. Nevertheless, molecular testing of glioblastomas is still encouraged by the panel, as patients with a detected driver mutation may be treated with a targeted therapy on a compassionate use basis, and these tests improve diagnostic accuracy and prognostic stratification.

Anaplastic Gliomas[a]/Glioblastoma



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[p]Within the first 3 months after completion of RT and concomitant temozolomide, diagnosis of recurrence can be indistinguishable from pseudoprogression on neuroimaging.
[q]MGMT= O6-methylguanine-DNA methyltransferase.
[r]Combination of modalities may lead to increased toxicity or radiographic changes.
[s]Benefit of treatment with temozolomide for glioblastomas beyond 6 months is unknown.
[u]Clinical benefit from temozolomide is likely to be lower in patients whose tumors lack MGMT promoter methylation.
[v]Alternating electric field therapy is only an option for patients with supratentorial disease.
[w]See NCCN Guidelines for Older Adult Oncology†.

*Available online, in these guidelines, at NCCN.org. †To view the most recent version of these guidelines, visit NCCN.org.

GLIO-4

Detection of genetic or epigenetic alterations could also expand clinical trial options for a brain tumor patient.

Low-Grade Gliomas

Low-grade gliomas (ie, pilocytic and diffusely infiltrative astrocytomas, oligodendrogliomas) are a diverse group of relatively uncommon malignancies classified as grade I and II under the WHO grading system.[1] Low-grade gliomas comprise approximately 5%–10% of all CNS tumors.[54] Seizure is a common symptom (81%) of low-grade gliomas, and is more frequently associated with oligodendrogliomas.[55,56] The median duration from onset of symptoms to diagnosis ranges from 6 to 17 months.

Grade I Gliomas

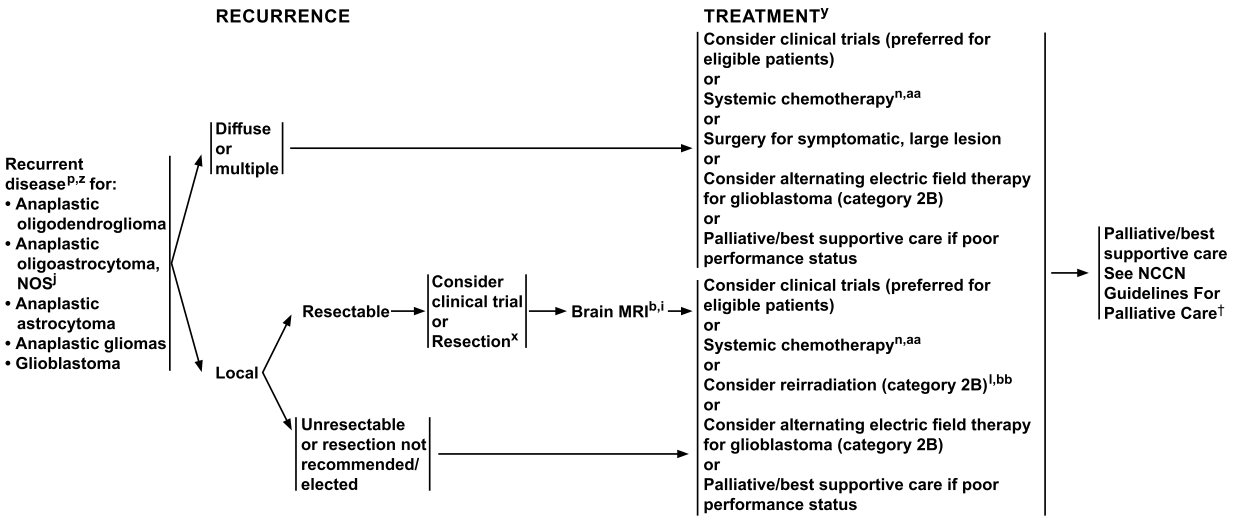
Diffuse astrocytomas are poorly circumscribed and invasive, and most gradually evolve into higher-grade astrocytomas. Although these were traditionally considered benign, they can behave aggressively and will undergo anaplastic transformation within five years in approximately half of patients.[57,58] The most common non-infiltrative astrocytomas are pilocytic astrocytomas. Other grade I gliomas in which treatment recommendations are included in the NCCN Guidelines for CNS Cancers are pleomorphic xanthoastrocytoma, subependymal giant cell astrocytoma (SEGA), and ganglioglioma, though these grade I gliomas are uncommon. Pleomorphic xanthoastrocytomas are associated with favorable prognosis,[59,60] though mitotic index is associated with survival outcomes.[60,61] Gangliogliomas are commonly located in the temporal lobe, and the most significant predictors of survival are low tumor grade and younger age.[62]

SEGAs are typically located at the caudothalamic groove adjacent to the foramen of Monro. Though they are generally slow-growing and histologically benign, they can also be associated with manifestations such as hydrocephalus, intracranial pressure, and seizures.[63] SEGAs can be distinguished from subependymal nodules by their characteristic serial growth.[64] These tumors occur in 5%–20% of individuals with tuberous sclerosis complex (TSC).[65–67]

Treatment

Grade I gliomas are usually curable by surgery alone. Indication for treatment of SEGAs is based on development

Anaplastic Gliomas[a]/Glioblastoma



[a]This pathway includes the classification of mixed AOA, AA, AO, and other rare anaplastic gliomas.
[b]See Principles of Brain and Spine Tumor Imaging (BRAIN-A)*.
[i]Postoperative brain MRI within 48 hours after surgery.
[j]The 2016 WHO Classification of Tumors of the CNS has deleted oligoastrocytoma as a category, although "anaplastic oligoastrocytoma, NOS" may continue to be used for 1) patients with mixed histology and no available molecular data (ie, no tissue available for analysis) for determining whether to classify as oligodendroglioma versus astrocytoma; or 2) rare instances in which the tumor has regions with histologic features of oligoastrocytoma with 1p19q-codeletion, and distinct regions with histologic features of astrocytoma without 1p19q-codeletion.
[l]See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C*).
[n]See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).
[p]Within the first 3 months after completion of RT and concomitant temozolomide, diagnosis of recurrence can be indistinguishable from pseudoprogression on neuroimaging.
[x]Consider carmustine (BCNU) wafer implant during resection. Treatment with carmustine wafer may impact enrollment in clinical trials.
[y]The efficacy of standard-of-care treatment for recurrent glioblastoma is suboptimal, so for eligible patients consideration of clinical trials is highly encouraged. Prior treatment may impact enrollment in clinical trials.
[z]Consider biopsy, MR spectroscopy, MR perfusion, brain PET/CT, or brain PET/MRI, or re-image to follow changes that may be due to progression versus radionecrosis.
[aa]Anaplastic oligodendrogliomas have been reported to be especially sensitive to chemotherapy. Chemotherapy using temozolomide or nitrosourea-based regimens may be appropriate.
[bb]Especially if long interval since prior RT and/or if there was a good response to prior RT.

*Available online, in these guidelines, at NCCN.org. †To view the most recent version of these guidelines, visit NCCN.org.

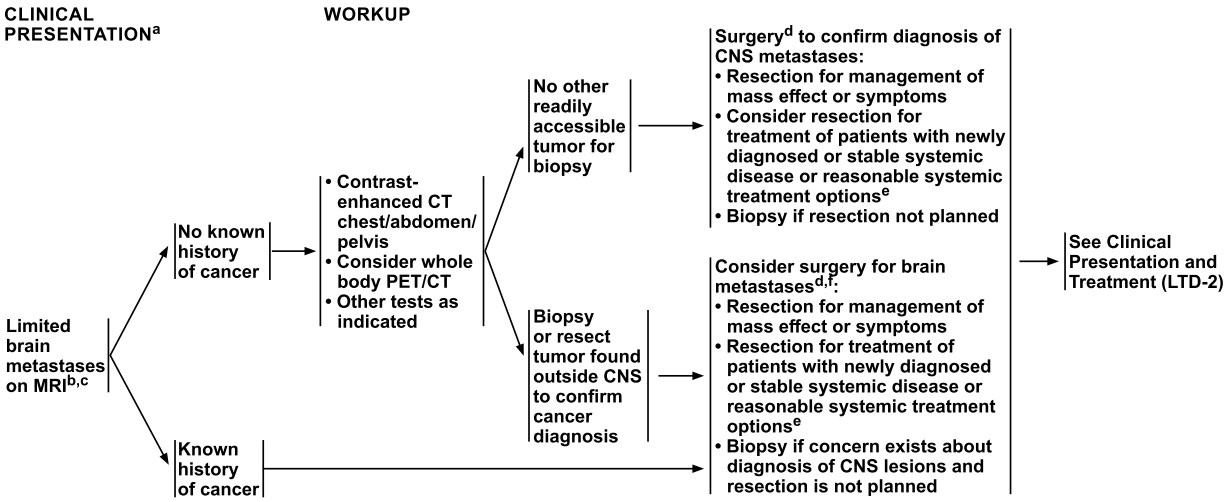
GLIO-5

of new symptoms or radiologic evidence of tumor growth.[64] Though surgery is sometimes a recommended option for SEGAs, many are in an area not amenable to resection, and recurrence may occur following resection.[68,69] Surgery may pose risks because of the frequent location of SEGAs near the foramen of Monro, but in specialized centers, morbidity is acceptable, and surgical mortality is extremely low.[70]

There is some evidence that BRAF inhibitors, as well as a BRAF/MEK inhibitor combination, may be used for treatment of low-grade gliomas that are BRAF mutated. The phase II VE-BASKET study showed that vemurafenib was efficacious in BRAF-mutated low-grade gliomas, particularly PXA, with an ORR of 42.9% (n=7), median PFS of 5.7 months, and median OS not reached.[50] Another phase II trial including 10 patients with low-grade glioma showed that dabrafenib/trametinib was associated with an ORR of 56% (5 patients with a partial response and 4 patients with stable disease).[71] Case reports have demonstrated clinical activity for the combination BRAF/MEK inhibitor dabrafenib/trametinib in patients with BRAF V600E mutant glioma.[72,73]

Reducing or stabilizing the volume of SEGAs through systemic therapy has been investigated. A phase III trial showed that 78 patients with SEGA and TSC who received everolimus, an mTOR inhibitor, had at least a 50% reduction in tumor volume, compared with 39 patients who received a placebo (35% vs 0%; $P<.001$), and 6-month PFS was 100% versus 86%, respectively ($P<.001$).[74] Analyses from a long-term follow-up showed that median duration of response was not reached, with response duration ranging from 2.1 months to 31.1 months.[75] Tumor volume reduction rates of 30% and 50% were maintained in patients in the everolimus arm for more than 3 years. This regimen was generally well-tolerated, with the most frequently reported grade 3 or 4 adverse events being stomatitis (8%) and pneumonia (8%). Everolimus has also been investigated in a phase II trial including 58 patients with recurrent grade II gliomas, with a 6-month PFS rate of 84%.[76] Medical therapy of SEGA, while effective, is a long-term commitment, unless it is being used short-term to facilitate surgical resection. Once mTOR

Limited Brain Metastases



[a]See Principles of Brain and Spine Tumor Imaging (BRAIN-A*).
[b]Consider a multidisciplinary review in treatment planning, especially once pathology is available. See Principles of Brain and Spine Tumor Management (BRAIN-E*).
[c]"Limited" brain metastases defines a group of patients for whom SRS is equally effective and offers significant cognitive protection compared with WBRT. The definition of "limited" brain metastases in terms of number of metastases or total intracranial disease volume is evolving and may depend on the specific clinical situation. (Yamamoto M, Serizawa T, Shuto T, et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. Lancet Oncol 2014;15:387-395.)
[d]See Principles of Brain Tumor Surgery (BRAIN-B*).
[e]For secondary CNS lymphoma, treatment may include systemic treatment, whole-brain or focal RT, or combination.
[f]The decision to resect a tumor may depend on the need to establish histologic diagnosis, the size of the lesion, its location, and institutional expertise. For example, smaller (<2 cm), deep, asymptomatic lesions may be considered for treatment with SRS versus larger (>2 cm), symptomatic lesions that may be more appropriate for surgery. (Ewend MG, Morris DE, Carey LA, Ladha AM, Brem S. Guidelines for the initial management of metastatic brain tumors: role of surgery, radiosurgery, and radiation therapy. J Natl Compr Cancer Netw 2008;6:505-513.)

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LTD-1

inhibitor therapy is stopped, lesions typically recur, usually within several months, and eventually reach pretreatment volume. The lesions will continue to grow unless therapy is reintroduced. Most patients tolerate long-term therapy with mTOR inhibitors quite well.[77]

NCCN Recommendations

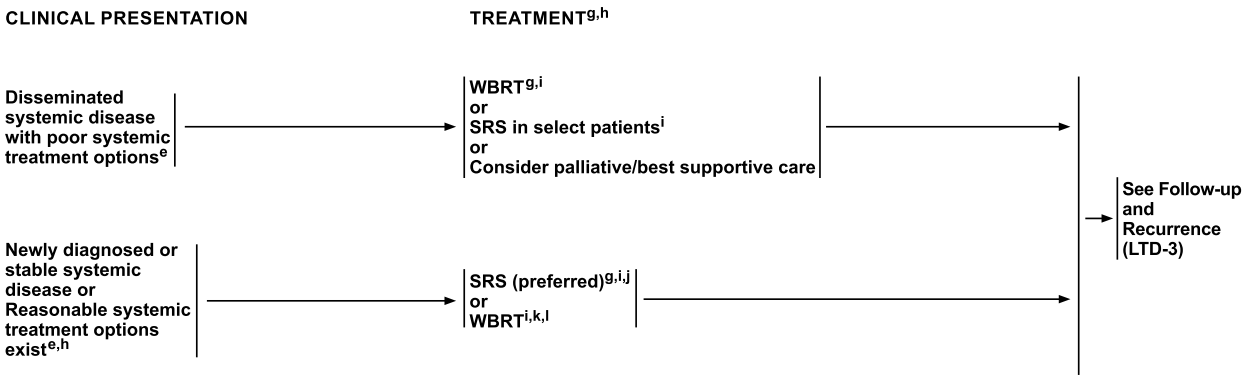
When possible, maximal safe resection is recommended for grade I gliomas, and the actual extent of resection should be documented with a T2-weighted or FLAIR MRI scan within 48 hours after surgery. Patients may be observed following surgery. If incomplete resection or biopsy, or if surgery was not feasible, then RT may be considered if there is significant tumor growth or if neurologic symptoms are present or develop. A BRAF/MEK inhibitor combination may be used for patients with BRAF V600E mutant low-grade glioma. Treatment with an mTOR inhibitor (eg, everolimus) should be considered for patients with SEGA,[74,75] though institutional expertise and patient preference should guide treatment decision-making for these rare tumors.[64] Full treatment recommendations can be found on ASTR-1 (page 1538).

Grade II Infiltrative Supratentorial Astrocytoma/Oligodendroglioma

Radiographically, low-grade oligodendrogliomas appear well demarcated, occasionally contain calcifications, and do not often enhance with contrast. In histology, the typical "fried egg" appearance of these tumors is evident as a fixation artifact in paraffin but not in frozen sections. Grade II oligodendrogliomas have a much better 5-year survival rate (82.7%) than diffuse astrocytomas (51.6%).[78]

Factors prognostic for PFS or OS in patients with grade II gliomas include age, tumor diameter, tumor crossing midline, neurologic or performance status (PS) prior to surgery, and the presence of certain molecular markers (see "Molecular Profiling for Gliomas," page 1538).[3,8,79–84] For example, *IDH1/2* mutation is associated with a favorable prognosis in patients with grade II and III gliomas,[4,5,26] supporting the emerging idea that molecular analysis should play a

Limited Brain Metastases



[e]For secondary CNS lymphoma, treatment may include systemic treatment, whole-brain or focal RT, or combination.
[g]If an active agent exists (eg, cytotoxic, targeted, or immune modulating), trial of systemic therapy with good CNS penetration may be considered in select patients (eg, for patients with small asymptomatic brain metastases from melanoma or ALK rearrangement-positive NSCLC or EGFR-mutated NSCLC); it is reasonable to hold on treating with radiation to see if systemic therapy can control the brain metastases. Consultation with a radiation oncologist and close MRI surveillance is strongly recommended. There are no data from prospective clinical trials comparing the two strategies to assess what the impact of delayed radiation would be in terms of survival or in delay of neurologic deficit development.
[h]See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).
[i]See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C*).
[j]SRS is preferred when safe, especially for low tumor volume, to both the resection cavity and any other non-resected brain metastases. WBRT is generally not recommended but may be appropriate in some rare clinical circumstances.
[k]For brain metastases not managed with resection, SRS + WBRT is generally not recomended but may be appropriate in some rare clinical circumstances. Brown 2016 showed that for tumors <3 cm, SRS + WBRT improved local control compared with SRS alone, but did not significantly improve survival, and was associated with greater cognitive decline and poorer quality of life. (Brown PD, Jaeckle K, Ballman KV, et al. Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases: a randomized clinical trial. JAMA 2016;316:401-409.)
[l]Hippocampal avoidance preferred. See BRAIN-C*.

*Available online, in these guidelines, at NCCN.org.

LTD-2

larger role in treatment decision-making, relative to histopathology.[56]

Treatment Overview

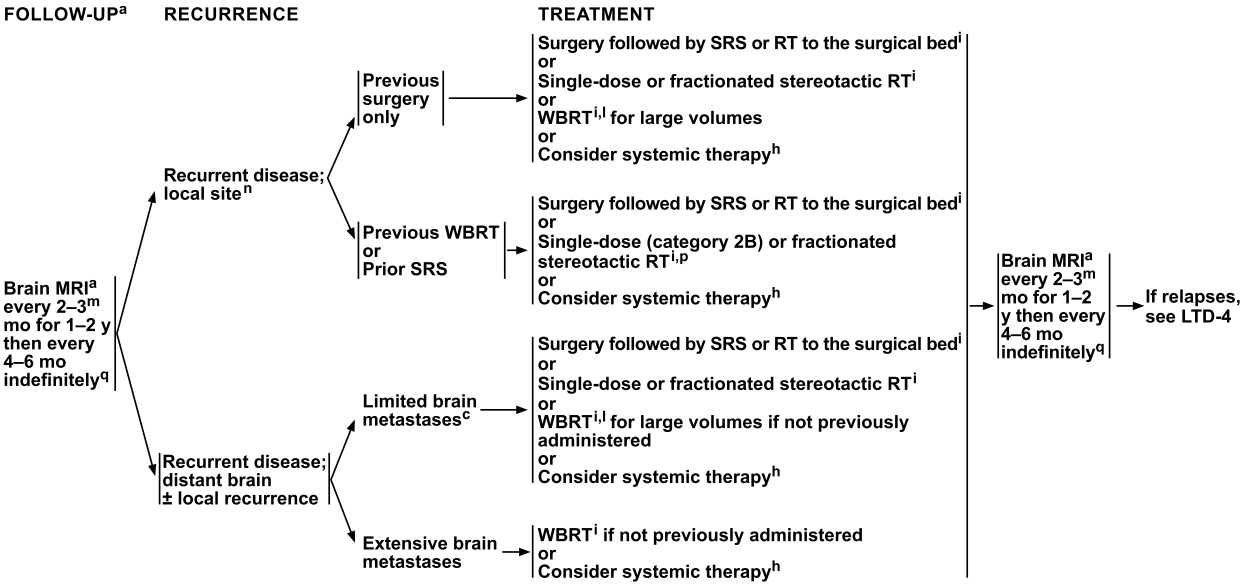
Surgery

Surgery remains an important diagnostic and therapeutic modality. The primary surgical goals are maximal safe resection to delay progression and improve survival, relief of symptoms, and provision of adequate tissue for a pathologic diagnosis and grading. Needle biopsies are often performed when lesions are in deep or critical regions of the brain. Biopsy results can be misleading, because gliomas often have varying degrees of cellularity, mitoses, or necrosis from one region to another; thus, small samples can provide erroneous histologic grade or diagnosis.[85,86]

Surgical resection plays an important role in the management of low-grade gliomas. A systematic review showed that gross total resection (GTR) was significantly associated with decreased mortality and lower risk of disease progression up to 10 years after treatment, compared with STR.[87] Because these tumors are relatively uncommon, published series generally include patients treated for decades, which introduces additional variables. For example, the completeness of surgical excision was based on the surgeon's report in older studies. This approach is relatively unreliable when compared with assessment by modern postoperative imaging studies. Furthermore, many patients also received RT, and thus the net effect of the surgical procedure on outcome is difficult to evaluate. Two meta-analyses including studies of primary low-grade gliomas show that extent of resection is a significant prognostic factor for PFS and/or OS.[88,89] Maximal safe resection may also delay or prevent malignant progression[89–91] and recurrence.[92] Patients who undergo an STR, open biopsy, or stereotactic biopsy are, therefore, considered to be at higher risk for progression. Gross total resection is also associated with improved seizure control compared with subtotal resection.[89]

Biologic considerations also favor an attempt at a complete excision of a low-grade glioma. First, the tumor may contain higher-grade foci, which may not be

Limited Brain Metastases



[a]See Principles of Brain and Spine Tumor Imaging (BRAIN-A*).
[c]"Limited" brain metastases defines a group of patients for whom SRS is equally effective and offers significant cognitive protection compared with WBRT. The definition of "limited" brain metastases in terms of number of metastases or total intracranial disease volume is evolving and may depend on the specific clinical situation. (Yamamoto M, Serizawa T, Shuto T, et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. Lancet Oncol 2014;15:387-395.)
[h]See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).
[i]See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C*).
[l]Hippocampal avoidance preferred. See BRAIN-C*.
[m]MRI every 2 months (instead of 3 mo) for those patients treated with SRS alone.
[n]After SRS, recurrence on MRI can be confounded by treatment effects; consider tumor tissue sampling if there is a high index of suspicion of recurrence.
[p]If patient had previous SRS with a good response >6 mo, then reconsider SRS if imaging supports active tumor and not necrosis.
[q]Imaging to evaluate emergent signs/symptoms is appropriate at any time.

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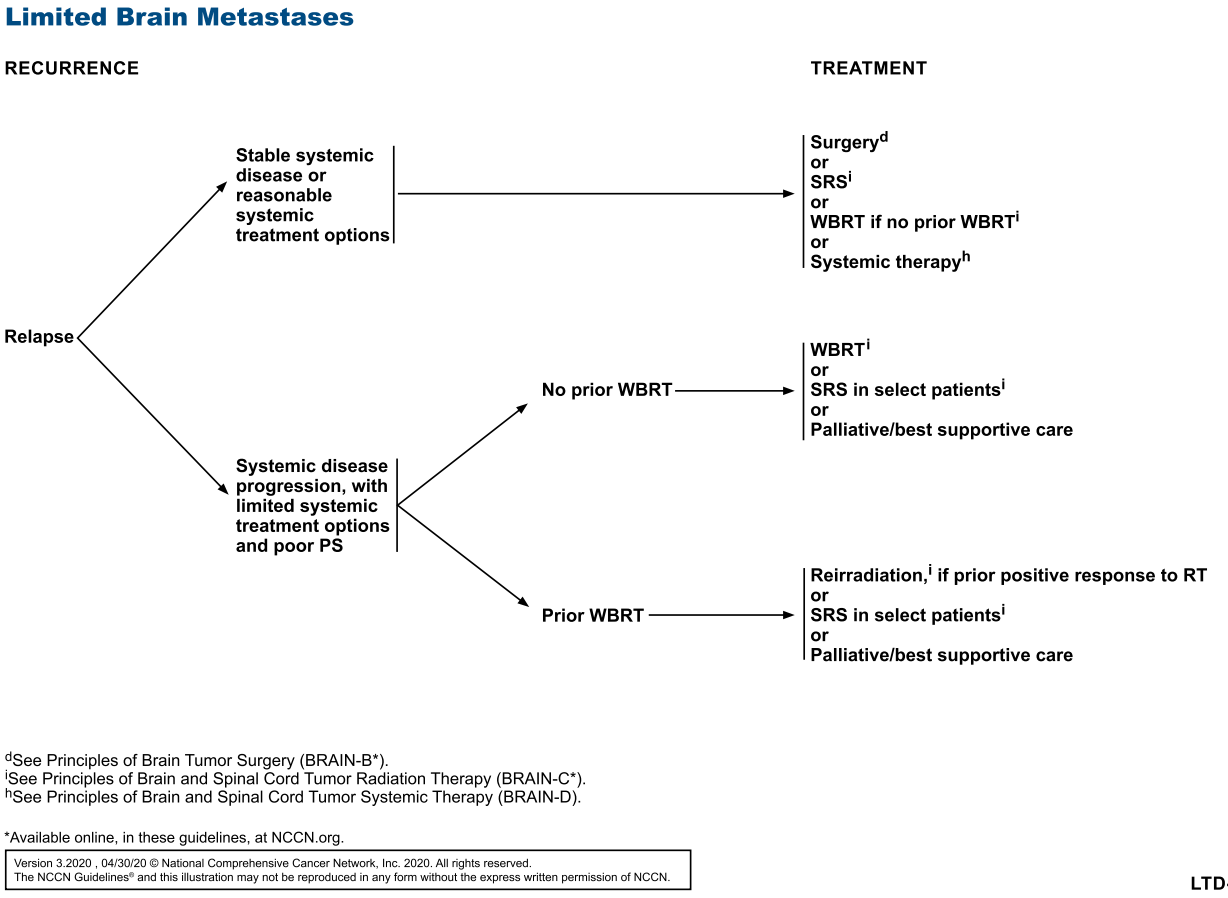
LTD-3

reflected in a small specimen. Second, complete excision may decrease the risk of future dedifferentiation to a more malignant tumor.[93] Third, removal of a large tumor burden may enhance the benefit of RT. As a result of these considerations, the general recommendation for treating a low-grade glioma is to first attempt as complete an excision of tumor as possible (based on postsurgical MRI verification) without compromising function. However, for tumors that involve eloquent areas, a total removal may not be feasible, and an aggressive approach could result in neurologic deficits. Residual tumor volume may also be a prognostic factor, with a randomized single institution study showing that the OS benefit of maximal safe resection was limited to patients with a residual tumor volume $<15 cm^3$.[94]

Adjuvant Therapy

A large meta-analysis, including data from phase 3 trials (EORTC 22844 and 22845,[95,96] and NCCTG 86-72-51[82]), confirmed that surgery followed by RT significantly improves PFS but not OS in patients with low-grade gliomas.[97] Early versus late postoperative RT did not significantly affect OS, however, suggesting that observation is a reasonable option for some patients with newly diagnosed gliomas.[96]

Final results of a phase 3 randomized clinical trial, RTOG 9802, which assessed the efficacy of adjuvant RT versus RT followed by 6 cycles of PCV in patients with newly diagnosed supratentorial WHO grade II gliomas and at least one of 2 risk factors for disease progression (STR or age ≥40 years)[98] showed significant improvements in both PFS and OS with the addition of PCV.[99] The median survival time increased from 7.8 years to 13.3 years (P=.02), and the 10-year survival rate increased from 41% to 62%. It is important to note, however, that roughly three-quarters of the study participants had a Karnofsky Performance Status (KPS) score of 90 to 100, and the median age was around 40 years.[98] Exploratory analyses based on histologic subgroups showed a statistically significant improvement in OS for all subgroups except for patients with astrocytoma.[99] Given that the study participants treated with PCV after RT experienced a significantly higher incidence of grade 3 or 4 adverse events (specifically neutropenia, gastrointestinal disorder,



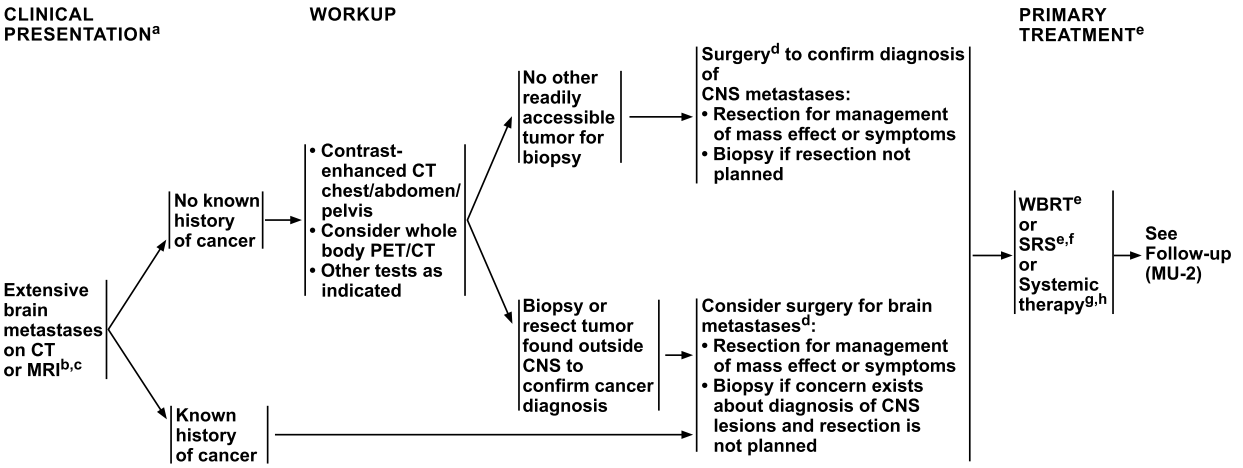
and fatigue),[98,99] PCV may be difficult to tolerate in patients who are older or with poor PS. A retrospective subgroup analysis suggest that the survival benefit with the addition of PCV was seen only in *IDH*-mut tumors; the *IDH*-wt subgroup did not appear to benefit from the chemotherapy.[100]

Combined treatment with RT plus TMZ is supported by a phase 2 multicenter trial (RTOG 0424) in patients with supratentorial WHO grade II tumors and additional risk factors (ie, age ≥40 years, astrocytoma, bihemispherical, tumor diameter ≥6 cm, neurologic function status >1).[101] However, since the historical controls included patients treated in an earlier time period using different RT protocols, prospective controlled trials are needed to determine whether treatment with TMZ concurrently and following RT is as efficacious as PCV following radiation. There are currently no phase III data to support the use of RT and TMZ over RT and PCV for the treatment of patients with newly diagnosed high-risk low-grade glioma. The phase 3 randomized EORTC 22033-26033 trial showed that PFS is not significantly different for adjuvant RT versus dose-dense TMZ in patients with resected or biopsied supratentorial grade II glioma and more than one risk factor (n=477).[9] However, analyses of OS have not yet been reported for this trial.

Radiation Therapy

When RT is given to patients with low-grade gliomas, it is administered with restricted margins. A T2-weighted (occasionally enhanced T1) and/or FLAIR MRI scan is the best means for evaluating tumor extent, because these tumors enhance weakly or not at all. The clinical target volume (CTV) is defined by the FLAIR or T2-weighted tumor with a 1- to 2-cm margin. Every attempt should be made to decrease the RT dose outside the target volume. This can be achieved with 3-dimensional planning or intensity-modulated RT (IMRT), with improved target coverage and normal brain/critical structure sparing often shown with IMRT.[102,103] The recommended dosing for postoperative RT is based on results from two phase 3 randomized trials showing that higher dose RT had no significant effect on OS or time to progression,[82,95] and on several retrospective analyses showing similar results.[81,83,104] Because higher doses offer no clear advantages, the NCCN

Extensive Brain Metastases



[a]See Principles of Brain and Spine Tumor Imaging (BRAIN-A*).
[b]Consider a multidisciplinary review in treatment planning, especially once pathology is available. See Principles of Brain and Spine Tumor Management (BRAIN-E).
[c]Includes all cases that do not fit the definition of "limited brain metastases" on LTD-1.
[d]See Principles of Brain Tumor Surgery (BRAIN-B*).
[e]See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C*).
[f]SRS can be considered for patients with good performance and low overall tumor volume and/or radioresistant tumors such as melanoma. (Yamamoto M, Serizawa T, Shuto T, et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. Lancet Oncol 2014;15:387-395.)
[g]If an active agent exists (eg, cytotoxic, targeted, or immune modulating), trial of systemic therapy with good CNS penetration may be considered in select patients (eg, for patients with small asymptomatic brain metastases from melanoma or ALK rearrangement-positive NSCLC or EGFR-mutated NSCLC); it is reasonable to hold on treating with radiation to see if systemic therapy can control the brain metastases. Consultation with a radiation oncologist and close MRI surveillance is strongly recommended. There are no data from prospective clinical trials comparing the two strategies to assess what the impact of delayed radiation would be in terms of survival or in delay of neurologic deficit development.
[h]See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).

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MU-1

CNS Panel recommends lower-dose RT (45–54 Gy) for treatment of low-grade gliomas (grades I/II), including high-risk cases. However, *IDH*-wt low-grade gliomas have similar survival only slightly better than *IDH*-wt glioblastomas.[4] Therefore, an RT dose of 59.4 to 60 Gy may be considered for this subset of patients with low-grade glioma. Preliminary data suggests that proton therapy could reduce the radiation dose to developing brain tissue and potentially diminish toxicities without compromising disease control.[105]

Recurrent or Progressive Disease

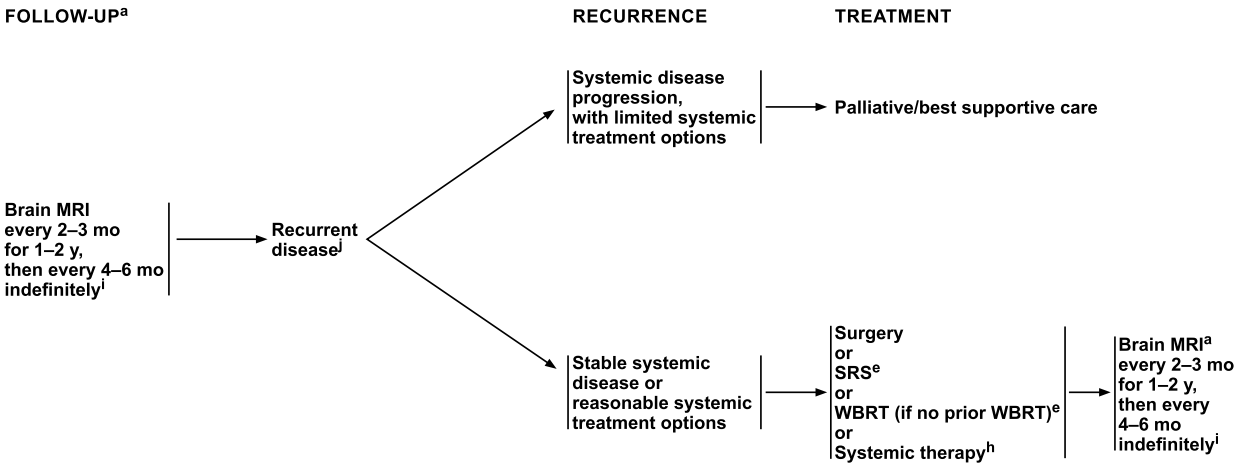
Though the survival impact is unclear, surgery for recurrent disease in patients with low-grade glioma may reduce symptoms, provide tissue for evaluation, and potentially allow for molecular characterization of the tumor.[106–109] Maximal safe resection could play an important role for optimizing survival outcomes; a threshold value is unknown, but >90% extent of resection is suggested.[109] For patients without previous RT, results of the RTOG 9802 trial[98,99] support use of chemotherapy with RT. Data from phase II trials inform recommendations for chemotherapy treatment of patients with recurrent or progressive low-grade glioma.[110–115] Patients should be enrolled in clinical trials evaluating systemic therapy options.

NCCN Recommendations

Primary and Adjuvant Treatment

For treatment recommendations for newly diagnosed grade II gliomas, the panel used the RTOG 9802[98,99] criteria for determining if a patient is considered to be at low or high risk for tumor progression: patients are categorized as being at low risk if they are 40 years or younger and underwent a GTR; high-risk patients are older than 40 years of age and/or underwent an STR. However, the panel acknowledges that other prognostic factors have been used to guide adjuvant treatment choice in other studies of patients with low-grade glioma,[116] such as tumor size, presence of neurologic deficits, loss of *CDKN2A* homozygous deletion and the *IDH* mutation status of the tumor.[9,79] If these other risk factors are considered, and treatment of a patient is warranted,

Extensive Brain Metastases



[a]See Principles of Brain and Spine Tumor Imaging (BRAIN-A*).
[e]See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C*).
[h]See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).
[i]Imaging to evaluate emergent signs/symptoms is appropriate at any time.
[j]After SRS, recurrence on MRI can be confounded by treatment effects; consider tumor tissue sampling if there is a high index of suspicion of recurrence.

*Available online, in these guidelines, at NCCN.org.

MU-2

then the panel recommends that the patient be treated as high-risk.

Patients with low-risk and low-grade glioma may be observed following surgery. Close follow-up is essential as over half of these patients will develop tumor progression within 5 years.[84] Following surgery, RT followed by PCV is a category 1 recommendation for patients with grade II glioma who are considered to be at high risk for tumor progression, based on the practice-changing results from the RTOG 9802 study,[98,99] as discussed above. There is currently a lack of prospective randomized phase 3 data for the use of radiation and TMZ in patients with low-grade glioma, but interim data from the phase III CATNON trial illustrate that there is a benefit from adjuvant TMZ in patients with newly diagnosed 1p19q noncodeleted anaplastic gliomas.[117] Therefore, RT followed by adjuvant TMZ is a category 2A option. Data from EORTC and NCIC studies, which included patients with glioblastoma, support RT with concurrent and adjuvant TMZ as an evidence-based regimen.[118,119] Therefore, this is also a category 2A option. Because PCV is generally a more difficult chemotherapy regimen to tolerate than TMZ, it may be reasonable to treat an elderly patient or a patient with multiple comorbidities with RT and TMZ instead of RT and PCV, but there are currently no data to show that doing so would result in similar improvement in OS.

Since the design of RTOG 9802[98,99] did not address whether all patients should be treated with RT followed by PCV immediately after a tissue diagnosis (an observation arm was not included for patients with high-risk glioma [defined as are older than 40 years of age and/or underwent an STR][84] in the study), observation after tissue diagnosis may be a reasonable option for some patients with high-risk grade II glioma who are neurologically asymptomatic or who have stable disease. However, close monitoring of such patients with brain MRI is important. Results from EORTC 22845, which showed that treatment with RT at diagnosis versus at progression did not significantly impact OS, provide rationale for observation in select cases with low-grade gliomas as an initial approach, deferring RT.[96] Long-term toxicity from radiation needs to be a consideration, especially for young patients with 1p19q codeletion, for whom there is slightly higher risk of radiation necrosis.[120]

Central Nervous System Cancers

PRINCIPLES OF BRAIN AND SPINAL CORD TUMOR SYSTEMIC THERAPY

ADULT LOW-GRADE GLIOMA/PILOCYTIC AND INFILTRATIVE SUPRATENTORIAL ASTROCYTOMA/OLIGODENDROGLIOMA

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Adjuvant Treatment	• RT + adjuvant PCV (category 1)[1,2] • RT + concurrent and adjuvant temozolomide[3-5] • RT + adjuvant temozolomide[3-5]	• Temozolomide[b,3,4] • PCV[b]	• Pilocytic astrocytoma, PXA, ganglioglioma if *BRAF* V600E activation mutation ▸ BRAF/MEK inhibitors: ◊ Dabrafenib/trametinib[6,7] ◊ Vemurafenib/cobimetinib[8,9] • Subependymal giant cell astrocytoma ▸ mTOR inhibitor (eg, everolimus)[10,11]
Recurrent or Progressive Disease[a]	• None	• RT + adjuvant PCV • RT + adjuvant temozolomide • RT+ concurrent and adjuvant temozolomide • Temozolomide[c,4,12,13] • Lomustine or carmustine • PCV[14] • Platinum-based regimens[d,15-17]	• None

[a]There are multiple reasonable options, but there is no uniform standard of care at this time for recurrent disease.
[b]In rare circumstances, treating a patient with chemotherapy without RT may be considered.
[c]For patients not previously treated.
[d]Platinum-based regimens include cisplatin or carboplatin.

BRAIN-D 1 OF 15

Full treatment recommendations can be found on ASTR-2 (page 1539); systemic therapy recommendations can be found on BRAIN-D 1 of 15 (above).

Recurrence

At the time of recurrence, surgery is recommended if resectable disease is present. Because recurrence on neuroimaging may be confounded by treatment effects, biopsy of unresectable disease should be considered to confirm recurrence. There is a propensity for low-grade gliomas to transform to higher-grade gliomas over time. Therefore, documenting the histopathological transformation of a low-grade glioma to a high-grade glioma may also enable patients to have clinical trial opportunities, since most clinical trials in the recurrent setting are for patients with high-grade gliomas. Moreover, sampling of tumor tissue to confirm recurrence is encouraged to obtain tissue for next-generation sequencing, the results of which may inform treatment selection and/or clinical trial eligibility.

Surgery for recurrent disease may be followed by the following treatment options for patients previously treated with fractionated EBRT: (1) chemotherapy; (2) consideration of reirradiation with or without chemotherapy; and (3) palliative/best supportive care. Reirradiation is a good choice if the new lesion is outside the target of previous RT or if the recurrence is small and geometrically favorable. For patients with low-risk features for whom GTR was achieved, observation with no further treatment may be considered.

Based on the strength of the RTOG 9802 results,[98,99] RT with chemotherapy is a treatment option for patients with recurrent or progressive low-grade gliomas who have not had prior RT. Options include RT + adjuvant PCV, RT + adjuvant TMZ, and RT + concurrent and adjuvant TMZ. RT alone is generally not the preferred treatment option except in select cases, such as a patient with a poor PS, or who does not want to undergo chemotherapy treatment. Chemotherapy alone (eg, TMZ, PCV, carmustine/lomustine) is also a treatment option for these patients, though this is a category 2B option based on less panel consensus.

Central Nervous System Cancers

PRINCIPLES OF BRAIN AND SPINAL CORD TUMOR SYSTEMIC THERAPY

ANAPLASTIC GLIOMAS

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Adjuvant Treatment Anaplastic oligodendroglioma (1p19q co-deleted) (KPS ≥60)	• RT with adjuvant PCV (category 1)[e,18] • RT with neoadjuvant PCV (category 1)[e,19]	• RT with concurrent and adjuvant TMZ[20] • RT with adjuvant TMZ[21,22]	• None
Adjuvant Treatment Anaplastic astrocytoma/anaplastic oligoastrocytoma, NOS[f] (KPS ≥60)	• RT with concurrent and adjuvant TMZ[23,24] • RT followed by adjuvant TMZ (12 cycles)[24]	• RT with adjuvant PCV[e,25,26] • RT with neoadjuvant PCV[e]	• None
Adjuvant Treatment Anaplastic gliomas (KPS <60)	• None	• TMZ[g] (category 2B)[27]	• None
Recurrence Therapy[h]	• TMZ[12,13,28,29] • Lomustine or carmustine[30] • PCV[31] • Bevacizumab[i, 32-34]	• Chemotherapy[j] + bevacizumab ▸ Carmustine or lomustine + bevacizumab[35] ▸ TMZ + bevacizumab[36]	• If failure or intolerance to the preferred or other recommended regimens ▸ Etoposide[37,38] (category 2B) ▸ Platinum-based regimens[d,39-41] (category 3)

[d]Platinum-based regimens include cisplatin or carboplatin.
[e]The panel recommends that PCV be administered after RT (as per EORTC 26951) since the intensive PCV regimen given prior to RT (RTOG 9402) was not tolerated as well.
[f]The WHO 2016 classification of CNS tumors has deleted oligoastrocytoma as a diagnostic category; however, oligoastrocytoma NOS and anaplastic oligoastrocytoma NOS may continue to be used for tumors that cannot be classified as either astrocytoma or oligodendroglioma due to the absence of appropriate molecular testing.
[g]Consider TMZ if tumor is MGMT promoter methylated.
[h]Strongly suggest consideration of clinical trials prior to treating recurrent disease with standard chemotherapy, as additional therapies may eliminate the majority of clinical trial options.
[i]Patients who have evidence of radiographic progression may benefit from continuation of bevacizumab to prevent rapid neurologic deterioration.
[j]Bevacizumab + chemotherapy can be considered if bevacizumab monotherapy fails and it is desirable to continue the steroid-sparing effects of bevacizumab.

Full treatment recommendations for recurrent or progressive low-grade gliomas can be found on ASTR-3 (page 1540).

Anaplastic Gliomas and Glioblastomas

High-grade gliomas (defined as WHO grade III and IV gliomas) are the most common type of brain cancer, accounting for more than half of all malignant primary tumors of the CNS.[78] Whereas the prognosis for glioblastoma (grade IV glioma) is grim (5-year survival rates between 1%–19%, depending on age), outcomes for anaplastic gliomas (grade III gliomas) are typically better, depending on the molecular features of the tumor.[54] Challenges regarding treatment of glioblastoma include the inability of most systemic therapy agents to penetrate the blood-brain barrier (BBB) and heterogeneity among genetic drivers.[121]

High-grade astrocytomas diffusely infiltrate surrounding tissues and frequently cross the midline to involve the contralateral brain. Patients with these neoplasms often present with symptoms of increased intracranial pressure, seizures, or focal neurologic findings related to the size and location of the tumor and associated vasogenic edema. High-grade astrocytomas usually do not have associated hemorrhage or calcification but can produce considerable edema and mass effect, and they enhance after the administration of intravenous contrast. Tumor cells have been found in peritumoral edema, which corresponds to the T2-weighted MRI abnormalities. Thus, this volume is frequently used to define RT treatment volumes.

It can be challenging to assess the results of therapy by MRI, because the extent and distribution of contrast enhancement, edema, and mass effect are a function of BBB integrity. Thus, factors that increase permeability of the BBB (such as surgery, RT, tapering of corticosteroids, and immunotherapies) can mimic tumor progression radiographically by increasing the presence of contrast enhancement and associated vasogenic edema. Furthermore, anti-VEGF therapy (ie, bevacizumab) suppresses vascular permeability and provides a radiographic appearance of a response, despite residual disease (pseudoresponse).[122]

Anaplastic oligodendrogliomas are relatively rare.[78] Although these tumors can be confused with glioblastoma

Central Nervous System Cancers

PRINCIPLES OF BRAIN AND SPINAL CORD TUMOR SYSTEMIC THERAPY

GLIOBLASTOMA

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Adjuvant Treatment	• RT with concurrent and adjuvant TMZ[42,43] ± TTF[44]		• RT with concurrent and adjuvant TMZ (for patients age 70 or younger and KPS <60)[45] • TMZ (for patients with MGMT promoter-methylated tumors and KPS <60 or age >70 years and KPS ≥60)[42,46] • RT with concurrent and adjuvant lomustine and TMZ (for patients with MGMT promoter-methylated tumors, KPS ≥60, and age ≤70 years) (category 2B)[k,47]
Recurrence Therapy[h,m]	• Bevacizumab[i,l, 48-51] • Temozolomide[13,29,52,53] • Lomustine or carmustine[54-57] • PCV[58,59] • Regorafenib[60]	• Chemotherapy[j] + bevacizumab ‣ Carmustine or lomustine + bevacizumab[61,62] ‣ TMZ + bevacizumab[63,64]	• If failure or intolerance to the preferred or other recommended regimens ‣ Etoposide (category 2B)[37] ‣ Platinum-based regimens[d] (category 3)[65,66]

[d]Platinum-based regimens include cisplatin or carboplatin.
[h]Strongly suggest consideration of clinical trials prior to treating recurrent disease with standard chemotherapy, as additional therapies may eliminate the majority of clinical trial options.
[i]Patients who have evidence of radiographic progression may benefit from continuation of bevacizumab to prevent rapid neurologic deterioration.
[j]Bevacizumab + chemotherapy can be considered if bevacizumab monotherapy fails and it is desirable to continue the steroid-sparing effects of bevacizumab.
[k]Moderate to significant myelosuppression was observed, but the toxicity profile for this regimen is not yet fully defined.
[l]An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[m]There are no identified targeted agents with demonstrated efficacy in glioblastoma. However, the panel encourages molecular testing of tumor because if a driver mutation is detected, it may be reasonable to treat with a targeted therapy on a compassionate use basis and/or the patient may have more treatment options in the context of a clinical trial. Molecular testing also has a valuable role in improving diagnostic accuracy and prognostic stratification that may inform treatment selection.

BRAIN-D 3 OF 15

histopathologically, if molecular analysis detects that the tumor is 1p19q codeleted and *IDH1*-mut or *IDH2*-mut, then the tumor is considered to be an anaplastic oligodendroglioma.[1] This distinct subtype has a much better prognosis compared with other high-grade gliomas (anaplastic astrocytomas and glioblastomas).

Treatment Overview

Surgery

The goals of surgery are to obtain a diagnosis, alleviate symptoms related to increased intracranial pressure or compression by tumor, increase survival, and decrease the need for corticosteroids. A meta-analysis including six studies with 1618 patients with glioblastoma showed that GTR is associated with superior OS and PFS, compared with incomplete resection and biopsy.[123] Unfortunately, the infiltrative nature of high-grade astrocytomas frequently renders GTR difficult. There are data suggesting that resection of all fluid-attenuated inversion recovery (FLAIR) signal abnormality in high-grade *IDH*-mut gliomas is associated with improved survival.[124] However, a newer and larger study did not find greater benefit of resection in *IDH*-mut tumors compared with *IDH*-wt high-grade gliomas.[125]

Unfortunately, nearly all high-grade gliomas recur. Reresection at the time of recurrence may improve the outcome for select patients.[126] According to an analysis by Park et al,[127] tumor involvement in specific critical brain areas, poor KPS score, and large tumor volume ($\geq$ 50 cm^3) were associated with unfavorable reresection outcomes.

Radiation Therapy

Conformal RT (CRT) techniques, which include 3-dimensional CRT (3D-CRT) and IMRT are recommended for performing focal brain irradiation. IMRT often will provide superior dosimetric target coverage and better sparing of critical structures than 3D-CRT.[103] Several randomized controlled trials conducted in the 1970s showed that radiation improved both local control and survival in patients with newly diagnosed high-grade gliomas.[128,129] Sufficient radiation doses are required to maximize this survival benefit. However, radiation dose escalation alone above 60 Gy has not been shown to be

beneficial.[130] The recommended radiation dose for high-grade astrocytomas is 60 Gy in 2.0 Gy fractions or 59.4 Gy in 1.8 Gy fractions with an initial RT plan to 46 Gy in 2 Gy fractions or 45 to 50.4 Gy in 1.8 fractions, respectively, followed by a boost plan of 14 Gy in 2 Gy fractions or 9 to 14.4 Gy in 1.8 Gy fractions, respectively.[130]

Anaplastic oligodendrogliomas are conventionally treated with the same dose of radiation as high-grade astrocytomas; however, given the better prognosis in patients with anaplastic oligodendroglioma, radiation treatments are generally administered in a lower dose per fraction (1.8 Gy/fraction vs 2.0 Gy/fraction) to theoretically decrease the risk of late side effects. Accordingly, as per trials such as RTOG 9813,[51] these gliomas are treated to 50.4 Gy in 1.8 Gy fractions for 28 fractions followed by a five-fraction boost of 1.8 Gy/fraction to a total of 59.4 Gy. RT targets for high-grade gliomas are generated from a gross tumor volume (GTV), CTV, and planning target volume (PTV). The GTV encompasses any gross tumor remaining after maximal safe resection as well as the surgical cavity as determined by postoperative imaging. Strategies for GTV definition vary with respect to the inclusion of edema in an initial target volume. When edema is included in an initial phase of treatment, fields are usually reduced for the last phase of treatment. The CTV is an expansion of the GTV by adding an approximately 2-cm margin for grade III and IV gliomas (although smaller CTV expansions are supported in the literature and can be appropriate) to account for a nonenhancing tumor. The CTV is then expanded to a PTV to account for daily setup errors and image registration. The boost target volume will typically encompass only the gross residual tumor and the resection cavity.

Special attention has been given to determining the optimal therapy in older adults with glioblastoma, given their especially poor prognosis, often limited functional status, and increased risk of developing side effects. Overall, the approach in these patients has been to reduce treatment time while maintaining treatment efficacy. Roa et al randomized patients 60 years or older with a poor PS (KPS < 70) to 60 Gy in 30 fractions given over 6 weeks versus 40 Gy in 15 fractions given over 3 weeks and found no difference in survival between these two regimens.[131] However, fewer patients who received 40 Gy over a shorter time period required a posttreatment increase in corticosteroid dose, compared with the patients who received 60 Gy over the longer time period (23% vs 49%, respectively; P=.02). A subsequent study also supports using a regimen of 34 Gy in 10 fractions over 2 weeks in older adult patients.[37] Moreover, another study performed by Roa et al showed that an even shorter course of focal brain radiation consisting of 25 Gy in 5 fractions over 1 week is a reasonable alternative to 40 Gy in 15 fractions over 3 weeks in patients with newly diagnosed glioblastoma who have a poor prognosis (ie, patients who are older adults and/or frail).[132] However, this was a small study that had some limitations, notably overly broad eligibility criteria and poorly defined noninferiority margin.[133,134]

A randomized trial of hypofractionated RT (40 Gy given over 3 weeks) with concurrent and adjuvant TMZ versus hypofractionated RT alone in patients 65 years and older showed an improvement in median OS and PFS with the addition of concurrent and adjuvant TMZ (5-year OS of 9.8% vs 1.9%, respectively; median OS of 14.6 months vs 12.1 months, respectively; HR for mortality, 0.63, 95% CI, 0.53—0.75, P<.001; 5-year PFS of 4.1% vs 1.3%, respectively; HR, 0.56; 95% CI, 0.47—0.66; P<.001).[135] The largest benefit was noted in patients with MGMT promoter methylation (see "Systemic Therapy for Glioblastoma," page 1554). Of note, a comparison of standard focal brain radiation (60 Gy given over 6 weeks) with concurrent and adjuvant TMZ versus hypofractionated radiation (40 Gy given over 3 weeks) with concurrent and adjuvant TMZ in elderly patients has not been performed in patients 65 years and older. Therefore, standard radiation (60 Gy given over 6 weeks) with concurrent and adjuvant TMZ (with or without alternating electric field therapy; see discussion of this treatment option in subsequent sections) is also a reasonable treatment option for an older adult patient who has a good PS and wishes to be treated aggressively. Ultimately, quality of life remains an important consideration in the optimal management of this patient population.

Systemic Therapy

Anaplastic Oligodendroglioma

The addition of PCV to RT for the treatment of newly diagnosed anaplastic oligodendrogliomas is supported by results from two phase III trials, one which tested RT followed by PCV for 6 cycles (EORTC 26951[136,137]) and the other which assessed 4 cycles of dose-intensive PCV administered prior to RT (RTOG 9402[27,138,139]). Both studies compared the combination therapy to RT alone and found significant increases in median OS when PCV was added to RT for the upfront management of 1p19q codeleted tumors.

The EORTC 26951 trial showed that, among the entire group of 368 histopathologically diagnosed study patients with anaplastic oligodendroglioma or anaplastic oligoastrocytoma, RT followed by 6 cycles of PCV significantly improved median PFS and OS (42.3 vs 30.6 months; HR, 0.75; 95% CI, 0.60–0.95; P=.018) compared with RT alone.[137] Moreover, in an exploratory subgroup analysis of the 80 patients whose tumors were 1p19q codeleted, the benefit was even more pronounced (OS not reached in the RT + PCV group vs 112 months in the RT group; HR, 0.56; 95% CI, 0.31–1.03).[14,136,137]

RTOG 9402 randomized 291 patients with histopathologically diagnosed anaplastic oligodendroglioma or anaplastic oligoastrocytoma to treatment with an intensive PCV regimen followed by RT or RT alone.[139] In contrast to the EORTC 26951 study, no difference in median OS was observed between the two arms (4.6 years vs 4.7 years; HR, 0.79; 95% CI, 0.60–1.04; *P*=.10). However, an unplanned subgroup analysis of the 126 patients whose tumors were1p19q codeleted found a doubling in median OS (14.7 vs 7.3 years; HR, 0.59; 95% CI, 0.37–0.95; *P*=.03) when PCV was added to RT as upfront treatment.

As would be predicted, in both studies toxicity was higher in the treatment arms that included PCV. In EORTC 26951, 70% of patients in the RT followed by PCV arm did not complete the planned 6 cycles of treatment.[136,137] In RTOG 9402, there was also a high rate of study treatment discontinuation and acute toxicities (mainly hematologic), including 2 early deaths attributed to PCV-induced neutropenia.[138,139] Given the similar efficacy results of the two studies, and the two deaths that occurred from the intensive PCV regimen in RTOG 9402, PCV administered after RT is optimal, as per EORTC 26951.

The phase III CODEL study was designed to assess the efficacy of TMZ for the treatment of newly diagnosed anaplastic oligodendrogliomas. The initial treatment arms were RT alone, RT + TMZ, and TMZ alone. Initial results showed that patients who received TMZ alone had significantly shorter PFS than patients treated with RT (either RT alone or with TMZ) (2.9 years vs not reached, respectively; HR, 3.12; 95% CI, 1.26—7.69; *P*=.009).[140] When the results of RTOG 9402 and EORTC 26951 were reported showing significant improvement in median OS with RT + PCV upfront, the CODEL study was redesigned to compare RT + PCV to RT + TMZ in patients with anaplastic oligodendroglioma as well as low-grade oligodendroglioma. This study is ongoing.

Anaplastic Astrocytoma

The RTOG 9813 trial showed that RT with concurrent TMZ resulted in similar outcomes as RT with concurrent nitrosourea (either CCNU [lomustine] or BCNU [carmustine]) therapy in patients with newly diagnosed anaplastic astrocytomas, with perhaps slightly better PFS with TMZ (HR, 0.70; 95% CI, 0.50–0.98; *P*=.039).[51] However, the toxicity of nitrosourea was significantly worse than for TMZ, and resulted in higher rates of discontinuation due to toxicity (79% vs 40%, respectively; *P*<.001). The ongoing CATNON phase 3 randomized trial is testing RT alone, as well as RT with adjuvant TMZ, concurrent TMZ, or both, in patients with newly diagnosed anaplastic astrocytoma. An initial interim analysis showed adjuvant TMZ significantly improved PFS (HR, 0.62; 95% CI, 0.50–0.76) and OS (HR, 0.67; 95% CI, 0.51–0.88).[117] Median OS for the group of patients treated with post-RT TMZ had not been reached, but median OS at 5 years was 55.9% (95% CI, 47.2–63.8) with and 44.1% (36.3–51.6) without adjuvant TMZ. A second interim analysis showed that patients with *IDH*-mut anaplastic astrocytomas benefit from treatment with adjuvant TMZ (HR, 0.41; 95% CI, 0.27–0.64), but not those with tumors that are *IDH*-wt (HR, 1.05; 95% CI, 0.73–1.52).[141] There was also no definite benefit to concurrent TMZ in patients with *IDH*-mut anaplastic astrocytomas (HR, 0.71; 95% CI, 0.35–1.42; *P*=.32). However, the findings from the second interim analysis are currently available in abstract form only. Further follow-up and molecular analyses are ongoing.

Glioblastoma

Adjuvant involved-field RT with concurrent and adjuvant TMZ is the standard recommended treatment of patients with newly diagnosed glioblastoma and good PS based on the results of the phase III, randomized EORTC-NCIC study of 573 patients with newly diagnosed glioblastoma who were age ≤70 years and had a WHO PS ≤ 2.[135] Patients received either 1) daily TMZ administered concomitantly with postoperative RT followed by 6 cycles of adjuvant TMZ; or 2) RT alone. The chemoradiation arm resulted in a statistically better median survival (14.6 vs 12.1 months) and 2-year survival (26.5% vs 10.4%) when compared with RT alone. Final analysis confirmed the survival advantage at 5 years (10% vs 2%).[135] However, the study design does not shed light on which component is responsible for the improvement: TMZ administered with RT, TMZ following RT, or possibly both.

The TMZ dose used in the EORTC-NCIC trial is 75 mg/m^2 daily concurrent with RT, then 150 to 200 mg/m^2 postirradiation on a 5-day schedule every 28 days. Alternate schedules, such as a 75-100 mg/m^2 for 21 out of 28 days regimen or 50 mg/m^2 daily, have been explored in a phase II trial for newly diagnosed glioblastoma.[142] However, a comparison of the dose-intense 21/28 and standard 5/28 schedules in the RTOG 0525 phase III study showed no difference in PFS, OS, or by MGMT methylation status with the postradiation dose-intense TMZ, compared with the standard postradiation TMZ dose.[143] A pooled analysis of individual patient data from 4 randomized trials[119,143–145] of patients with newly diagnosed glioblastoma determined that treating with postradiation TMZ beyond 6 cycles does not improve OS, even for patients whose tumors are MGMT promoter methylated.[146] A recent prospective, randomized phase II study showed no improvement in 6-month PFS, PFS, or OS with continuing treatment with TMZ beyond 6 cycles, and doing so was associated with greater toxicity.[147]

MGMT Promoter Methylated Glioblastoma

The presence of MGMT promoter methylation in glioblastoma is both a prognostic marker and a predictive one for response to treatment with alkylating agents. In the small (n=31), single arm phase II UKT-03 trial,[148,149] postoperative RT and TMZ combined with lomustine in patients with newly diagnosed glioblastoma resulted in a median OS of 34.3 months,[148] which compared favorably to the historical control data of 23.4 months in patients with MGMT promoter methylated tumors who were treated with RT and TMZ in the EORTC-NCIC trial.[135] Based on this improvement in survival with combination alkylating agents in patients with MGMT promoter methylated glioblastoma, the phase III CeTeG/NOA-09 trial randomized patients with newly diagnosed MGMT promoter methylated glioblastoma (age 18-70 and KPS ≥ 70) to treatment with RT and lomustine+TMZ or RT and TMZ alone.[150] Analysis of the modified intent-to-treat population (n=129) showed that OS was significantly improved in the TMZ + lomustine arm vs the TMZ arm (median OS of 48.1 months vs 31.4 months, respectively; P=.049). Of note, PFS was not significantly improved, which the investigators hypothesized could have been due to a higher incidence of pseudoprogression in the TMZ+lomustine arm. Grade 3 and 4 adverse events were only slightly higher in the TMZ+lomustine arm (59% vs 51%, respectively), but the study was too small to adequately define the toxicity profile of RT with TMZ+lomustine. Analysis of health-related quality of life showed no significant differences between the study arms.[151]

Older Adults

Building on the findings that hypofractionated RT alone has similar efficacy and is better tolerated compared with standard RT alone in older adults with newly diagnosed glioblastoma, a phase III randomized trial with 562 newly diagnosed patients 65 years of age or older compared hypofractionated RT with concurrent and adjuvant TMZ to hypofractionated radiation alone. Patients in the combination therapy arm had better PFS (5.3 months vs 3.9 months; HR, 0.50; 95% CI, 0.41–0.60; P<.001) and median OS (9.3 months vs 7.6 months; HR, 0.67; 95% CI, 0.56–0.80; P<.001) compared with patients treated with hypofractionated RT alone.[118] The greatest improvement in median OS was seen in patients with MGMT promoter methylated tumors (13.5 months RT + TMZ vs 7.7 months RT alone; HR, 0.53; 95% CI, 0.38–0.73; P<.001). The benefit of adding TMZ to RT was smaller in patients with MGMT promoter unmethylated tumors and did not quite reach statistical significance (10.0 months vs 7.9 months, respectively; HR, 0.75; 95% CI, 0.56–1.01; P=.055; P=.08 for interaction).

Two phase III studies in elderly newly diagnosed glioblastoma patients assessed treatment with TMZ alone versus radiation.[37,38] The Nordic trial randomized 291 patients aged 60 years and older with good PS across 3 treatment groups: TMZ, hypofractionated RT, or standard RT.[37] Patients older than 70 years had better survival with TMZ or hypofractionated RT compared with standard RT, and patients whose tumors were MGMT promoter methylated benefitted more from treatment with TMZ compared with patients with MGMT promoter unmethylated tumors (median OS 9.7 vs 6.8 months; HR, 0.56; 95% CI, 0.34–0.93; P=.02). The NOA-08 study assessed the efficacy of TMZ alone compared with standard RT in 373 patients aged 65 years and older.[38] TMZ was found to be noninferior to standard RT; median OS was similar in both groups (8.6 months in the TMZ arm vs 9.6 months in the standard RT arm; HR, 1.09; 95% CI, 0.84–1.42; P (noninferiority) = 0.033). For patients whose tumors were MGMT promoter methylated, event-free survival was longer with TMZ treatment compared with standard RT (8.4 months vs 4.6 months). Neither the Nordic trial nor the NOA-08 trial included a combination RT and TMZ control arm, which is the treatment regimen typically offered to patients who are fit enough to tolerate it, regardless of age. Although radiation in combination with TMZ is recommended over single-modality therapy for newly diagnosed patients with glioblastoma who are older than 70 years of age and have good PS, the results of these two phase III studies support the recommendation that TMZ alone as initial therapy may be a reasonable option for those elderly patients who have MGMT promoter methylated tumors and would initially prefer to delay treatment with radiation.[37,38]

Alternating Electric Field Therapy

In 2015, the FDA approved alternating electric field therapy for the treatment of patients with newly diagnosed glioblastoma based on the results of the open-label phase III EF-14 clinical trial. This portable medical device generates low-intensity alternating electric fields to stop mitosis/cell division. In the EF-14 trial, 695 patients with newly diagnosed glioblastoma and good PS (KPS≥70) were randomized to TMZ alone on a 5/28-day schedule or the same TMZ and alternating electric field therapy, following completion of standard focal brain radiation and daily TMZ.[152] The results of the study showed an improvement in median PFS (6.7 vs 4.0 months, respectively; HR, 0.63; 95% CI, 0.52–0.76; P<.001) and OS (20.9 vs 16.0 months, respectively; HR, 0.63; 95% CI, 0.53–0.76; P<.001) in patients who received TMZ plus alternating electric field therapy.[153] The number of adverse events was not statistically different between the two treatment groups except for a greater frequency of mild to moderate local skin irritation/itchiness in the

patients treated with the alternating electric fields.[154] There was no increased frequency of seizures.[155,156] Based on the results of this study, concurrent treatment with adjuvant TMZ and alternating electric fields is a category 1 recommendation for newly diagnosed glioblastoma patients 70 years of age or younger who have a good PS. This is also considered a reasonable treatment option for patients older than 70 years of age with good PS and newly diagnosed glioblastoma who are treated with standard focal brain radiation and concurrent daily TMZ.

Therapy for Recurrence

Patients with malignant gliomas eventually develop tumor recurrence or progression. Surgical resection of locally recurrent disease is reasonable followed by treatment with chemotherapy. Unfortunately, there is no established second-line therapy for recurrent gliomas. If there has been a long time interval between stopping TMZ and development of tumor progression, it is reasonable to restart a patient on TMZ,[157] particularly if the patient's tumor is MGMT methylated. Similarly, a nitrosourea, such as carmustine or lomustine,[158–161] would be a reasonable second-line therapy, especially in a patient whose tumor is MGMT methylated. Although no studies of bevacizumab in patients with recurrent glioblastoma have demonstrated an improvement in survival, bevacizumab is FDA approved for the treatment of recurrent glioblastoma based on improvement in PFS.[162–164] Of note, improvement in PFS may be due to bevacizumab's ability to decrease BBB permeability (resulting in less contrast enhancement and vasogenic edema) rather than a true antitumor effect.[165,166] Treatment with regorafenib for recurrent glioblastoma is supported by the results of a randomized phase II trial in which OS was greater for patients randomized to receive regorafenib, compared with those who received lomustine (median OS of 7.4 months vs 5.6 months, respectively; HR, 0.50; 95% CI, 0.33—0.75; $P<.001$).[167] Of note, the median OS in the lomustine arm in this trial was lower than reported in other randomized phase II and III trials. A phase III study of regorafenib is being planned.

Other routes of chemotherapy delivery have been evaluated. Local administration of carmustine using a biodegradable polymer (wafer) placed intraoperatively in the surgical cavity has demonstrated a statistically significant improvement in survival for patients with recurrent high-grade gliomas (31 vs 23 weeks; adjusted HR, 0.67; $P=.006$).[168] Patients who receive carmustine wafers are at greater risk for seizures and postoperative infections. When wafers are used, it is important to achieve a watertight dural closure and have sufficient use of steroids and antiepileptics in the perioperative period to prevent adverse events.[169] Clinicians and patients should be aware that treatment with the carmustine wafer may prevent participation in a clinical trial involving a locally delivered investigational agent.

Alternating electric field therapy is also FDA approved for treating recurrent glioblastoma based on the safety results of this medical device from the EF-11 clinical trial.[170] This phase III study randomized 237 patients with recurrent glioblastoma to alternating electric field therapy or the treating oncologist's choice of chemotherapy. The study did not meet its primary endpoint of demonstrating an improvement in survival in the cohort of patients treated with alternating electric field therapy. Although median OS was similar in both of the treatment arms (6.6 vs 6 months), the study had not been powered for a noninferiority determination. Due to lack of clear efficacy data for alternating electric field therapy in EF-11, the panel is divided about recommending it for the treatment of recurrent glioblastoma. Similarly, reirradiation may be reasonable to consider for some recurrent glioblastoma patients, but the panel is also divided about this option. A systematic review including 50 noncomparative studies of 2095 patients with recurrent glioblastoma who were treated with reirradiation showed pooled 6- and 12-month OS rates of 73% and 36%, respectively, and 6- and 12-month PFS rates of 43% and 17%, respectively.[171] Over half of the studies (29 out of 50) were rated as poor quality, indicating a need for better quality studies in this area. Further, there is no recommended dose or type of radiation used in the recurrent setting due to inconsistent trial design among these studies.

NCCN Recommendations

Primary Treatment

When a patient presents with a clinical and radiologic picture suggestive of a high-grade glioma, neurosurgical input is needed regarding the feasibility of maximal safe resection. For first-line treatment of high-grade glioma, the NCCN Guidelines recommend maximal safe resection whenever possible. Use of intraoperative MRI and intraoperative fluorescence-guided surgery with 5-ALA may potentially allow for more complete resection.[172,173] One exception is when CNS lymphoma is suspected; a biopsy should be performed before steroids are administered, and management should follow the corresponding pathway if the diagnosis is confirmed. When maximal resection is performed, the extent of tumor debulking should be documented with a postoperative MRI scan with and without contrast performed within 48 hours after surgery. Multidisciplinary consultation is encouraged once the pathology is available. See GLIO-1 in the algorithm (page 1541).

Adjuvant Therapy

RT is generally recommended after maximal safe resection for the treatment of high-grade gliomas to

improve local control and survival. For postoperative treatment of anaplastic gliomas in patients with good PS (KPS ≥60), combination therapy with focal brain radiation combined with PCV or TMZ are among the recommended options. For patients with anaplastic oligodendroglioma, RT plus PCV, given before or after RT, is preferred, based on the results of the RTOG 9402[27,139] and EORTC 26951 studies.[136,137] The panel advises administering PCV after RT as per EORTC 26951 instead of the dose-intensive PCV used prior to RT in the RTOG 9402 study[139] due to better patient tolerance. RT, with or without concurrent TMZ, followed by adjuvant TMZ is also a reasonable option,[174] particularly if it is predicted that the patient might have significant difficulty tolerating PCV due to age or coexisting medical conditions. The panel awaits the results of CODEL to see if treatment with TMZ will be as efficacious as PCV in this patient population.

In the case of patients with anaplastic astrocytoma and anaplastic oligoastrocytoma (NOS) and good PS, RT, with or without concurrent TMZ and followed by adjuvant TMZ is preferred based on the first interim analysis results of the CATNON trial showing improvement in survival with RT followed by 12 cycles of TMZ compared with RT alone.[117] However, for newly diagnosed anaplastic oligoastrocytoma patients, RT with PCV administered before or afterward is also an acceptable treatment option.[175,176]

For patients with anaplastic gliomas and a poor PS (KPS <60), treatment options recommended in the NCCN Guidelines are limited to single-modality therapies due to concerns about the ability of these patients to tolerate the toxicity associated with combination regimens. Patients with a poor PS can be managed by RT (hypofractionation is preferred over standard fractionation), TMZ alone (considered for patients whose tumors are MGMT promoter methylated but is a category 2B option), or palliative/best supportive care.

Full treatment recommendations for anaplastic gliomas can be found on GLIO-2 (page 1542); systemic therapy recommendations can be found on BRAIN-D 2 of 15 (page 1553).

For patients diagnosed with glioblastoma, the adjuvant options mainly depend on the patient's age, PS (as defined by KPS), and MGMT promoter methylation status (see GLIO-3 and GLIO-4 on pages 1543 and 1544).[34,37,135,177] Category 1 recommendations for patients aged 70 years and younger with a good PS, regardless of the tumor's MGMT methylation status, include standard brain RT plus concurrent and adjuvant TMZ with or without alternating electric field therapy. Because patients with newly diagnosed MGMT promoter unmethylated glioblastoma are likely to receive less benefit from TMZ, RT alone is included as a reasonable option, particularly if the patient is eligible to participate in a clinical trial, which omits the use of upfront TMZ.

Category 1 treatment recommendations for patients older than 70 years of age with newly diagnosed glioblastoma, a good PS, and MGMT promoter methylated tumors include hypofractionated brain RT plus concurrent and adjuvant TMZ[118] or standard brain RT plus concurrent and adjuvant TMZ and alternating electric field therapy. For those patients older than 70 years with newly diagnosed glioblastoma, a good PS, and with MGMT unmethylated or indeterminant tumors, hypofractionated brain radiation with concurrent and adjuvant TMZ[118] is preferred, but standard brain RT plus concurrent and adjuvant TMZ and alternating electric field therapy is also a reasonable option (category 1)[152,153] for those elderly patients who want to be treated as aggressively as possible. The complete list of recommendations that the panel did not consider category 1 can be found in the treatment algorithms for patients with glioblastoma who are older than 70 years.

Treatment recommendations for patients with newly diagnosed glioblastoma and KPS below 60 (regardless of age) include hypofractionated brain RT possibly with concurrent and adjuvant TMZ for patients aged 70 years or younger, TMZ alone (for patients with MGMT promoter methylated tumors), or palliative/best supportive care.

Follow-up and Recurrence

Patients should be followed closely with serial brain MRI scans (at 2–8 weeks postirradiation, then every 2–4 months for 3 years, then every 3–6 months indefinitely) after the completion of treatment of newly diagnosed disease. Scans may appear worse during the first 3 months or longer after completion of RT even though there may be no actual tumor progression.[121] This finding of "pseudoprogression" occurs more often in patients whose tumors are MGMT promoter methylated.[178,179] Early MRI scans allow for appropriate titration of corticosteroid doses based on the extent of mass effect and brain edema. Later scans are used to identify tumor recurrence. Early detection of recurrence is warranted, because local and systemic treatment options are available for patients with recurrent disease. Biopsy, MR spectroscopy, MR perfusion, or brain PET/CT can be considered to try to determine if the changes seen on brain MRI are due to pseudoprogression or RT-induced necrosis versus actual disease progression.[180,181] RT-induced necrosis tends to be detected between 6 and 24 months following RT treatment.[179]

Management of recurrent tumors depends on the extent of disease and patient condition (see GLIO-5 on page 1545). The efficacy of current treatment options for recurrent disease remains poor; therefore, enrollment in a clinical trial, whenever possible, is preferred for the

management of recurrent disease. Preferred chemotherapy options for recurrent disease include retreatment with TMZ (if there has been a long interval between completion of adjuvant TMZ and development of recurrent disease),[111,157,182–184] carmustine/lomustine,[158–161,185] bevacizumab,[162,186–191] regorafenib,[167] and PCV[112,192,193] (see BRAIN-D 3 of 15 for the list of systemic therapy recommendations, page 1554). A patient with a poor PS should receive palliative/best supportive care.

Brain Metastases

Metastases to the brain are the most common intracranial tumors in adults and may occur up to 10 times more frequently than primary brain tumors. Population-based data reported that about 8%–10% of patients with cancer are affected by symptomatic metastatic tumors in the brain.[194,195] Based on autopsy studies, brain metastases have been shown to be present in 25% of patients with cancer.[196]

As a result of advances in diagnosis and treatment, many patients improve with proper management and do not die of progression of these metastatic lesions. Primary lung cancers are the most common source,[197] although melanoma has a high predilection to spread to the brain.[198] Diagnosis of CNS involvement is increasing in patients with breast cancer as therapy for metastatic disease is improving.[199]

Nearly 80% of brain metastases occur in the cerebral hemispheres, an additional 15% occur in the cerebellum, and 5% occur in the brainstem.[200] These lesions typically follow a pattern of hematogenous spread to the gray-white junction where the relatively narrow caliber of the blood vessels tends to trap tumor emboli. The majority of cases have multiple brain metastases evident on MRI scans. The presenting signs and symptoms of metastatic brain lesions are similar to those of other mass lesions in the brain, such as headache, seizures, and neurologic impairment.

Treatment Overview

Surgery

Despite advances in surgical technique, surgery alone for brain metastases is not sufficient for achieving local control.[201,202] The objectives of surgery for brain metastasis include retrieval of tissue for diagnosis, reduction of mass effect, and improvement of edema.[203] To promote local control following resection of a brain metastasis, adjuvant RT represents an acceptable treatment strategy, discussed further below. Randomized trials reported in the 1990s demonstrated an OS benefit with surgical resection for patients with single brain metastases. In a study of 48 patients, Patchell et al[204] demonstrated that surgery followed by WBRT compared with WBRT alone improved OS (40 vs 15 weeks in WBRT arm; $P<.01$) and functional dependence (38 vs 8 weeks; $P<.005$), as well as decreased recurrence (20% vs 52%; $P<.02$). Similarly, combined surgery and WBRT led to longer survival and functional independence compared with WBRT alone in another randomized study by Vecht and colleagues (n=63).[205] A third study of 84 patients found no difference in survival between the two strategies; however, patients with extensive systemic disease and lower performance level were included, which likely resulted in poorer outcomes in the surgical arm.[206]

Stereotactic Radiosurgery

SRS offers an excellent minimally invasive ablative treatment option for brain metastases. Patients undergoing SRS avoid the risk of surgery-related morbidity, and SRS is generally preferred over surgery for patients with small, asymptomatic lesions that do not require surgery and for patients with lesions that are not surgically accessible.[203] Late side effects of SRS such as symptomatic edema and RT necrosis are relatively uncommon, but may be observed at higher rates when treating larger lesions.[207]

The role of stereotactic SRS alone for limited brain metastases has been established by multiple phase III randomized trials comparing SRS alone to SRS plus WBRT.[208–211] Collectively, these studies demonstrate comparable OS and superior cognitive preservation and quality of life with SRS alone compared with SRS plus WBRT. The role of SRS for patients with multiple metastases has also continued to expand. A prospective trial of 1194 patients found no differences in OS or neurologic mortality with SRS for 2 to 4 versus 5 to 10 brain metastases.[212] A number of analyses have suggested that total volume of brain metastases and the rate of developing new brain metastases may be more important prognostic factors for OS than the number of discrete brain metastases.[213–216] Taken together, patients with multiple lesions but a low total volume of disease, as well as those with relatively indolent rates of developing new CNS lesions, can represent suitable candidates for SRS. Additionally, patients with a favorable histology of the primary tumor (such as breast cancer) or controlled primary tumors can often benefit from SRS regardless of the number of brain metastases present.[217,218] While brain metastases arising from small-cell lung cancer have historically been treated with WBRT, an international retrospective study suggested that SRS may be suitable in some cases.[219] Some brain metastases of radioresistant primary tumors such as melanoma and renal cell carcinoma have also been shown to achieve good local control with SRS.[220] Other predictors of longer survival with SRS include younger age, good PS, and primary tumor control.[213,217,218,221] However, there are a number of contemporary series supporting SRS in

patients with a poor prognosis, with poor KPS, or who are older.[222–225]

Maximal marginal doses for SRS use should be based on tumor volume and range from 15 to 24 Gy when treating lesions with a single fraction of SRS.[208,212,226] Multifraction SRS may be considered for larger tumors, with the most common doses being 27 Gy in 3 fractions and 30 Gy in 5 fractions.[227–229] Contouring guidelines have been published elsewhere.[230] In the recurrence setting, several patient series have demonstrated local control rates greater than 70% with SRS for patients with good PS and stable disease who have received prior WBRT.[231–234]

Postoperative SRS also represents an important strategy to improve local control after resection of brain metastases. After resection alone, the rates of local recurrence are relatively high, and have been reported in the range of 50% at 1 to 2 years in prospective trials. Postoperative SRS to the surgical cavity is supported by a randomized phase III trial including 132 patients with resected brain metastases (1–3 lesions). This trial demonstrated that postoperative SRS was associated with a higher 12-month local recurrence-free rate compared with no postoperative treatment (72% vs 43%, respectively; HR, 0.46; 95% CI, 0.24–0.88; P=.015).[201] A separate randomized phase III trial comparing postoperative SRS with postoperative WBRT demonstrated similar OS and better cognitive preservation with a strategy of postoperative SRS, despite superior CNS control outcomes with WBRT.[235]

Whole-Brain Radiation Therapy

Historically, WBRT was the mainstay of treatment of metastatic lesions in the brain. Although the role of WBRT has diminished over the last several decades, WBRT continues to play a role in the modern era, primarily in clinical scenarios where SRS and surgery are not feasible or indicated (eg, diffuse brain metastases). The standard dosing for WBRT is 30 Gy in 10 fractions or 37.5 Gy in 15 fractions. For patients with poor prognosis, 20 Gy in 5 fractions may also be used.

The impact of WBRT in addition to SRS has been evaluated in multiple randomized controlled studies.[208–211,236] A 2018 Cochrane meta-analysis of randomized controlled trials found that the addition of WBRT to SRS alone was associated with better brain control, no differences in OS, and worse neurocognitive outcomes or quality of life in several trials.[237] The randomized phase III EORTC 22952 trial failed to show an OS benefit from WBRT following resection or SRS, compared with observation,[211] even in subgroup analyses including only patients with controlled extracranial disease and a favorable prognostic score.[238] Overall, for patients treated with SRS for brain metastases, the routine addition of WBRT is not recommended due to increased cognitive and quality-of-life toxicity and the lack of an OS benefit.

The randomized phase III noninferiority QUARTZ trial compared WBRT to optimal supportive care in patients with nonsmall cell lung cancer (NSCLC) who were not candidates for SRS, due to various factors including age, PS, and extent of disease. No differences in OS or quality of life were observed with WBRT versus optimal supportive care, which suggests that this population may derive minimal benefit from WBRT.[239] Moreover, as noted above, a number of studies support SRS for older patients and those with poor prognosis who have historically received WBRT.[222–225,240] The optimal treatment strategy of brain metastases for patients with a poor prognosis is highly individualized and may call for best supportive care, WBRT, SRS, or trials of CNS-active systemic agents depending on the clinical scenarios.

In light of the well-characterized deleterious cognitive effects of WBRT,[209,210,235] a number of trials have evaluated strategies to promote cognitive preservation in patients with brain metastases including investigation of neuroprotective agents, anatomic avoidance strategies, and deferral of WBRT in favor of alternate strategies such as SRS or trials of CNS-active systemic agents. In patients undergoing WBRT for brain metastases, the RTOG 0614 (n=554) compared concurrent and adjuvant memantine, an *N*-methyl-D-aspartate receptor antagonist, to placebo. Memantine was well-tolerated in patients receiving WBRT for brain metastases, and the rates of toxicity were similar to patients receiving placebo.[241] There was possibly less decline in episodic memory (HVLT-R Delayed Recall) in the memantine arm compared with placebo at 24 weeks (P=.059). The memantine arm had significantly longer time to cognitive decline (HR, 0.78; 95% CI, 0.62–0.99; P=.01), and the probability of cognitive function failure at 24 weeks was 54% in the memantine arm and 65% in the placebo arm. However, for most cognitive endpoints, no significant differences were observed between memantine and placebo, despite numerical trends that generally favored the memantine arm. For patients with a good prognosis, memantine may be considered during WBRT, as well as after treatment of as long as 6 months.

To evaluate an anatomic-avoidance strategy to promote cognitive preservation, the nonrandomized phase II RTOG-0933 trial showed that reduced radiation dose to the hippocampal neural stem-cell compartment was associated with a smaller decline in recall (P<.001), compared with a historical control.[242] Based on these results, the phase III NRG-CC001 trial evaluated WBRT with memantine with or without hippocampal avoidance.[243] There were no significant differences in survival outcomes. However, risk of cognitive failure was significantly lower in the hippocampal avoidance arm than in

the control arm (HR, 0.76; 95% CI, 0.60—0.98; P=.03). For patients without tumor in or around the hippocampus, hippocampal-sparing WBRT may be preferred in select patients (eg, those with good prognosis).

In the postoperative setting, phase 3 trials have evaluated the role of WBRT after surgical resection of brain metastases. Patchell conducted a study that randomized 95 patients with single intracranial metastases to surgery with or without adjuvant WBRT.[244] Postoperative RT was associated with a dramatic reduction in tumor recurrence (18% vs 70%; P<.001) and likelihood of neurologic deaths (14% vs 44%; P=.003). OS, a secondary endpoint, showed no difference between the arms. The aforementioned EORTC 22952 trial randomized patients treated with local therapy (surgery or SRS) to observation versus WBRT.[211] Patients randomized to WBRT were found to have superior brain disease control and less death form neurologic causes, but inferior QOL and no differences in OS.[211,245] The NCCTG N107C/CEC-3 randomized phase III trial included 194 patients with resected brain metastases randomized to either postoperative SRS or WBRT.[235] Although there was no significant difference between the treatment arms for OS, cognitive deterioration at 6 months was less frequent in the SRS arm than in the WBRT arm (52% vs 85%, respectively; P<.001), and cognitive deterioration-free survival was also greater for postoperative SRS compared with WBRT (median 3.7 months vs median 3.0 months; HR, 0.47; 95% CI, 0.35–0.63; P<.001). In another phase III trial, 215 patients with 1-3 brain metastases from melanoma were randomized to either WBRT or observation following local treatment with surgery or SRS.[246] Though local failure rate was significantly lower in the WBRT arm (20.0% vs 33.6%, respectively; P=.03), there were no significant differences between the study arms for intracranial failure, OS, and deterioration in performance status. Further, grade 1 to 2 toxicity during the first 2-4 months was more frequently reported in the WBRT arm.

Systemic Therapy

Many tumors that metastasize to the brain are not chemosensitive or have already been heavily pretreated with organ-specific effective agents. Poor penetration through the BBB is an additional concern.[198] However, there are increasing numbers of systemic treatment options with demonstrated activity in the brain, and it is now reasonable to treat some of these patients (ie, those with asymptomatic brain metastases) with systemic therapy upfront instead of upfront SRS or WBRT. Specific recommended regimens are based on effective treatment of the primary tumor. Studies have demonstrated that some regimens are effective for treatment of brain metastases for certain types of cancer, notably melanoma (eg, dabrafenib/trametinib for BRAF v600E positive disease,[247] ipilimumab/nivolumab[248]), NSCLC (eg, osimertinib for EGFR T790M positive disease,[249–251] brigatinib, alectinib, and ceritinib for ALK-positive disease,[252,253] pembrolizumab and nivolumab for PD-L1-positive disease[254,255]), and specific combinations for certain breast cancers (capecitabine with lapatinib or neratinib for HER2-positive disease,[256–258] tucatinib/trastuzumab/capecitabine for previously treated HER2-positive disease[259]). There are also an increasing number of "basket" studies that evaluate the efficacy of targeted therapy options for a specific mutation or biomarker, regardless of tumor type. For example, the TRK inhibitors larotrectinib and entrectinib were found to be active in patients with brain metastases from NTRK gene fusion-positive solid tumors.[260,261]

As CNS-active systemic agents are changing paradigms for the management of brain metastases, it is important to acknowledge that there is a paucity of prospective data to characterize optimal strategies regarding radiation and systemic therapy combinations or sequencing. When considering a trial of upfront systemic therapy alone for brain metastases, a multidisciplinary discussion between medical and radiation oncology is recommended. Ongoing CNS surveillance with brain MRIs is essential to allow early interventions in cases of progression or inadequate response.

NCCN Recommendations

Workup

Patients who present with a single mass or multiple lesions on MRI or CT imaging suggestive of metastatic cancer to the brain, and who do not have a known primary, require a careful systemic workup with chest X-ray or CT with contrast, abdominal or pelvic CT with contrast, or other tests as indicated. Whole-body PET/CT may be considered. If no other readily accessible tumor is available for biopsy, a stereotactic or open biopsy resection is indicated to establish a diagnosis. Workup recommendations can be found on LTD-1 for limited brain metastases (see page 1546) and on MU-1 for extensive brain metastases (see page 1550).

Treatment of Limited Metastatic Lesions

The panel defines "limited" brain metastases as patients for whom SRS represents an effective alternative to WBRT, but with more cognitive protection.[212] Because brain metastases are often managed by physicians from multiple disciplines, the NCCN Panel encourages multidisciplinary consultation prior to treatment of optimal planning. Treatment recommendations for limited brain metastases can be found on LTD-2 (page 1547).

Surgical resection may be considered in select cases (eg, for management of mass effect or other symptoms;

for tumors >3 cm that are surgically accessible; if there is no other readily accessible tumor to be biopsied). For patients with newly diagnosed or stable systemic disease, treatment options include SRS (preferred) and WBRT. When patients are managed with SRS, NCCN does not recommend the routine addition of WBRT, as this approach has been consistently associated with cognitive deterioration and no difference in survival.[209] The management of patients with disseminated systemic disease or poor prognosis should be individualized and may include strategies of best supportive care, WBRT, SRS, or a trial of CNS-active systemic agents; multidisciplinary evaluation is encouraged.

In patients with systemic cancers with options for CNS-active systemic therapies, (eg, ALK or EGFR mutations in NSCLC; *BRAF* mutations in metastatic melanoma), upfront systemic therapy alone may be considered in carefully selected, asymptomatic patients. When considering a trial of upfront systemic therapy alone for brain metastases, NCCN recommends a multidisciplinary discussion between medical and radiation oncologists and ongoing CNS surveillance with brain MRIs to allow for early interventions in cases of progression or inadequate response.

Patients should be followed with brain MRI every 2 to 3 months for 1-2 years and then every 4 to 6 months indefinitely. Closer follow-up every 2 months may be particularly helpful for patients treated with SRS or systemic therapy alone.[210] Evaluation of potential disease recurrence can be confounded by treatment effects of SRS. Tumor sampling may be indicated to discern recurrence versus treatment effect in some cases. Upon detection of recurrent disease, prior therapy clearly influences the choice of further therapies. Patients with recurrent CNS disease should be assessed for local versus systemic disease, because therapy will differ. For local recurrences, patients who were previously treated with surgery only can receive the following options: 1) surgery with consideration of SRS or RT to the surgical bed, 2) single-dose or fractionated SRS, 3) WBRT, or 4) systemic therapy. However, patients who previously received WBRT generally should not undergo WBRT at recurrence due to concern regarding neurotoxicity. If the patient had previous SRS with a durable response for >6 months, reconsider SRS if imaging or biopsy supports active tumor and not necrosis. Repeat SRS to a prior location is a category 2B recommendation.

If isolated CNS disease progression occurs in the setting of limited systemic treatment options and poor PS, management of brain metastases should be individualized and may include best supportive care, WBRT, SRS, and CNS-active systemic agents. WBRT reirradiation is generally discouraged due to toxicity to cognition and quality of life and should be administered only in highly selected circumstances. Full treatment recommendations can be found on LTD-3 for recurrent disease (see page 1548) and on LTD-4 for relapsed disease (see page 1549).

Treatment of Extensive Metastatic Lesions

Patients diagnosed with extensive metastatic lesions should generally be treated with WBRT or SRS as primary therapy. For WBRT dosing, the standard regimens are 30 Gy in 10 fractions or 37.5 Gy in 15 fractions. For patients with poor neurologic performance, a more rapid course of RT can be considered (20 Gy, delivered in 5 fractions). SRS may be considered in select patients, particularly those with good PS and low overall tumor volume. Some patients may be eligible for upfront systemic therapy treatment. Palliative neurosurgery may also be considered if a lesion is causing a life-threatening mass effect, hemorrhage, or hydrocephalus. Full treatment recommendations for extensive brain metastases can be found on MU-1 (page 1550).

After WBRT or SRS, patients should have a repeat contrast-enhanced MRI scan every 2 to 3 months for 1-2 years, then every 4 to 6 months indefinitely. Treatment of recurrences are individualized and may include best supportive care, surgery, WBRT, SRS, or a trial of CNS-active systemic therapy; multidisciplinary review is recommended. Repeat WBRT is generally discouraged due to toxicity to cognition and quality of life and should only be administered in highly selected circumstances. Treatment recommendations for recurrent disease can be found on MU-2 (page 1551).

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The NCCN Guidelines Staff have no conflicts to disclose.

[a]The following individuals have disclosed that they have an employment/governing board, patent, equity, or royalty:
Manmeet Ahluwalia, MD: Cytodyn; Doctible; and Mimivax
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