National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Central Nervous System Cancers

NCCN Evidence Blocks™

Version 3.2019 — November 11, 2019

NCCN.org

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NCCN Guidelines Version 3.2019
Central Nervous System Cancers
NCCN Evidence Blocks™

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Þ Internal medicine/Primary care
† Medical oncology
Ψ Neurology/Neuro-oncology
≠ Pathology
¥ Patient Advocacy
§ Radiotherapy/Radiation oncology
¶ Surgery/Surgical oncology
* Discussion Section Writing Committee

NCCN Guidelines Panel Disclosures

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- Brain Tumor Surgery (BRAIN-B)
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- Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D)
- Brain and Spine Tumor Management (BRAIN-E)
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Clinical Trials: NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/clinicians.aspx.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

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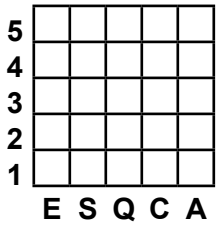
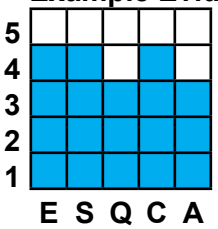
NCCN EVIDENCE BLOCKS CATEGORIES AND DEFINITIONS



E = Efficacy of Regimen/Agent
S = Safety of Regimen/Agent
Q = Quality of Evidence
C = Consistency of Evidence
A = Affordability of Regimen/Agent

Example Evidence Block



E = 4
S = 4
Q = 3
C = 4
A = 3

Efficacy of Regimen/Agent

5	**Highly effective:** Cure likely and often provides long-term survival advantage
4	**Very effective:** Cure unlikely but sometimes provides long-term survival advantage
3	**Moderately effective:** Modest impact on survival, but often provides control of disease
2	**Minimally effective:** No, or unknown impact on survival, but sometimes provides control of disease
1	**Palliative:** Provides symptomatic benefit only

Safety of Regimen/Agent

5	**Usually no meaningful toxicity:** Uncommon or minimal toxicities; no interference with activities of daily living (ADLs)
4	**Occasionally toxic:** Rare significant toxicities or low-grade toxicities only; little interference with ADLs
3	**Mildly toxic:** Mild toxicity that interferes with ADLs
2	**Moderately toxic:** Significant toxicities often occur but life threatening/fatal toxicity is uncommon; interference with ADLs is frequent
1	**Highly toxic:** Significant toxicities or life threatening/fatal toxicity occurs often; interference with ADLs is usual and severe

Note: For significant chronic or long-term toxicities, score decreased by 1

Quality of Evidence

5	**High quality:** Multiple well-designed randomized trials and/or meta-analyses
4	**Good quality:** One or more well-designed randomized trials
3	**Average quality:** Low quality randomized trial(s) or well-designed non-randomized trial(s)
2	**Low quality:** Case reports or extensive clinical experience
1	**Poor quality:** Little or no evidence

Consistency of Evidence

5	**Highly consistent:** Multiple trials with similar outcomes
4	**Mainly consistent:** Multiple trials with some variability in outcome
3	**May be consistent:** Few trials or only trials with few patients, whether randomized or not, with some variability in outcome
2	**Inconsistent:** Meaningful differences in direction of outcome between quality trials
1	**Anecdotal evidence only:** Evidence in humans based upon anecdotal experience

Affordability of Regimen/Agent (includes drug cost, supportive care, infusions, toxicity monitoring, management of toxicity)

5	**Very inexpensive**
4	**Inexpensive**
3	**Moderately expensive**
2	**Expensive**
1	**Very expensive**

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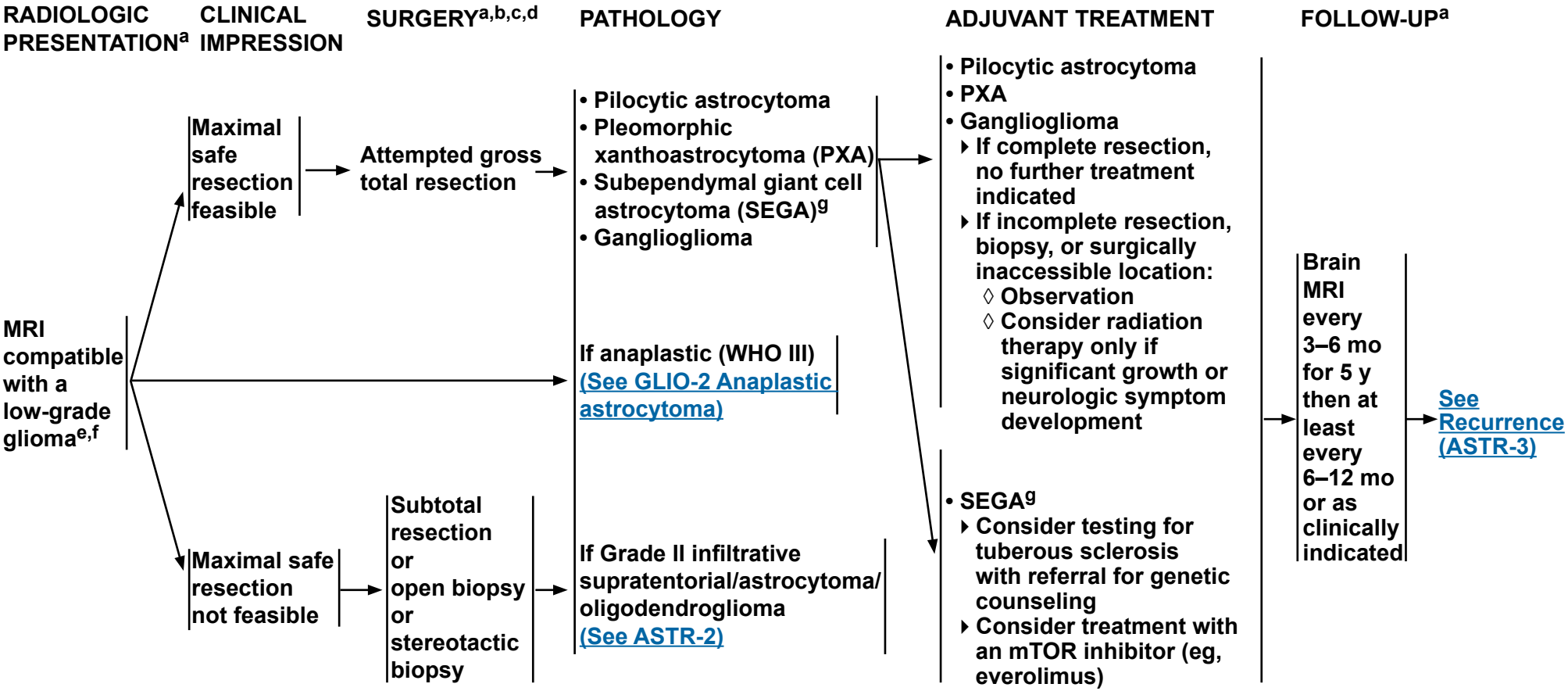

[a] See Principles of Brain and Spine Tumor Imaging (BRAIN-A).
[b] See Principles of Brain Tumor Surgery (BRAIN-B).
[c] Recommended molecular diagnostics include 1p19q chromosomal status and IDH1/2 mutation status. See Principles of Brain Tumor Pathology (BRAIN-F).
[d] Postoperative brain MRI within 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.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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Adult Low-Grade (WHO Grade I or II) Glioma/Pilocytic and Infiltrative Supratentorial Astrocytoma/Oligodendoglioma
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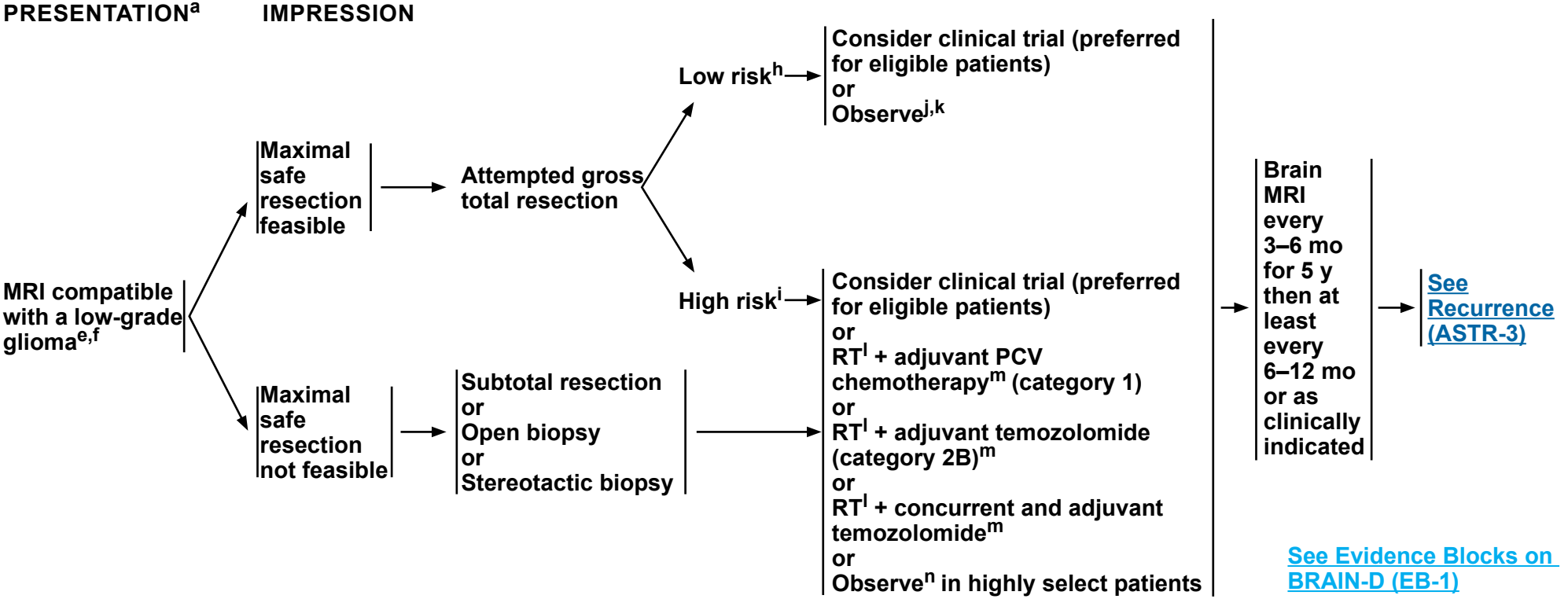

[a] See Principles of Brain and Spine Tumor Imaging (BRAIN-A).
[b] See Principles of Brain Tumor Surgery (BRAIN-B).
[c] Recommended molecular diagnostics include 1p19q chromosomal status and IDH1/2 mutation status. See Principles of Brain Tumor Pathology (BRAIN-F).
[d] Postoperative brain MRI within 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.
[h] Low-risk features: ≤40 y and gross total resection (GTR).
[i] High-risk features: >40 y or subtotal resection (STR). Other high-risk factors that are sometimes taken into consideration are tumor size, neurologic deficits, and presence of sequencing verified IDH wild type.
[j] Regular follow-up is essential for patients receiving observation alone after resection.
[k] 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).
[l] For low-grade gliomas, See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C).
[m] See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).
[n] 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.

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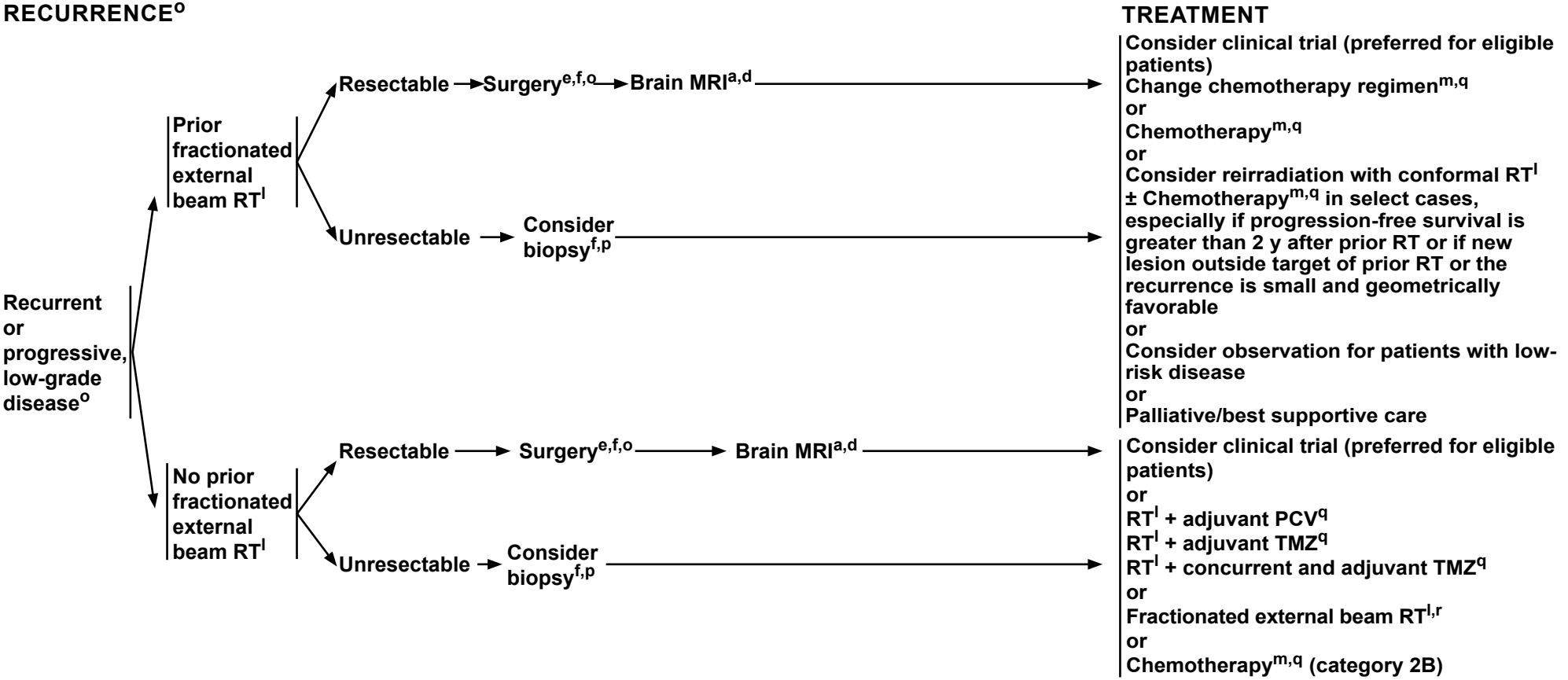

See Evidence Blocks on BRAIN-D (EB-1)

[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 and IDH1/2 mutation status. See Principles of Brain Tumor Pathology (BRAIN-F).
[d] Postoperative brain MRI within 48 hours after surgery.
[l] For low-grade gliomas, See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C).
[m] See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).
[o] If GTR is achieved in a patient with low-risk disease, consider further observation.
[p] 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.
[q] 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).
[r] RT alone is not encouraged, but may be appropriate for select cases (eg, poor performance status).

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NCCN Guidelines Version 3.2019
Anaplastic Gliomas[a]/Glioblastoma
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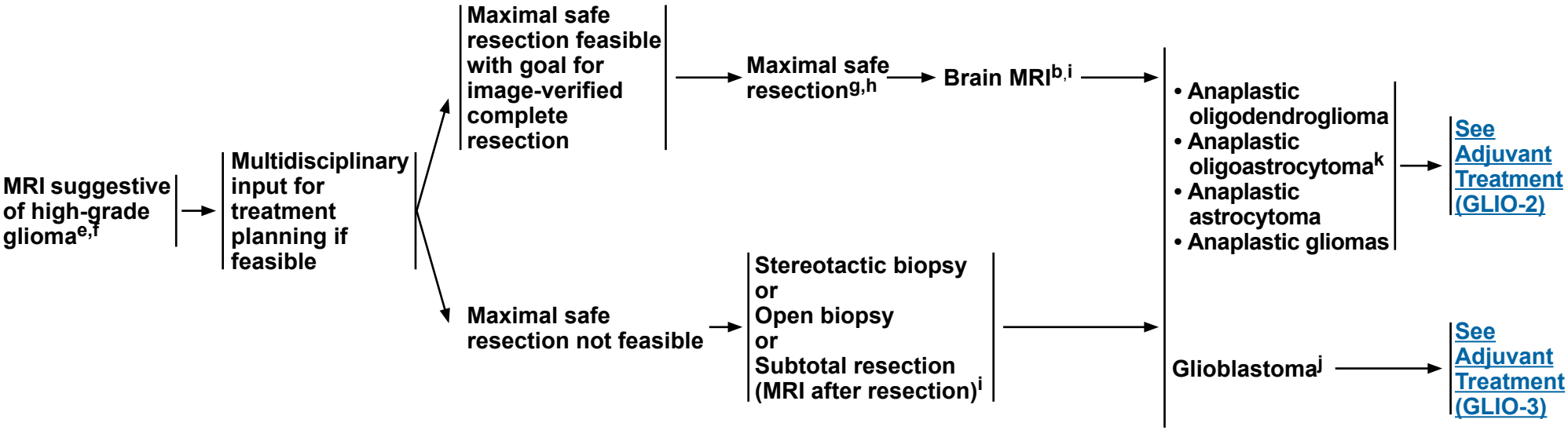

[a]This pathway includes the classification of mixed anaplastic oligoastrocytoma (AOA), anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), and other rare anaplastic gliomas.
[b]See Principles of Brain and Spine Tumor Imaging (BRAIN-A).
[c]See Principles of Brain Tumor Surgery (BRAIN-B).
[d]See Principles of Brain Tumor Pathology (BRAIN-F).
[e]Biopsy first 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]This pathway also includes gliosarcoma.
[k]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.

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ANAPLASTIC GLIOMAS (SEE GLIO-3/GLIO-4 FOR GLIOBLASTOMA)

PATHOLOGY[d]	ADJUVANT TREATMENT	FOLLOW-UP[b]
Anaplastic oligodendroglioma (1p19q codeleted)	Consider clinical trial (preferred for eligible patients) or Fractionated external beam RT[l] and neoadjuvant or adjuvant[m] PCV (category 1)[n] or Fractionated external beam RT[l] with concurrent and adjuvant temozolomide[n] or Fractionated external beam RT[l] and adjuvant temozolomide[n]	Brain MRI 2–6 wks after RT,[p] then every 2–4 mo for 3 y, then every 3–6 months indefinitely → See Recurrence (GLIO-5)
Anaplastic astrocytoma, Anaplastic oligoastrocytoma, NOS[k]	Consider clinical trial (preferred for eligible patients) or Fractionated external beam RT followed by adjuvant temozolomide[n] or Fractionated external beam RT[l] with concurrent and adjuvant temozolomide[n] or Fractionated external beam RT[l] + neoadjuvant or adjuvant[m] PCV	
Anaplastic gliomas[a] Poor performance status (KPS <60)	Fractionated external beam RT[l] (hypofractionated [preferred] or standard) or Temozolomide (category 2B)[n,o] or Palliative/best supportive care	

See Evidence Blocks on BRAIN-D (EB-2)

[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).
[d]See Principles of Brain Tumor Pathology (BRAIN-F).
[k]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.

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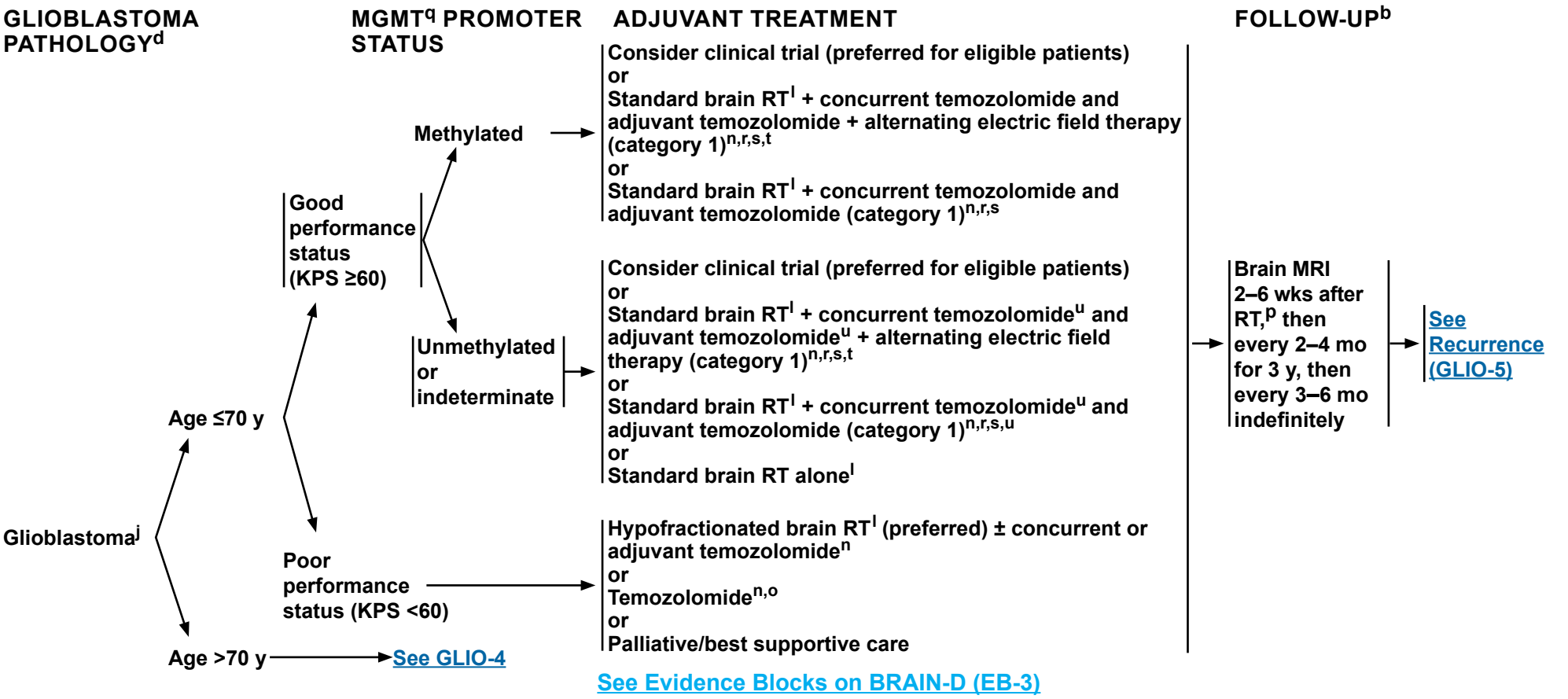

[a]This pathway includes the classification of mixed AOA, AA, AO, and other rare anaplastic gliomas.
[b]See Principles of Brain and Spine Tumor Imaging (BRAIN-A).
[d]See Principles of Brain Tumor Pathology (BRAIN-F).
[j]This pathway also includes gliosarcoma.
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[n]See 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 agents may lead to increased toxicity or radiographic changes.
[s]Benefit of treatment with temozolomide for glioblastomas beyond 6 months is unknown.
[t]Alternating electric field therapy is only an option for patients with supratentorial disease.
[u]Clinical benefit from temozolomide is likely to be lower in patients whose tumors lack MGMT promoter methylation.

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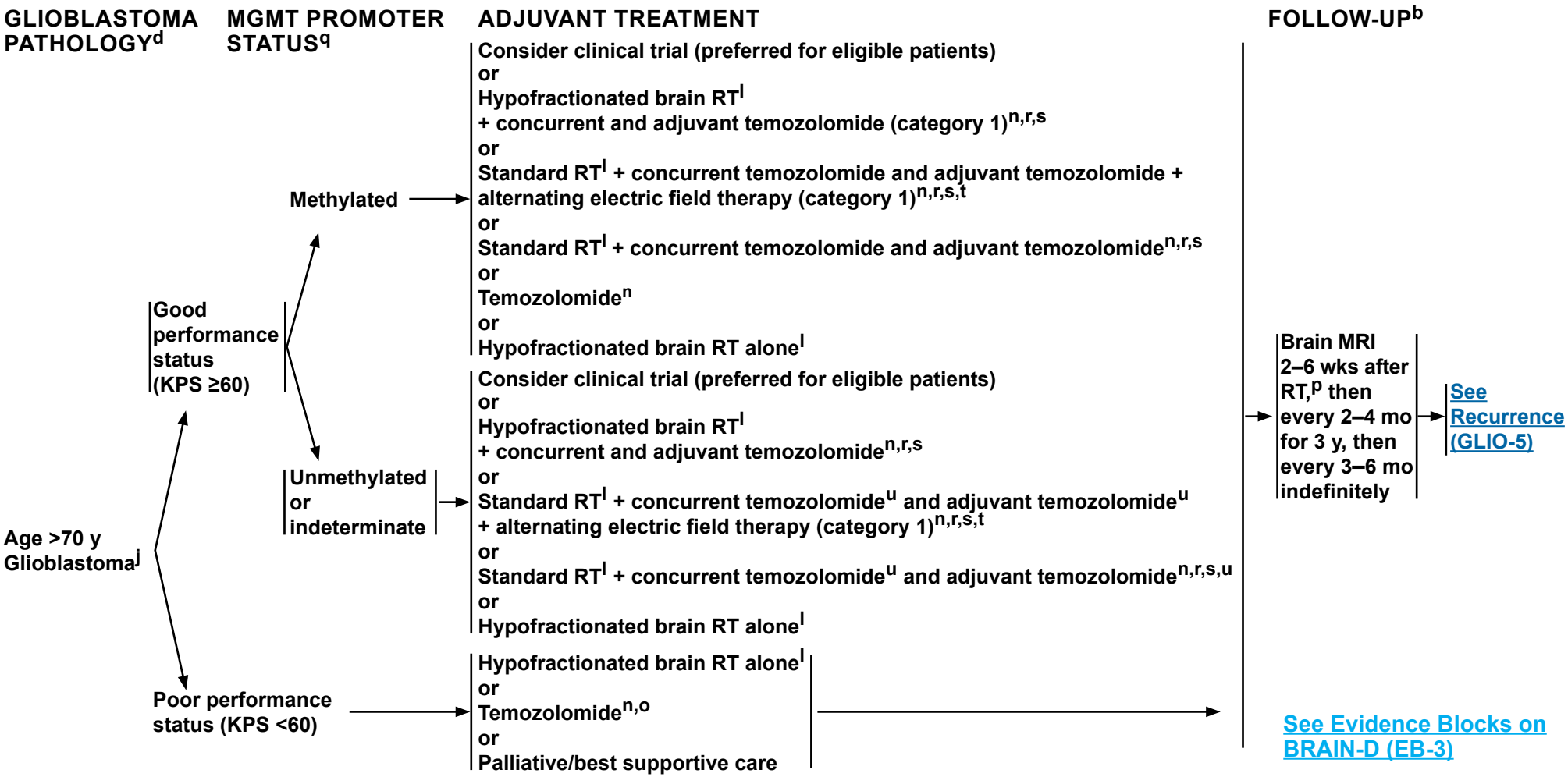

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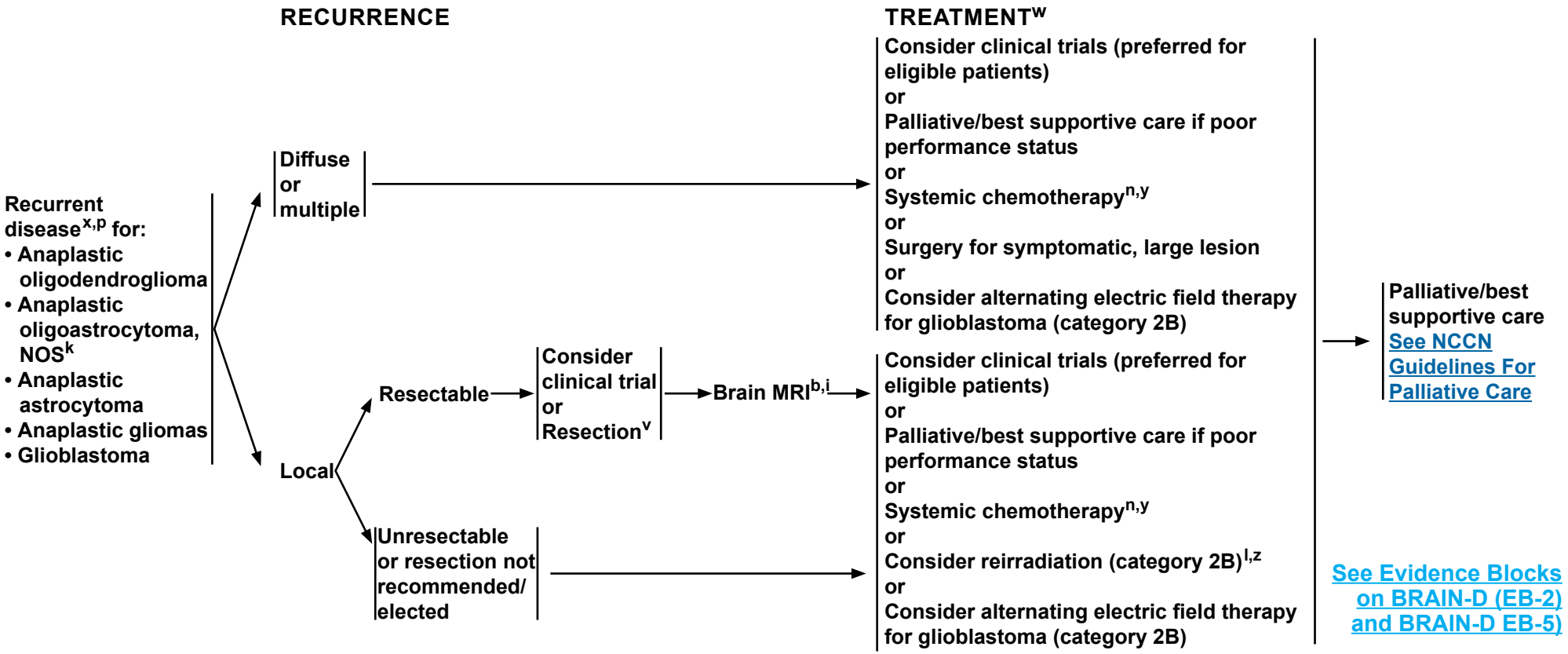

[a]This pathway includes the classification of mixed AOA, AA, AO, and other rare anaplastic gliomas.
[b]See Principles of Brain and Spine Tumor Imaging (BRAIN-A).
[i]Postoperative brain MRI within 48 hours after surgery.
[k]The 2016 WHO Classification of Tumors of the CNS has deleted oligoastrocytoma 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.
[v]Consider carmustine (BCNU) wafer implant during resection. Treatment with carmustine wafer may impact enrollment in clinical trials.
[w]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.
[x]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.
[y]Anaplastic oligodendrogliomas have been reported to be especially sensitive to chemotherapy. Chemotherapy using temozolomide or nitrosourea-based regimens may be appropriate.
[z]Especially if long interval since prior RT and/or if there was a good response to prior RT.

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NCCN Guidelines Version 3.2019
Adult Intracranial and Spinal Ependymoma (Excluding Subependymoma)
NCCN Evidence Blocks™

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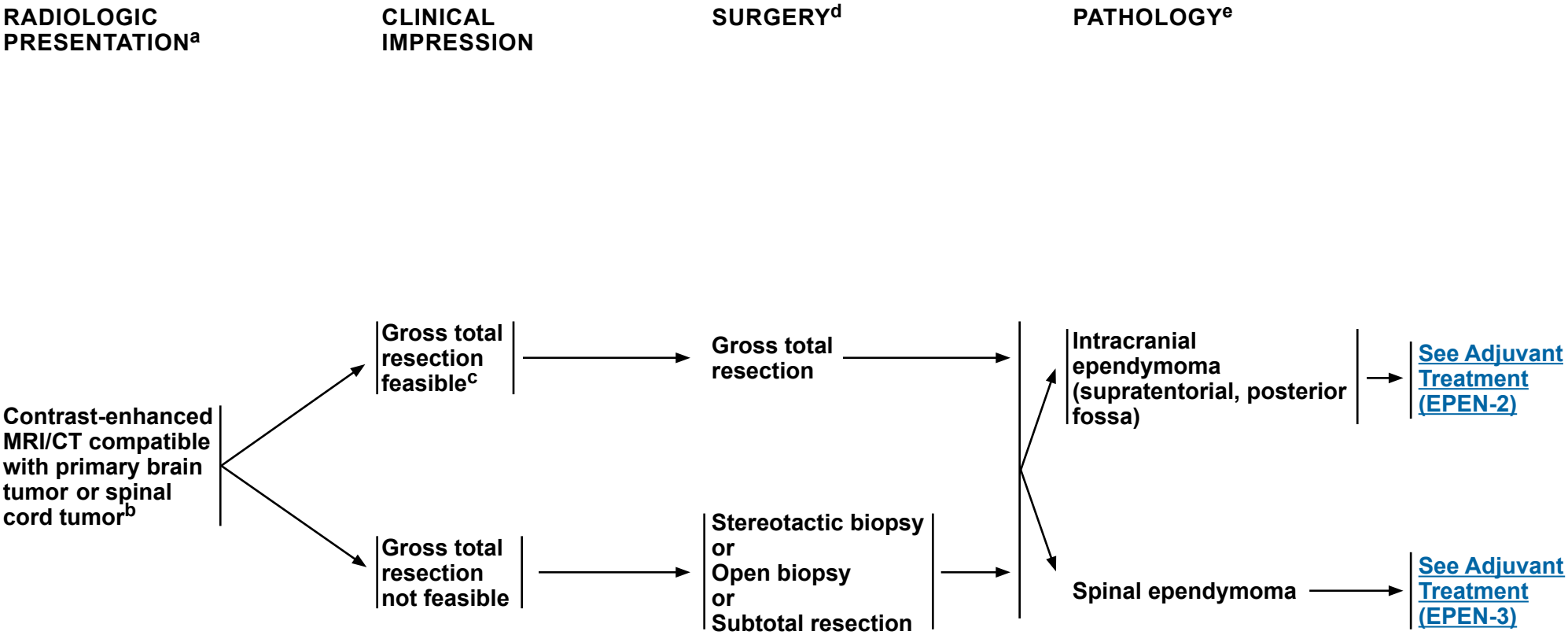

[a] See Principles of Brain and Spine Tumor Imaging (BRAIN-A).
[b] Consider a multidisciplinary review in treatment planning, especially once pathology is available. See Principles of Brain and Spine Tumor Management (BRAIN-E).
[c] If image-confirmed GTR not achieved, consider multidisciplinary review and reresection.
[d] See Principles of Brain Tumor Surgery (BRAIN-B).
[e] Testing for RELA fusion may be recommended for ependymomas. See Principles of Brain Tumor Pathology (BRAIN-F).

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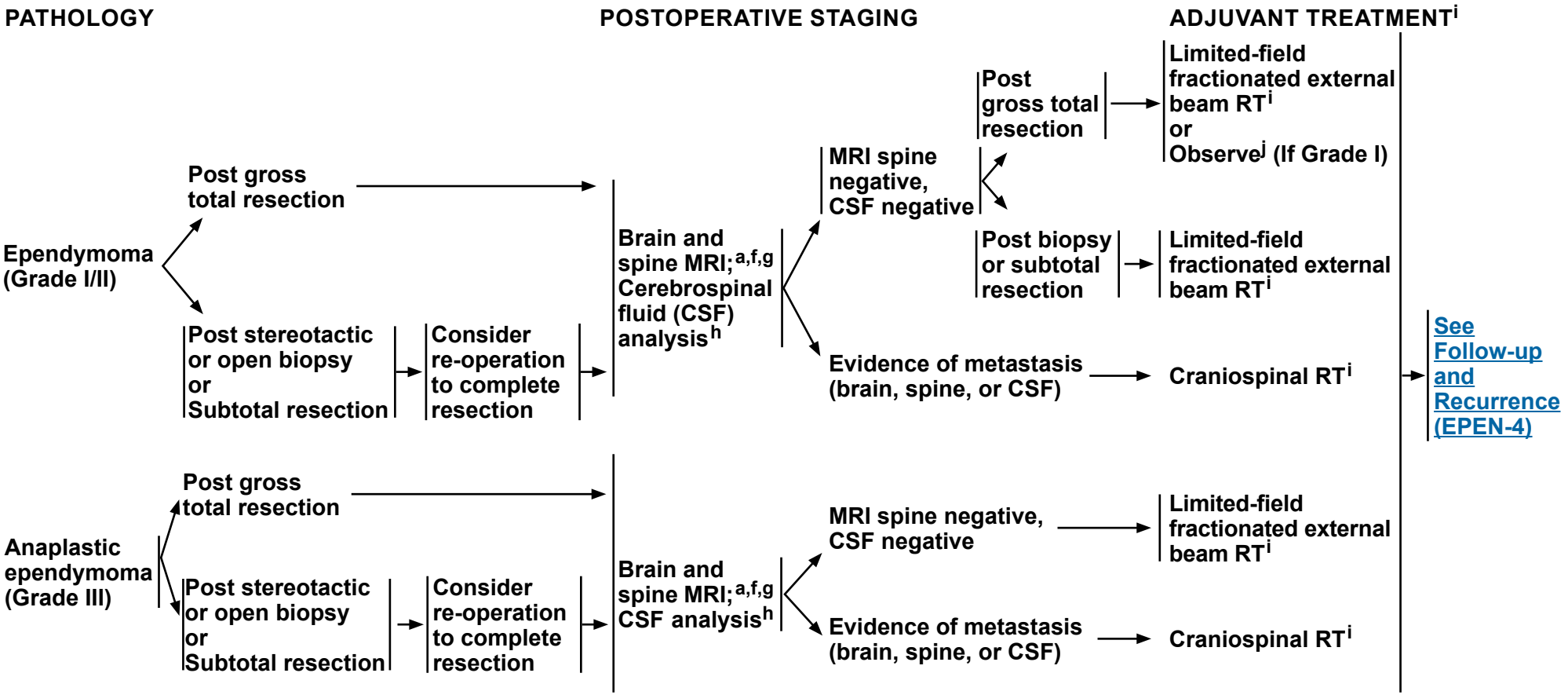
INTRACRANIAL EPENDYMOMA



[a] See Principles of Brain and Spine Tumor Imaging (BRAIN-A).
[f] Postoperative brain MRI within 48 hours after surgery.
[g] If not done preoperatively, spine MRI should be delayed by at least 2–3 weeks post surgery to avoid post-surgical artifacts.
[h] Lumbar puncture should be done after MRI of spine is performed to avoid a false-positive imaging result. Lumbar puncture for CSF should be delayed at least 2 weeks after surgery to avoid possible false-positive cytology. Lumbar puncture may be contraindicated (eg, posterior fossa mass).
[i] See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C).
[j] Data supporting observation alone are based on retrospective studies.

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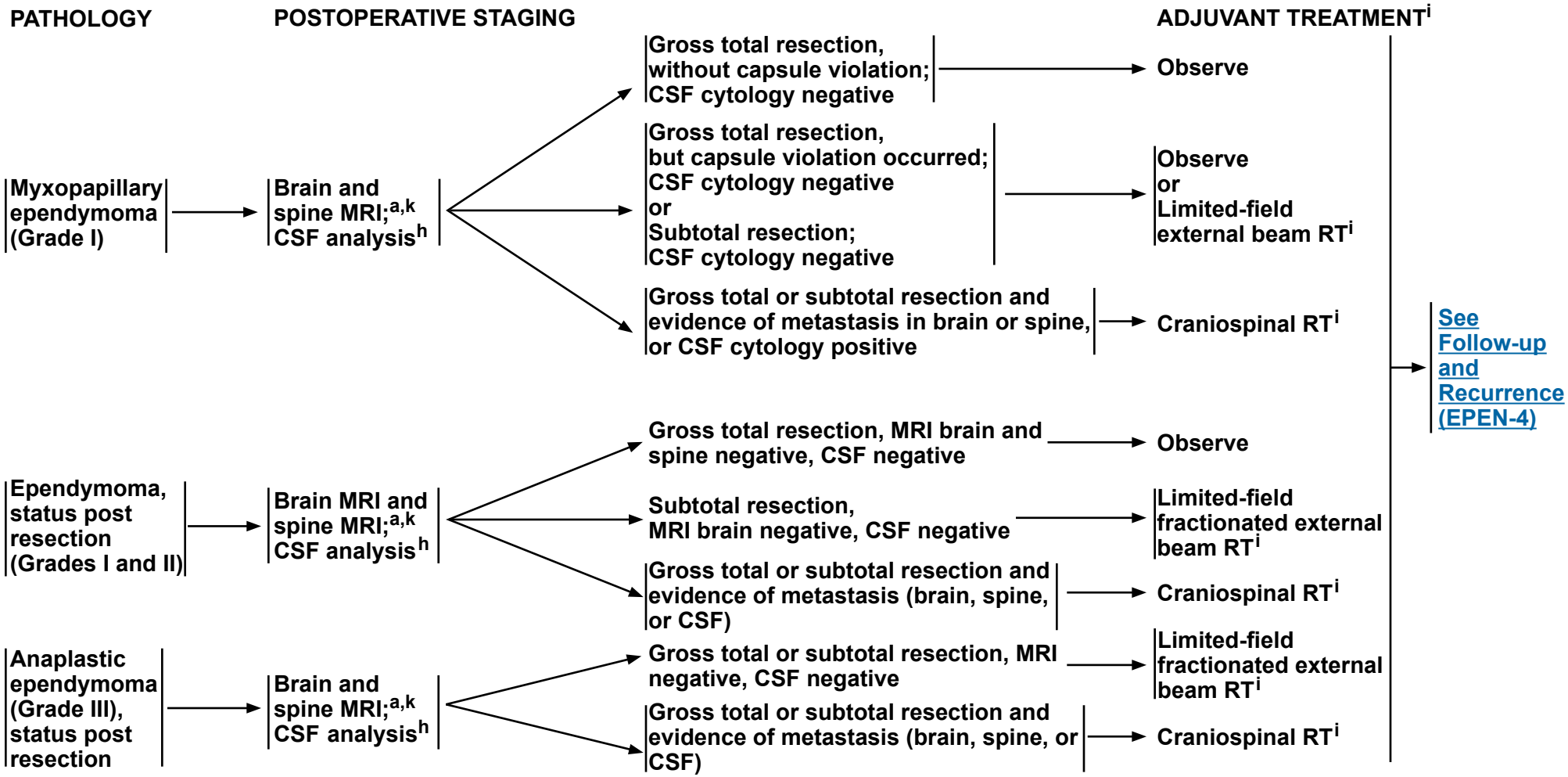
SPINAL EPENDYMOMA



[a] See Principles of Brain and Spine Tumor Imaging (BRAIN-A).
[h] Lumbar puncture should be done after MRI of spine is performed to avoid a false-positive imaging result. Lumbar puncture for CSF should be delayed at least 2 weeks after surgery to avoid possible false-positive cytology. Lumbar puncture may be contraindicated (eg, posterior fossa mass).
[i] See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C).
[k] If not done preoperatively, spine MRI should be performed 48 h post surgery.

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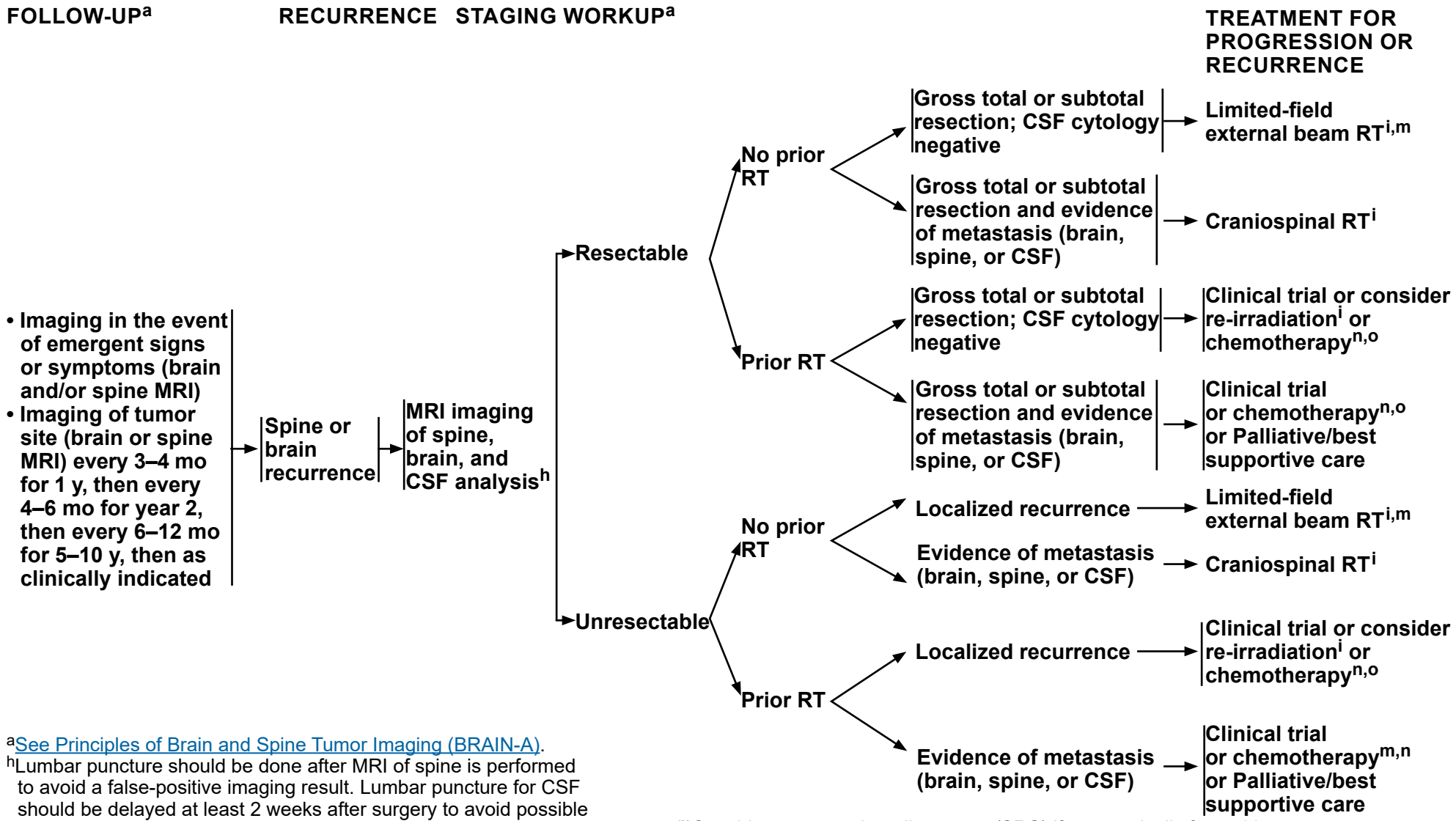

[a] See Principles of Brain and Spine Tumor Imaging (BRAIN-A).
[h] Lumbar puncture should be done after MRI of spine is performed to avoid a false-positive imaging result. Lumbar puncture for CSF should be delayed at least 2 weeks after surgery to avoid possible false-positive cytology. Lumbar puncture.
[i] See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C).
[m] Consider stereotactic radiosurgery (SRS) if geometrically favorable.
[n] Chemotherapy should be reserved for patients who are refractory to surgery or radiation.
[o] See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).

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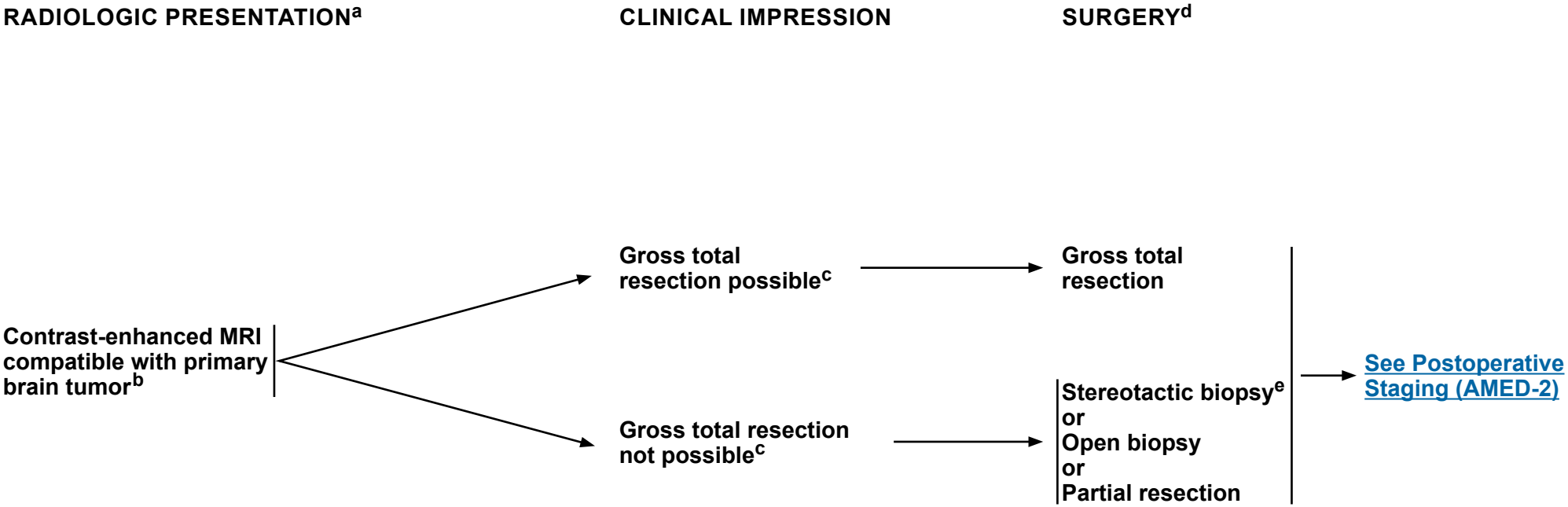

[a] See Principles of Brain and Spine Tumor Imaging (BRAIN-A).
[b] Consider a multidisciplinary review in treatment planning, before surgery and once pathology is available. See Principles of Brain and Spine Tumor Management (BRAIN-E).
[c] Placement of ventriculoperitoneal (VP) shunt for management of hydrocephalus is acceptable if needed.
[d] See Principles of Brain Tumor Surgery (BRAIN-B).
[e] Strongly recommend referring patient to a brain tumor center to be evaluated for possible further, more complete surgical resection.

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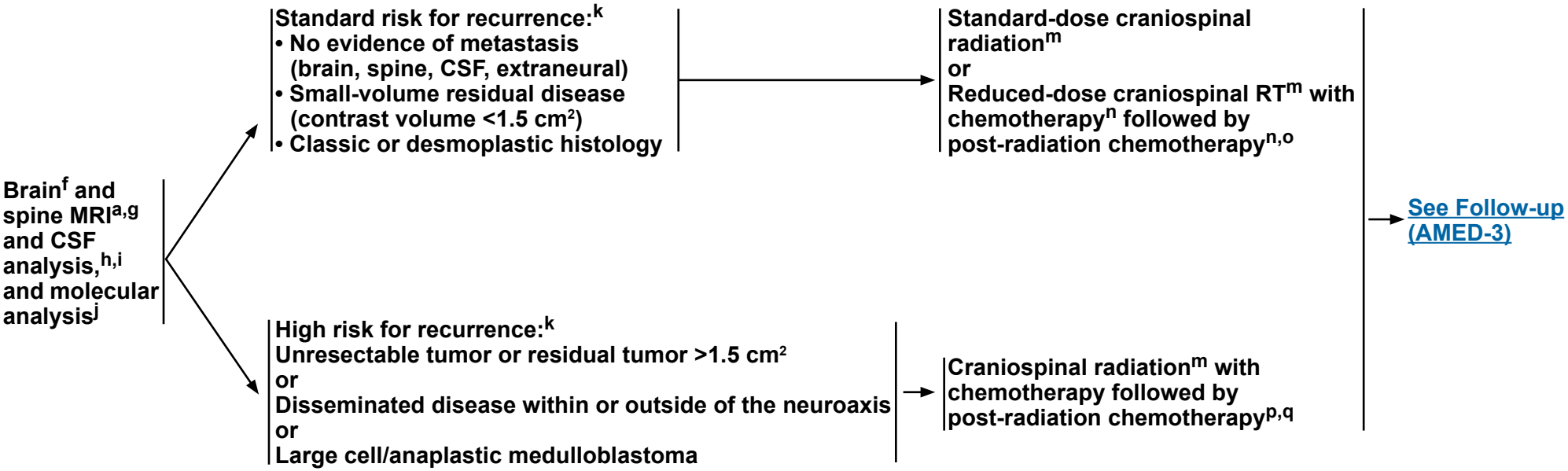

[a] See Principles of Brain and Spine Tumor Imaging (BRAIN-A).

[f] Postoperative brain MRI within 48 hours after surgery.

[g] Spine MRI should be delayed by at least 2–3 weeks post surgery to avoid post-surgical artifacts.

[h] Lumbar puncture should be done after spine MRI. Lumbar puncture for CSF should be delayed at least 2 weeks after surgery to avoid possible false-positive cytology.

[i] Bone scan; CT with contrast of chest, abdomen, and pelvis or whole body PET/CT; and bone marrow biopsy only if clinically indicated.

[j] Molecular profiling to identify clinically relevant subtypes is recommended to encourage opportunities for clinical trial involvement. See Principles of Pathology (BRAIN-F).

[k] See the modified Chang system for staging medulloblastoma. (Chang CH, Housepain EM, Herbert, C. Radiology 1969;93:1351 and Cohen ME, Duffner PK (Eds). Brain Tumors in children, 2nd ed, McGraw-Hill, New York, 1994, p.187.)

[l] If only biopsy is possible, consider an attempt at resection at a center that specializes in the treatment of brain tumors.

See Evidence Blocks on BRAIN-D (EB-6)

[m] See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C).

[n] Omission of vincristine during radiotherapy phase of therapy or dose modification may be required for adults because they do not tolerate this regimen as well. Data supporting vincristine's use have been found in pediatric trials only. Patients should be closely monitored for neurologic toxicity with periodic exams. (Packer RJ, Gajjar A, Vezina G, et al. Phase III study of craniospinal radiation therapy followed by adjuvant chemotherapy for newly diagnosed average-risk medulloblastoma. J Clin Oncol 2006;24:4202-4208.)

[o] See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).

[p] Recommend a platinum-based chemotherapy regimen such as either of the treatment arms used in the Children's Oncology Group study referenced in footnote "n."

[q] Consider collecting stem cells before craniospinal radiation.

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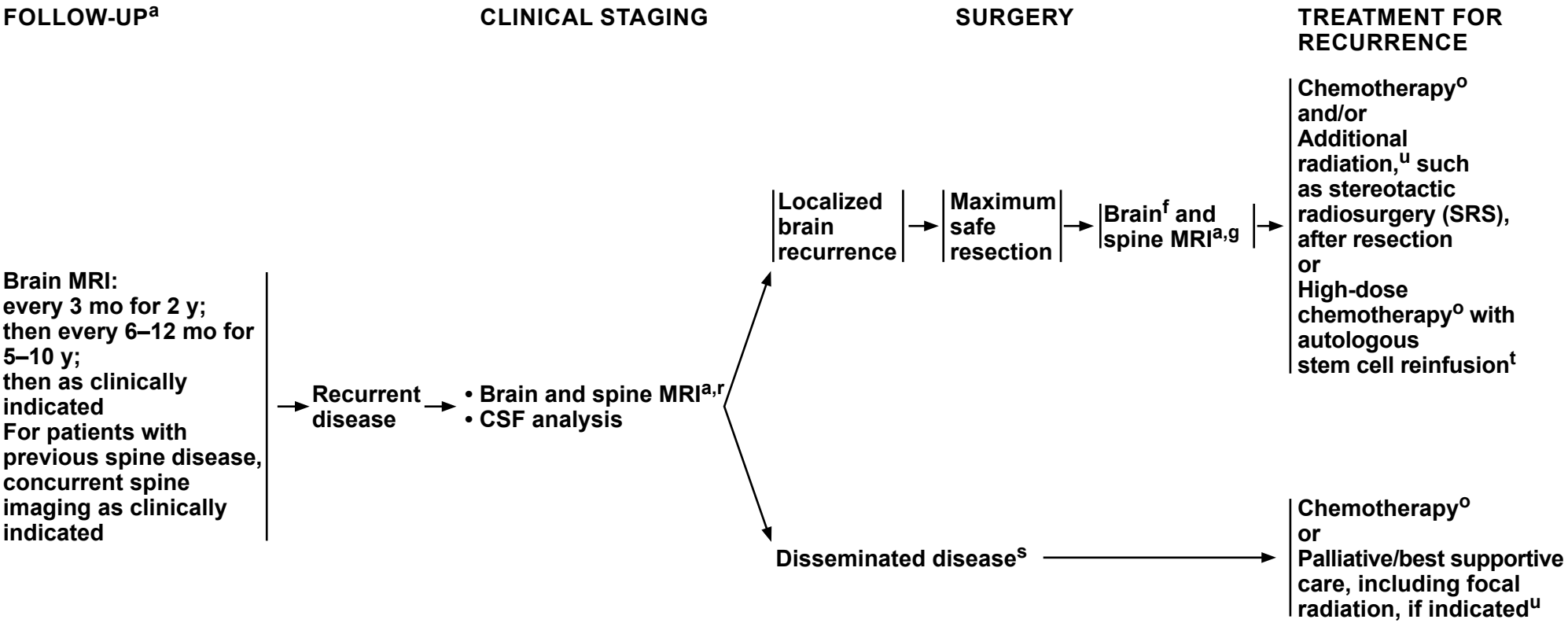

See Evidence Blocks on BRAIN-D (EB-6)

[a] See Principles of Brain and Spine Tumor Imaging (BRAIN-A).
[f] Postoperative brain MRI within 48 hours after surgery.
[g] Spine MRI should be delayed by at least 2–3 weeks post surgery to avoid post-surgical artifacts.
[o] See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).
[r] As clinically indicated, consider bone scan; contrast-enhanced CT scans of chest, abdomen, and pelvis; and/or bone marrow biopsy.
[s] Consider resection for palliation of symptoms where indicated.
[t] Only if the patient is without evidence of disease after surgery or conventional dose re-induction chemotherapy.
[u] See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C).

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DIAGNOSIS BY TISSUE EVALUATION

Brain MRI[c] suggestive of primary CNS lymphoma[d]

- **Biopsy of brain lesion with least invasive approach[e]**
- **Consider CSF sampling (15–20 mL spinal fluid to increase diagnostic yield), if safe, and if it will not delay the diagnostic process or treatment[f]**
- **Hold initiation of steroids, if possible, prior to diagnostic procedure**

Positive diagnosis of primary CNS lymphoma → **See (PCNS-2)**

Biopsy not diagnostic of primary CNS lymphoma → **See (PCNS-2)**

Other CNS tumor → **See NCCN Guidelines for Central Nervous System Cancers Table of Contents**

[a]If patient is HIV positive, antiretroviral therapy should be part of his/her treatment. Antiretrovirals (ARVs) can be administered safely with chemotherapy but consultation with an HIV specialist or pharmacist is important to optimize compatibility. See NCCN Guidelines for Cancer in People Living with HIV.

[b]For additional guidance on management of transplant recipients with PCNSL, see NCCN Guidelines for Diffuse Large B-Cell Lymphoma, sub-algorithm for Post-Transplant Lymphoproliferative Disorders.

[c]See Principles of Brain and Spine Tumor Imaging (BRAIN-A).

[d]Includes primary CNS lymphoma of the brain, spine, CSF, and leptomeninges. For lymphoma with primary tumor outside the CNS or involving only the eye, See NCCN Guidelines for Diffuse Large B-Cell Lymphomas.

[e]If stereotactic biopsy is not available refer to a specialized center.

[f]Brain biopsy is recommended as the primary procedure to obtain diagnosis. CSF analysis should include flow cytometry and CSF cytology and possibly gene rearrangements.

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NCCN Guidelines Version 3.2019
Primary CNS Lymphoma[a,b]
NCCN Evidence Blocks™

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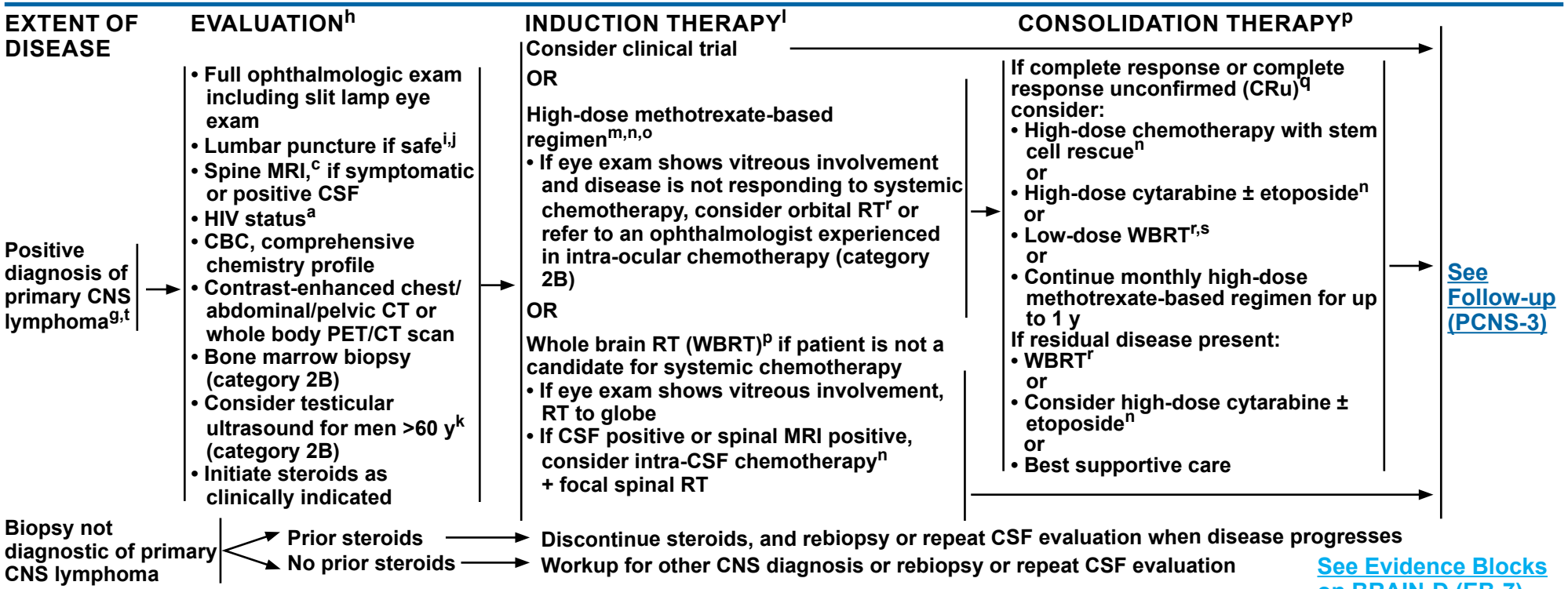

[a] If patient is HIV positive, antiretroviral therapy should be part of his/her treatment. ARVs can be administered safely with chemotherapy but consultation with an HIV specialist or pharmacist is important to optimize compatibility. See NCCN Guidelines for Cancer in People Living with HIV.

[b] For additional guidance on management of transplant recipients with PCNSL, see NCCN Guidelines for Diffuse Large B-Cell Lymphoma, sub-algorithm for Post-Transplant Lymphoproliferative Disorders.

[c] See Principles of Brain and Spine Tumor Imaging (BRAIN-A).

[g] May institute primary therapy and workup simultaneously.

[h] For full details regarding evaluation of extent of disease and response criteria for primary CNS lymphoma, refer to Abrey LE, Batchelor TT, Ferreri AJM, et al. Report of an international workshop to standardize baseline evaluation and response criteria for primary CNS lymphoma. J Clin Oncol 2005;23:5034-5043.

[i] CSF analysis should include flow cytometry, and CSF cytology, and may consider gene rearrangements.

[j] Caution is indicated in patients who are anticoagulated, thrombocytopenic, or who have a bulky intra-cranial mass.

[k] Recommend regular testicular exams. If PET/CT scan is negative, then there is no need for testicular ultrasound.

[l] A low KPS should not be a reason to withhold chemotherapy. KPS may improve dramatically after treatment.

[m] Dose adjusted for GFR.

[n] See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).

[o] If CSF positive or spinal MRI positive, consider alternative systemic chemotherapy regimens and/or intra-CSF chemotherapy (category 2B), especially for patients who cannot tolerate systemic methotrexate ≥3 g/m^2.

[p] Due to a lack of strong evidence, it is not clear which consolidation regimen provides the most benefit.

[q] For CRu criteria, see: Abrey LE, et al. Report of an international workshop to standardize baseline evaluation and response criteria for primary CNS lymphoma. J Clin Oncol 2005;23:5034-5043.

[r] See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C).

[s] WBRT may increase neurotoxicity, especially in patients >60 y.

[t] Includes primary CNS lymphoma of the brain, spine, CSF, and leptomeninges.

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NCCN Guidelines Version 3.2019
Primary CNS Lymphoma[a,b]
NCCN Evidence Blocks™

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FOLLOW-UP

- Brain MRI:[c]
  - every 3 mo until 2 y,
  - every 6 mo until 5 y,
  - then annually indefinitely
- For patients with previous spine disease, concurrent spine imaging[c] and CSF sampling as clinically indicated
- For patients with prior ocular involvement, concurrent ophthalmologic follow-up as clinically indicated

RELAPSED OR REFRACTORY PRIMARY CNS LYMPHOMA

TREATMENT

Any type of treatment history → Consider clinical trial

Prior WBRT → Consider chemotherapy (systemic and/or intra-CSF)[n]
or
Consider high-dose therapy[v] with stem cell rescue[u] (category 2B)
or
Consider focal irradiation[r]
or
Palliative/best supportive care

Prior high-dose methotrexate-based regimen without prior RT

- **Previous response with long duration (≥12 mo)** → Re-treat with high-dose methotrexate ± other chemotherapy[n]
  or
  Other systemic chemotherapy[n]
  or
  Consider high-dose therapy with stem cell rescue[u] (category 2B)
  or
  Palliative/best supportive care
- **No response or short duration (<12 mo)** → Other systemic chemotherapy[n]
  or
  WBRT or involved-field RT[r] ± chemotherapy[n]
  or
  Consider high-dose therapy with stem cell rescue[u] (category 2B)
  or
  Palliative/best supportive care

Prior high-dose chemotherapy with stem cell rescue

- **Previous response with long duration (≥12 mo)** → Consider second high-dose chemotherapy with stem cell rescue[u]
  or
  Other systemic chemotherapy[n]
  or
  Best supportive care
- **No response or short duration (<12 mo)** → WBRT or involved-field RT[r] or
  or
  Other systemic chemotherapy[n]
  or
  Palliative/best supportive care

See footnotes on PCNS-3A

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FOOTNOTES

[a]If patient is HIV positive, antiretroviral therapy should be part of his/her treatment. ARVs can be administered safely with chemotherapy but consultation with an HIV specialist or pharmacist is important to optimize compatibility. See NCCN Guidelines for Cancer in People Living with HIV.

[b]For additional guidance on management of transplant recipients with PCNSL, see NCCN Guidelines for Diffuse Large B-Cell Lymphoma, sub-algorithm for Post-Transplant Lymphoproliferative Disorders.

[c]See Principles of Brain and Spine Tumor Imaging (BRAIN-A).

[n]See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).

[r]See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C).

[u]If the recurrent disease goes into complete remission with reinduction chemotherapy.

[v]The risk of neurotoxicity should be considered before administrating high-dose therapy to a patient with prior WBRT.

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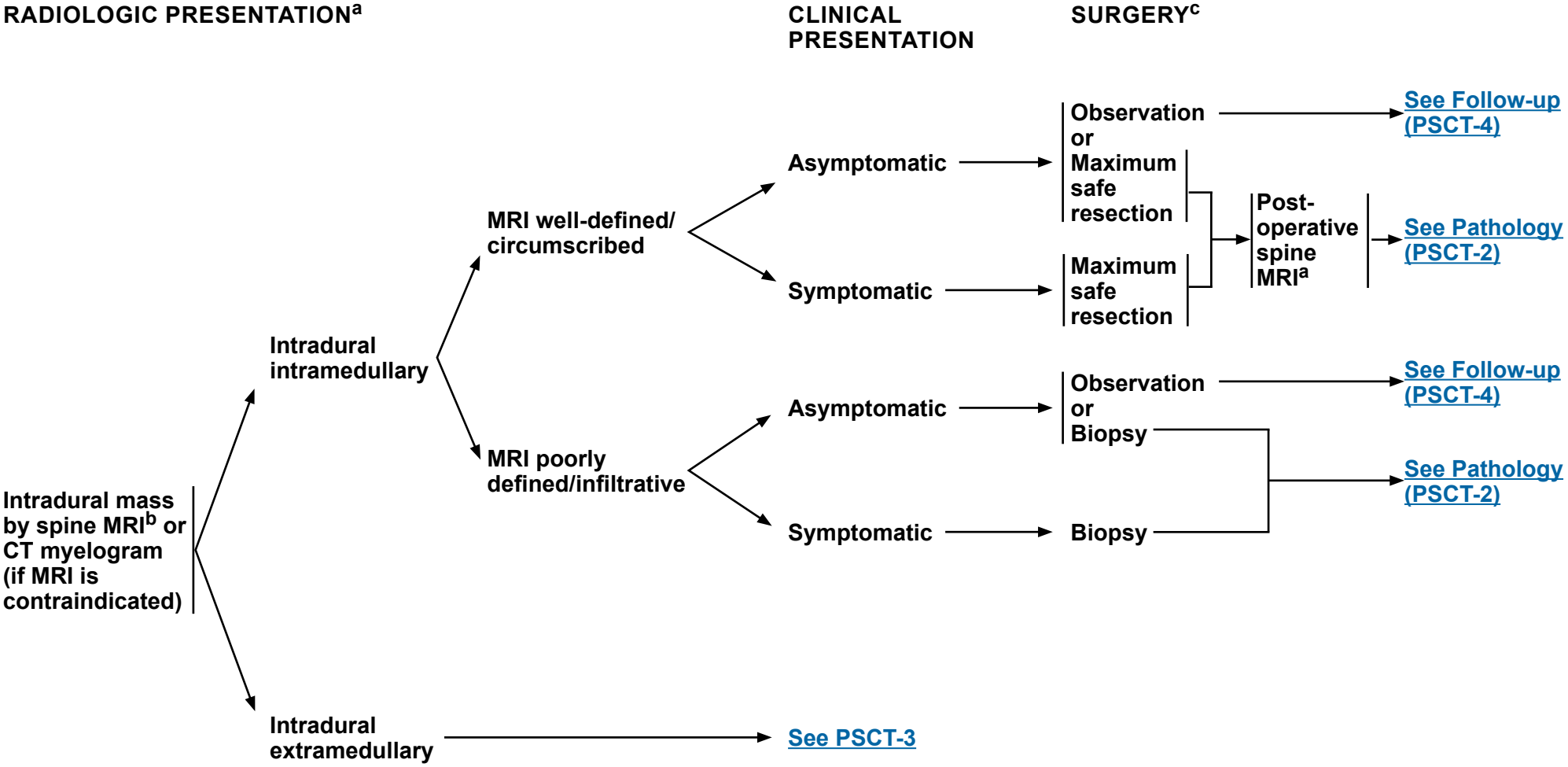

[a]See Principles of Brain and Spine Tumor Imaging (BRAIN-A).
[b]Consider a multidisciplinary review in treatment planning, before surgery and once pathology is available. See Principles of Brain and Spine Tumor Management (BRAIN-E).
[c]See Principles of Brain Tumor Surgery (BRAIN-B).

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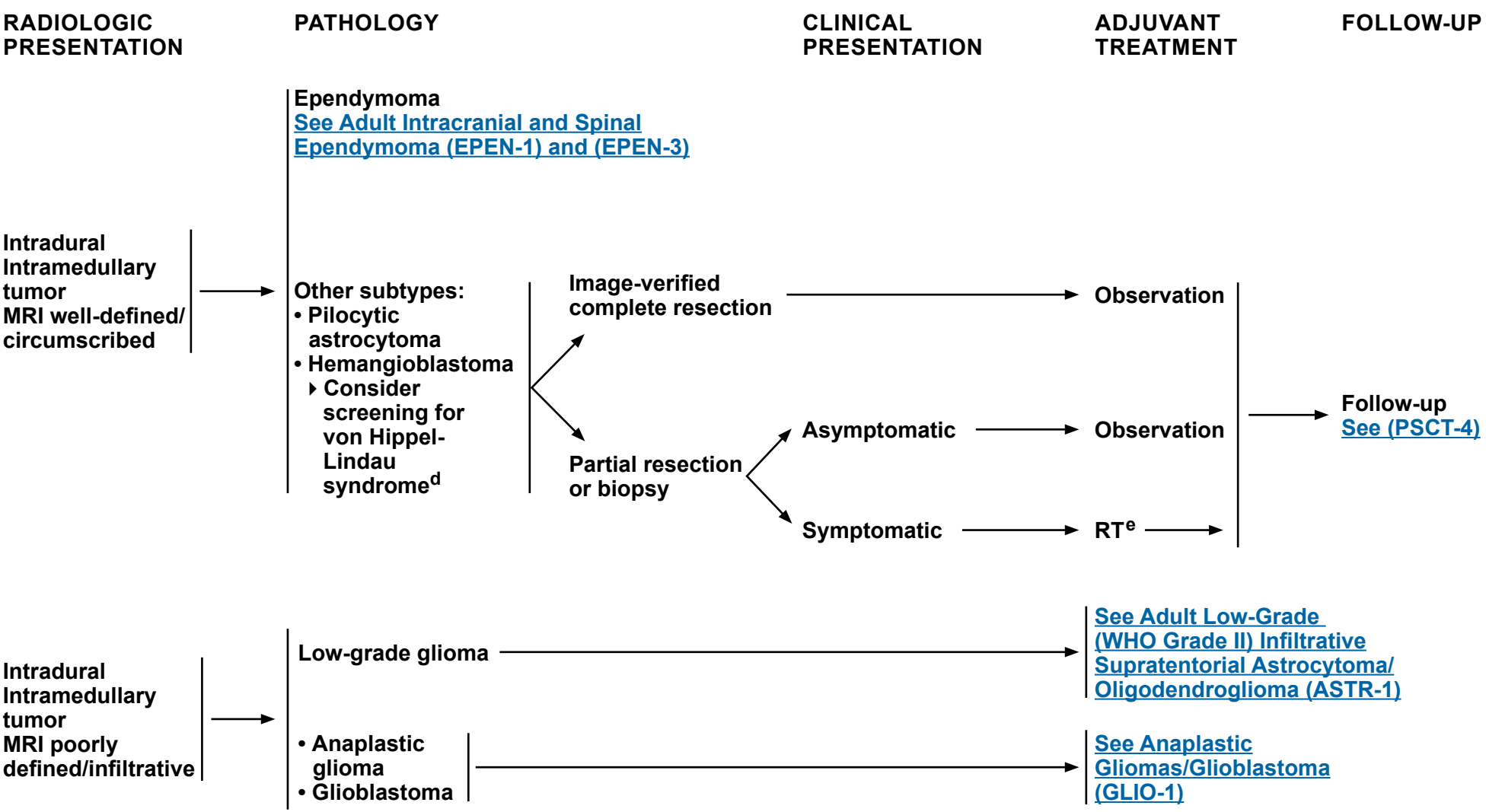

[d]VHL Family Alliance: The VHL Handbook: What You Need to Know About VHL: A Reference Handbook for People with von Hippel-Lindau Disease, Their Families, and Support Personnel. Boston, MA, 2014 VHL Family Alliance.
[e]See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C).

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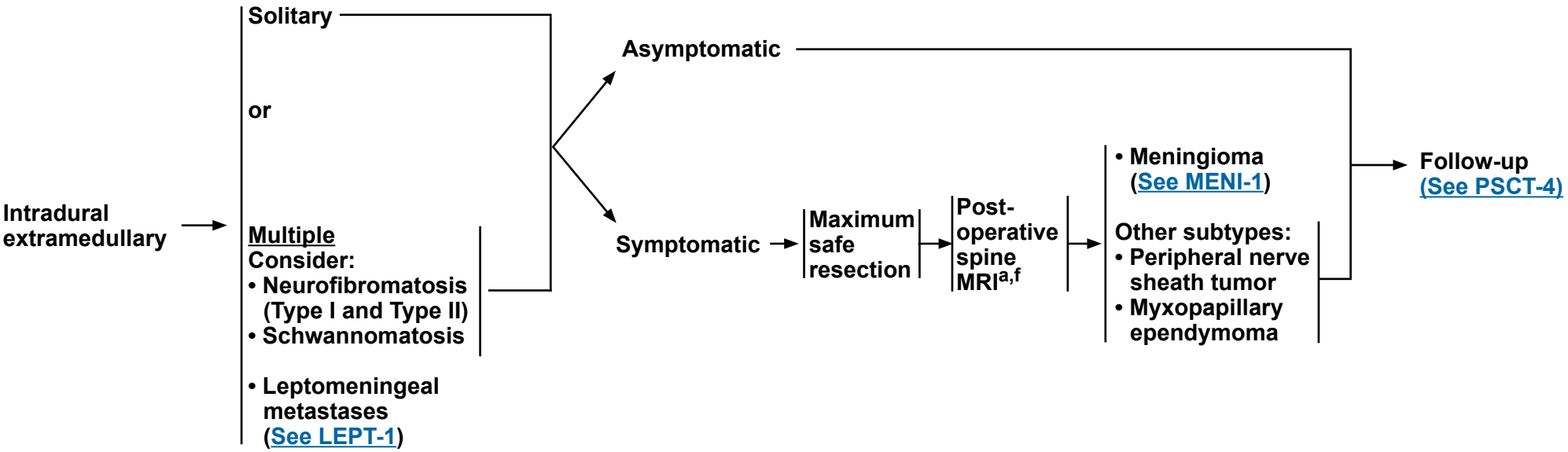

[a] See Principles of Brain and Spine Tumor Imaging (BRAIN-A).
[c] See Principles of Brain Tumor Surgery (BRAIN-B).
[f] Spine MRI should be delayed by at least 2–3 weeks post surgery to avoid post-surgical artifacts.

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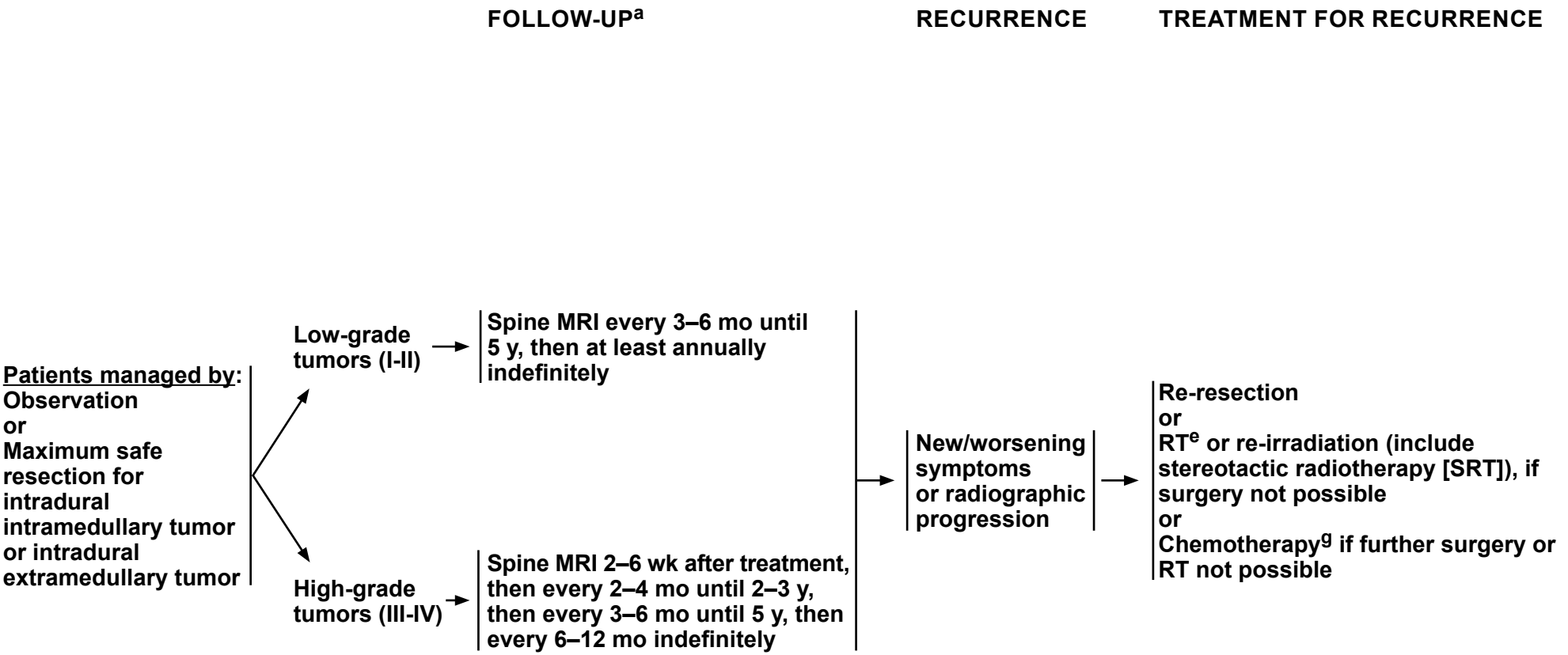

[a] See Principles of Brain and Spine Tumor Imaging (BRAIN-A).
[e] See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C).
[g] See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D) for options according to disease histology.

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NCCN Guidelines Version 3.2019
Meningiomas
NCCN Evidence Blocks™

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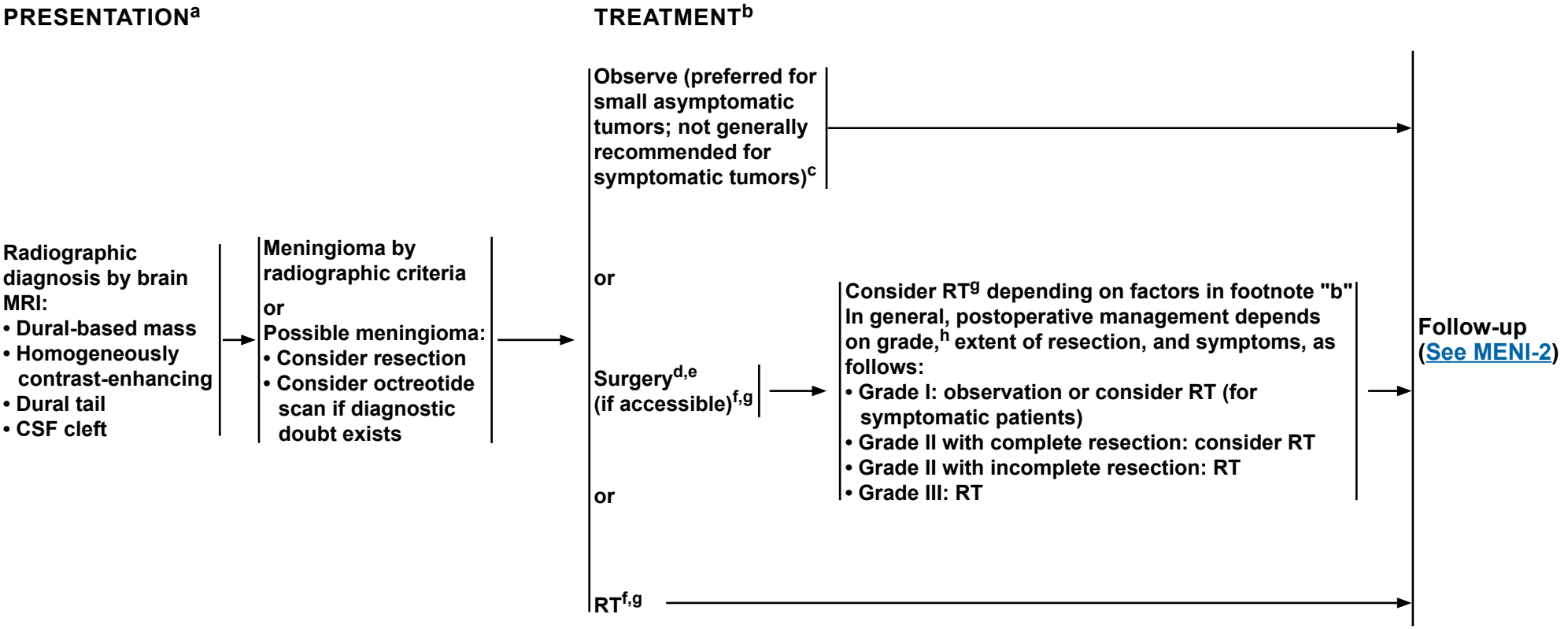

[a]Multidisciplinary input for treatment planning if feasible.

[b]Treatment selection should be based on assessment of a variety of inter-related factors, including patient features (eg, age, performance score, comorbidities, treatment preferences), tumor features (eg, size, grade, growth rate, location [proximity to critical structures], potential for causing neurologic consequences if untreated, presence and severity of symptoms), and treatment-related factors (eg, potential for neurologic consequences from surgery/RT, likelihood of complete resection and/or complete irradiation with SRS, treatability of tumor if it progresses, available surgical or radiation oncology expertise and resources). The decision to administer RT after surgery also depends on the extent of resection achieved. Multidisciplinary input for treatment planning is recommended.

[c]For asymptomatic meningiomas, observation is preferred for small tumors, with a suggested cutoff of ≤3 cm. Active treatment with surgery and/or RT is recommended in cases with one or more tumor- and/or treatment-related risk factors, such as proximity to the optic nerve.

[d]Postoperative brain MRI within 48 hours after surgery.

[e]See Principles of Brain and Spine Tumor Imaging (BRAIN-A).

[f]RT can be either external-beam or SRS.

[g]See Principles of Brain Tumor Radiation Therapy (BRAIN-C).

[h]WHO Grade I = Benign meningioma, WHO Grade II = Atypical meningioma, WHO Grade III = Malignant (anaplastic) meningioma.

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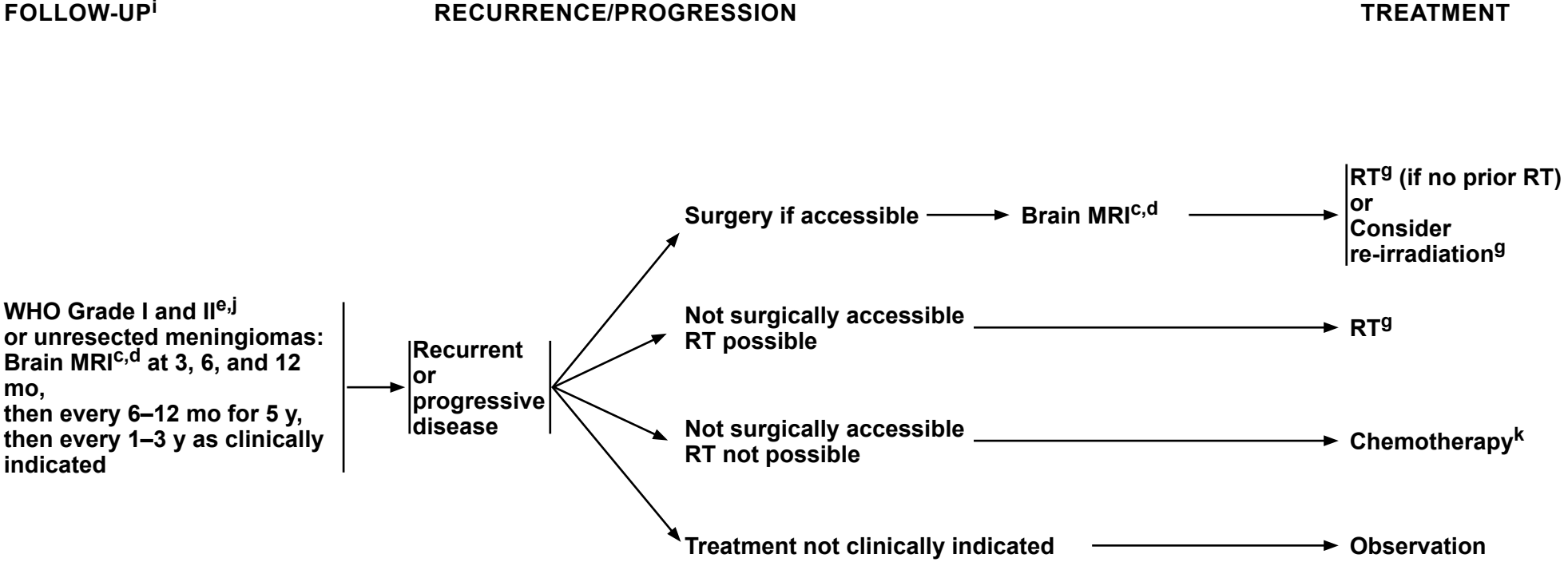

See Evidence Blocks on BRAIN-D (EB-8)

[c]Postoperative brain MRI within 48 hours after surgery.
[d]See Principles of Brain and Spine Tumor Imaging (BRAIN-A).
[h]WHO Grade I = Benign meningioma, WHO Grade II = Atypical meningioma, WHO Grade III = Malignant (anaplastic) meningioma.
[g]See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C).
[i]Consider less frequent follow-up after 5–10 y.
[j]More frequent imaging may be required for WHO Grade 3 meningiomas, and for meningiomas of any grade that are treated for recurrence or with chemotherapy.
[k]See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).

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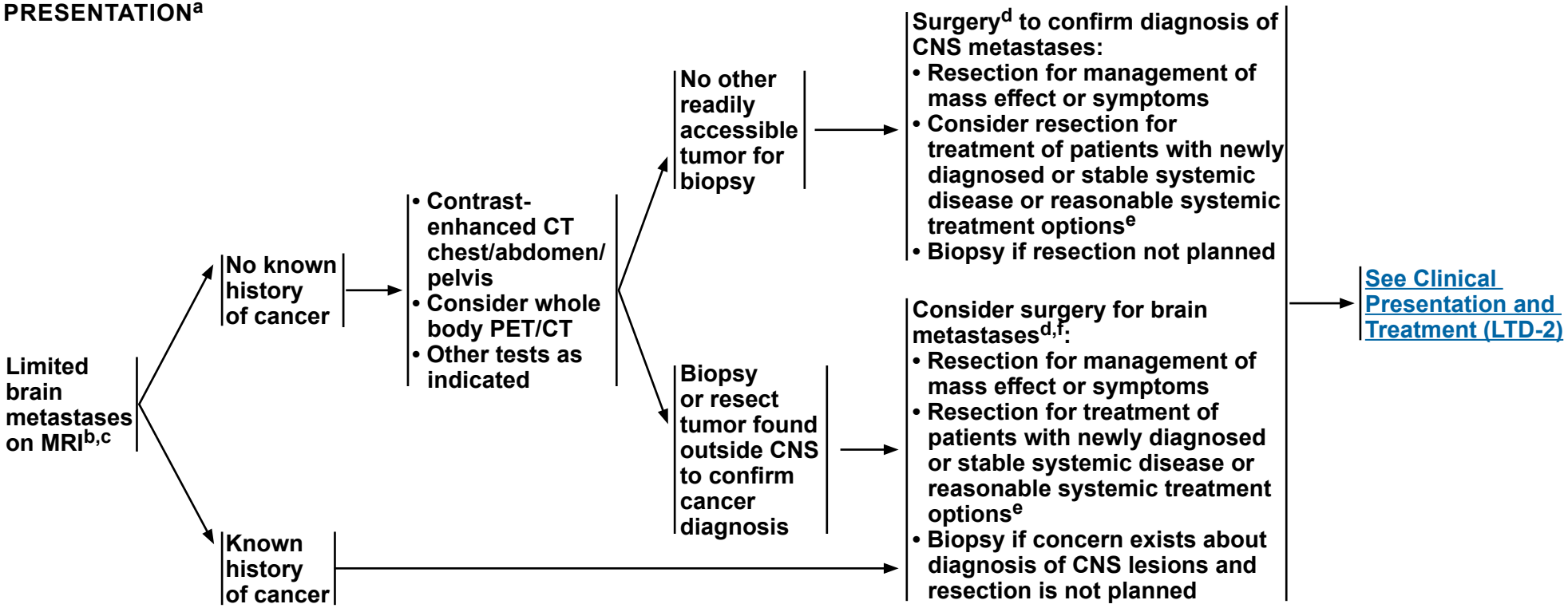

[a] See Principles of Brain and Spine Tumor Imaging (BRAIN-A).

[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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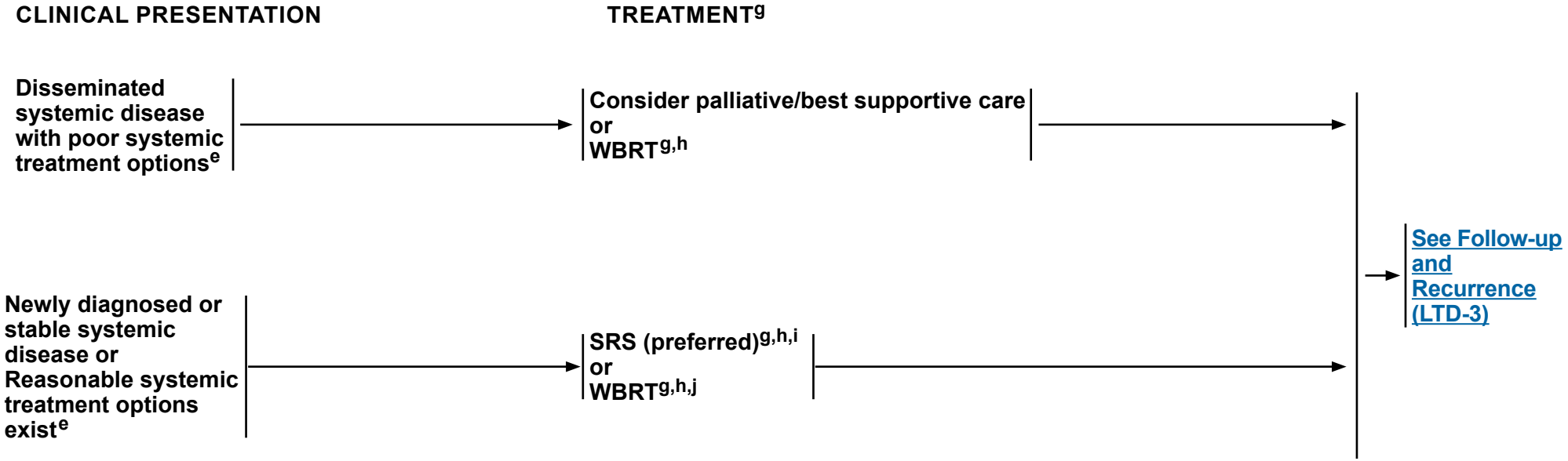

See Evidence Blocks on BRAIN-D (EB-9)

[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. 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. See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).

[h]See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C).

[i]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.

[j]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.)

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NCCN Guidelines Version 3.2019
Limited Brain Metastases
NCCN Evidence Blocks™

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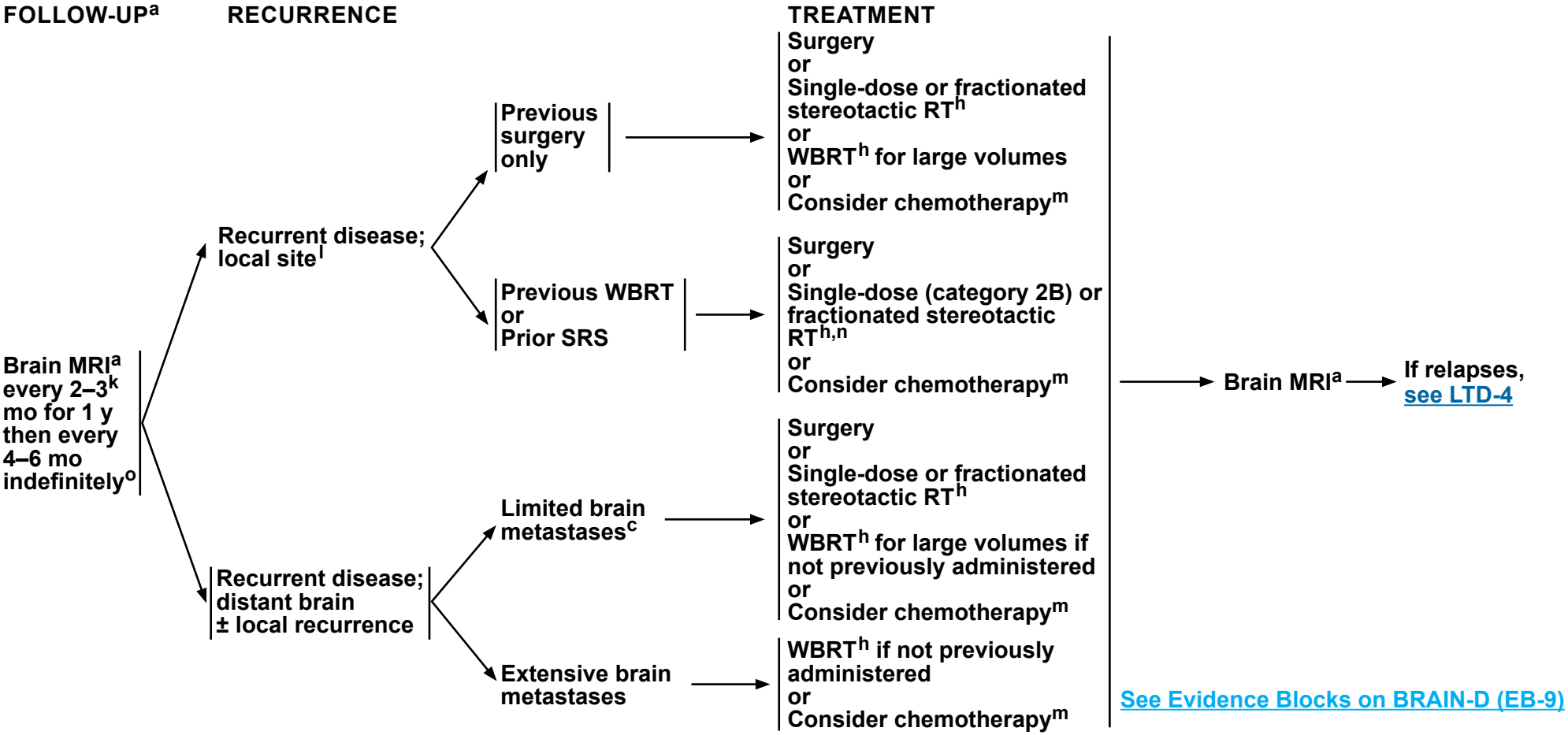

[a] See Principles of Brain and Spine Tumor Imaging (BRAIN-A).

[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 Radiation Therapy (BRAIN-C).

[k] MRI every 2 months (instead of 3 mo) for those patients treated with SRS alone.

[l] After SRS, recurrence on radiograph can be confounded by treatment effects; consider tumor tissue sampling if there is a high index of suspicion of recurrence.

[m] See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).

[n] If patient had previous SRS with a good response >6 mo, then reconsider SRS if imaging supports active tumor and not necrosis.

[o] Imaging to evaluate emergent signs/symptoms is appropriate at any time.

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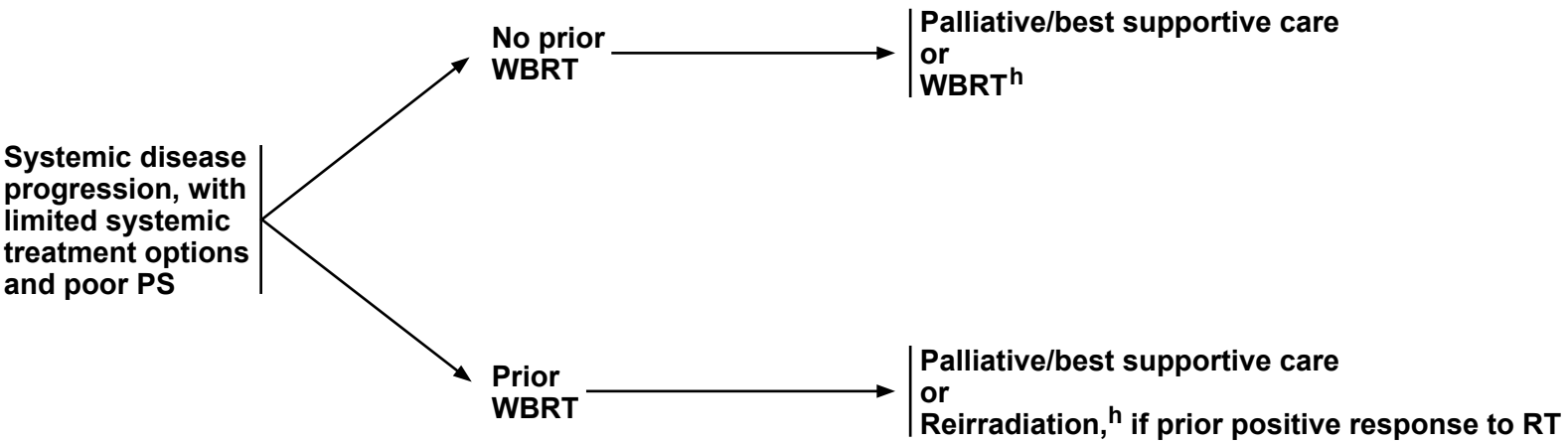
RECURRENCE | **TREATMENT**



[h] See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C).

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Extensive Brain Metastases
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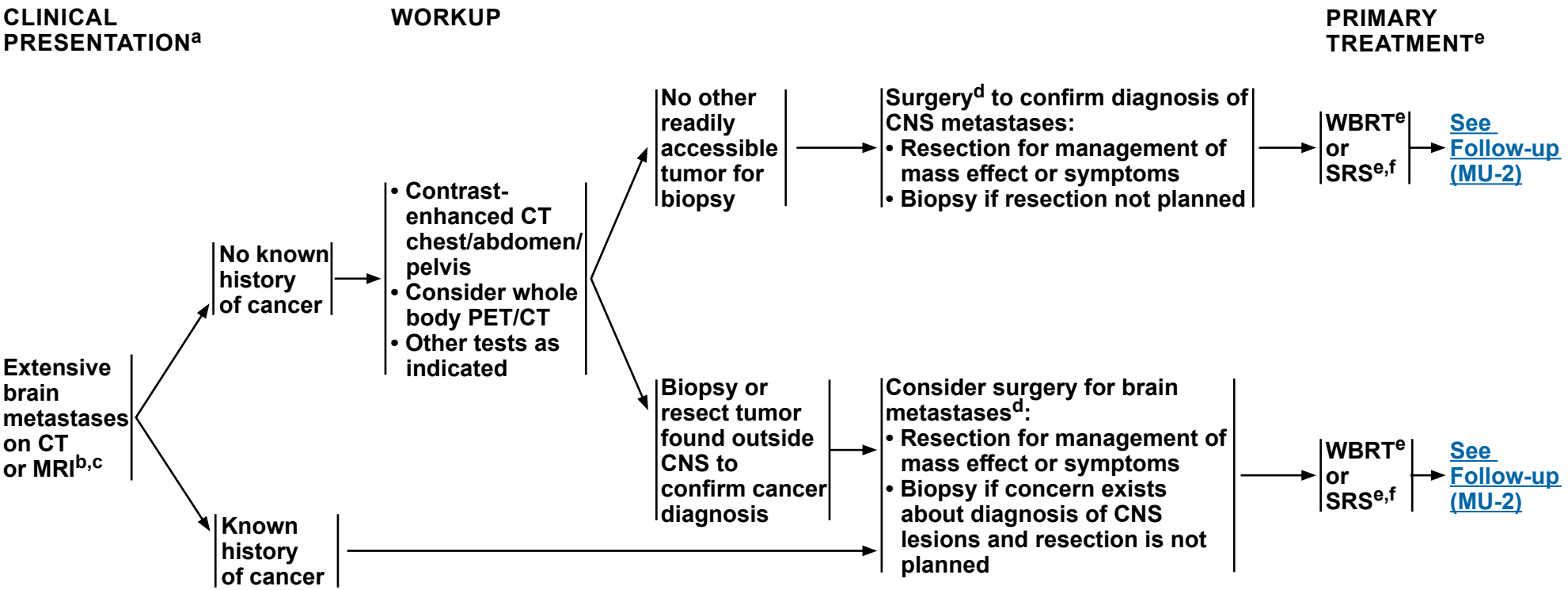

[a] See Principles of Brain and Spine Tumor Imaging (BRAIN-A).
[b] Consider a multidisciplinary review in treatment planning, especially once pathology is available. See Principles of Brain and Spine Tumor Management (BRAIN-E).
[c] Includes all cases that do not fit the definition of "limited brain metastases" 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.)

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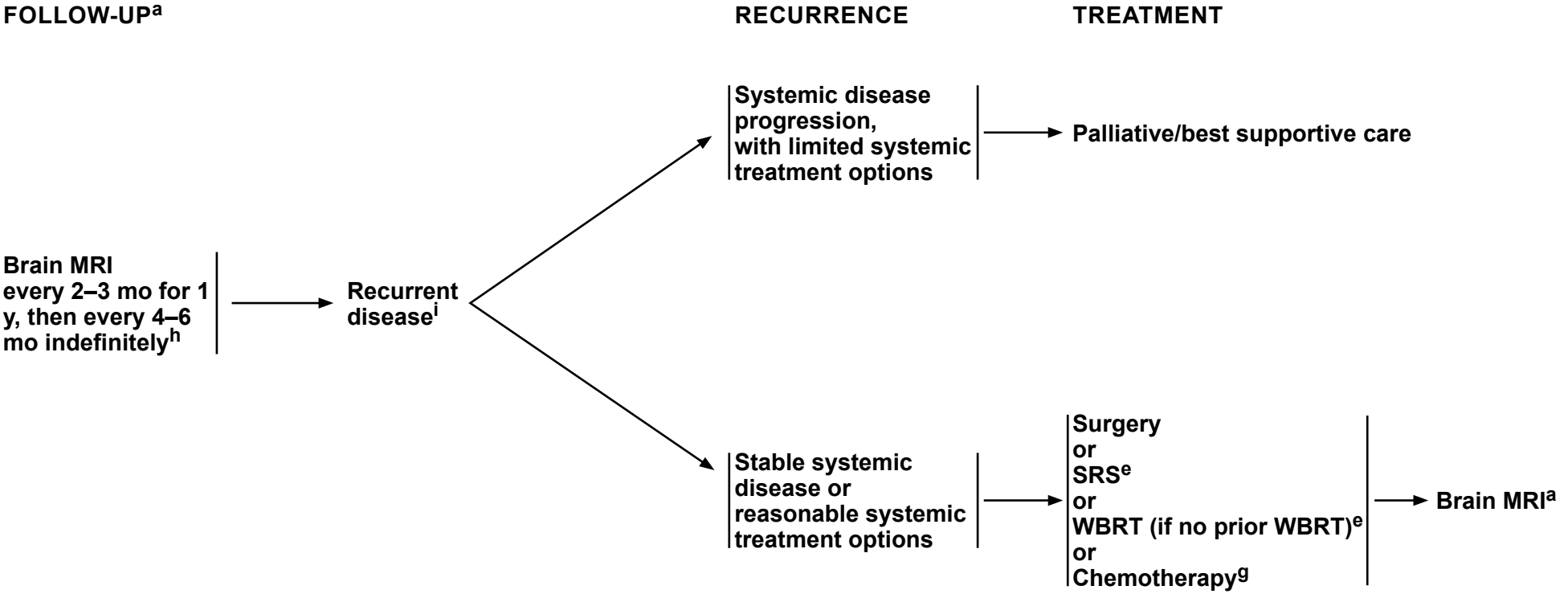

See Evidence Blocks on BRAIN-D (EB-9)

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

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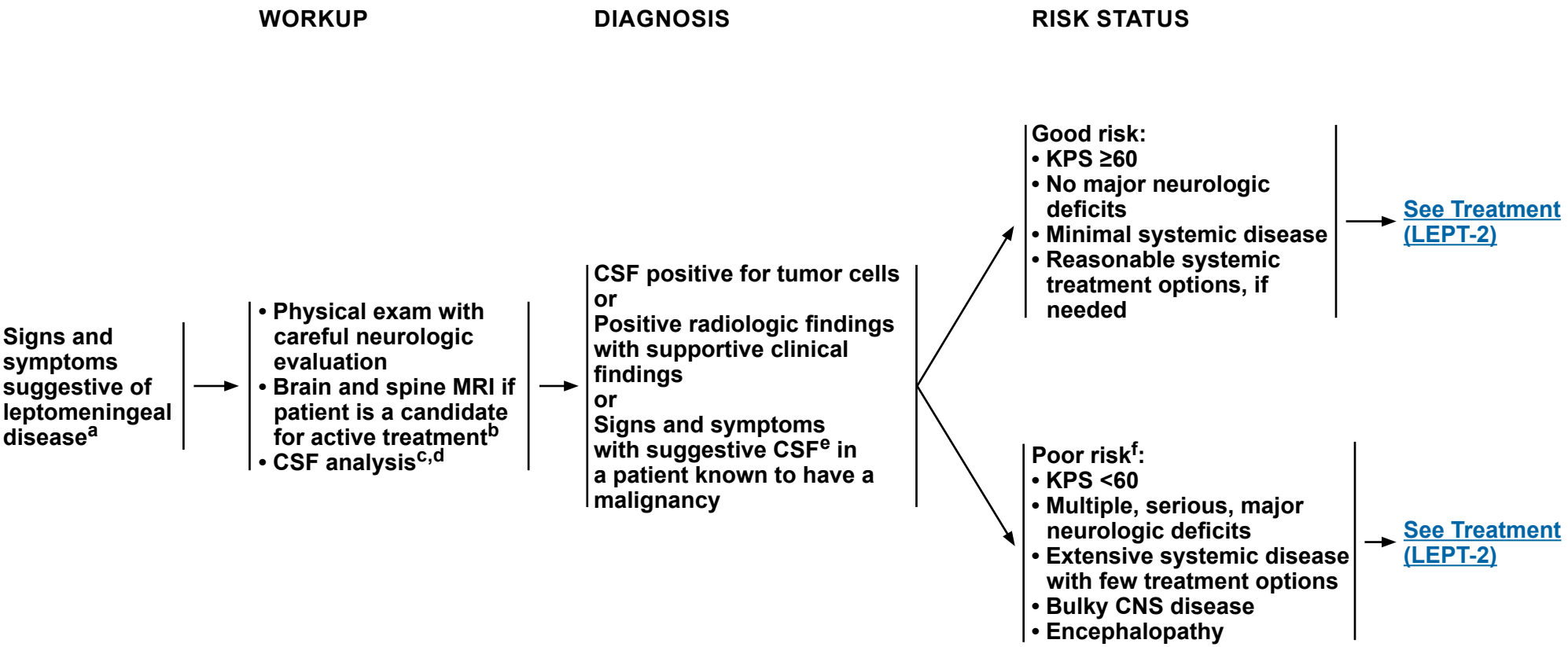

[a]Consider a multidisciplinary review in treatment planning, especially once pathology is available. See Principles of Brain and Spine Tumor Management (BRAIN-E).
[b]See Principles of Brain and Spine Tumor Imaging (BRAIN-A).
[c]Caution is indicated in patients who are anticoagulated, thrombocytopenic, or who have a bulky intra-cranial mass.
[d]CSF analysis should include: a cell count, differential, glucose, and protein. For solid malignancies, order cytopathology. When available, assessment of circulating tumor cells (CTC) increases sensitivity of tumor cell detection and assessment of response to treatment. For hematologic malignancies, use flow cytometry.
[e]Suggestive CSF includes high WBC, low glucose, and high protein. If CSF is not positive for tumor cells, a second lumbar puncture is sometimes helpful. This is a volume-dependent test, and ideally ≥10 mL should be sent for cytologic analysis.
[f]Patients with exceptionally chemosensitive tumors (eg, small cell lung cancer, lymphoma) may be treated. Patients with a good risk status who do not desire further therapy may also be treated with palliative and/or best supportive care.

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RISK STATUS

Good risk:
- **KPS ≥60**
- **No major neurologic deficits**
- **Minimal systemic disease**
- **Reasonable systemic treatment options, if needed**

TREATMENT

- **Systemic chemotherapy[g]**
- **Intra-CSF chemotherapy[g,h]**
  - **If symptoms or imaging suggest CSF flow blockage, perform a CSF flow scan prior to starting intra-CSF chemotherapy.**
    If flow abnormalities confirmed:
    - ◊ **Fractionated external beam RT[i] to painful metastatic sites of obstruction and repeat CSF flow scan to see if flow abnormalities have resolved.**
      or
    - ◊ **High-dose methotrexate if breast cancer or lymphoma**
- **WBRT and/or involved-field RT[i,j] to bulky disease and neurologically symptomatic (such as cranial neuropathies) or painful sites.**

→ **See Assessment of response (LEPT-3)**

Poor risk:[f]
- **KPS <60**
- **Multiple, serious, major neurologic deficits**
- **Extensive systemic disease with few treatment options**
- **Bulky CNS disease**
- **Encephalopathy**

→ **Palliative/best supportive care**
and
Consider involved-field RT[i] to neurologically symptomatic or painful sites for palliation (including spine and intracranial disease)

[f]Patients with exceptionally chemosensitive tumors (eg, small cell lung cancer, lymphoma) may be treated. Patients with a good risk status who do not desire further therapy may also be treated with palliative and/or best supportive care.
[g]See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).
[h]Strongly consider Ommaya reservoir/intraventricular catheter.
[i]See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C).
[j]Due to substantial toxicity, craniospinal RT should only be considered in highly select patients (eg, leukemia, lymphoma).

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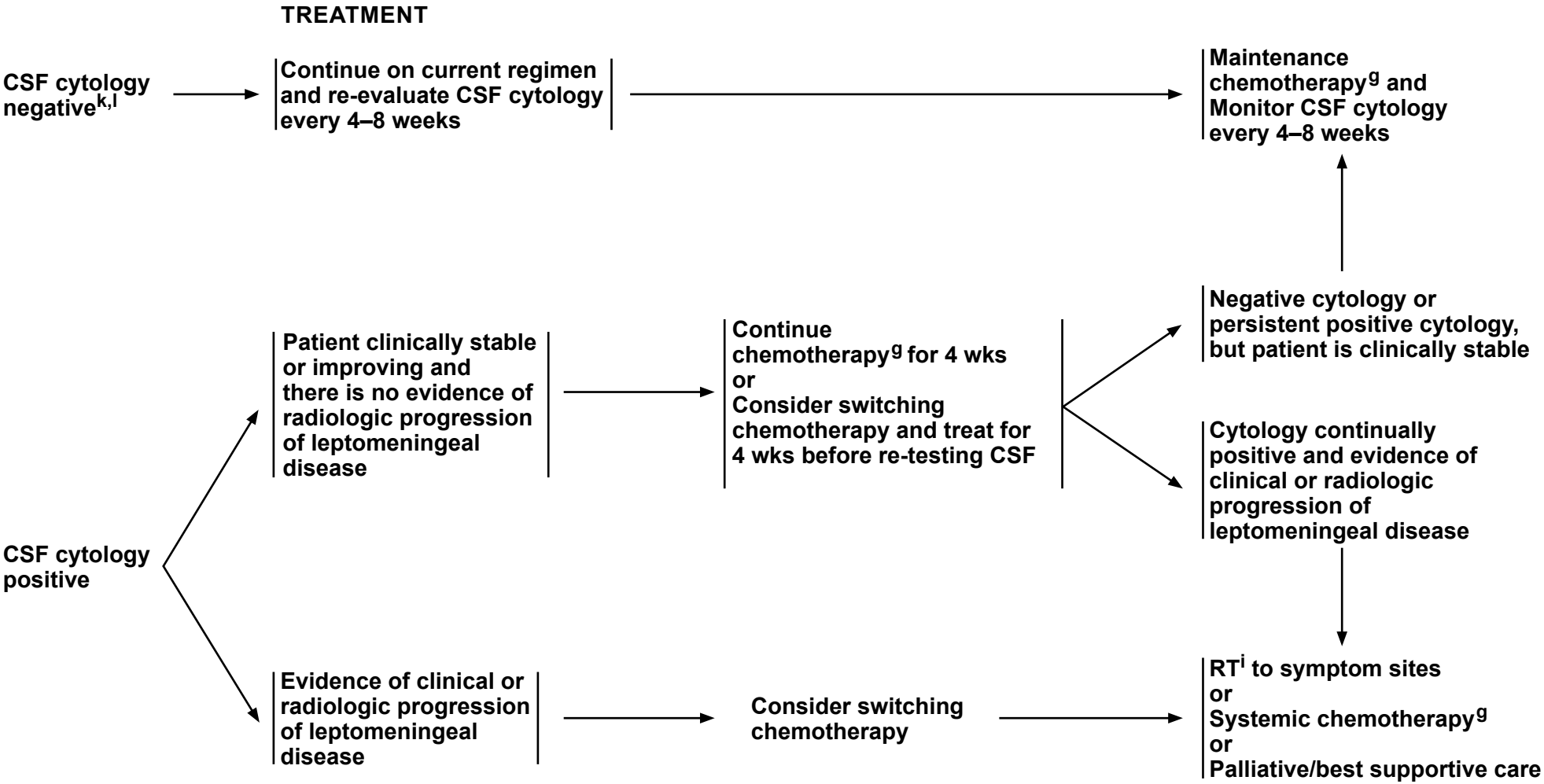

[g] See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).
[i] See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C).
[k] If CSF cytology was initially negative, then assess response with MRI of spine/brain.
[l] If cytologic analysis is negative from CSF obtained from an Ommaya reservoir, then assess CSF obtained via a lumbar puncture to confirm CSF cytology is negative.

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Metastatic Spine Tumors
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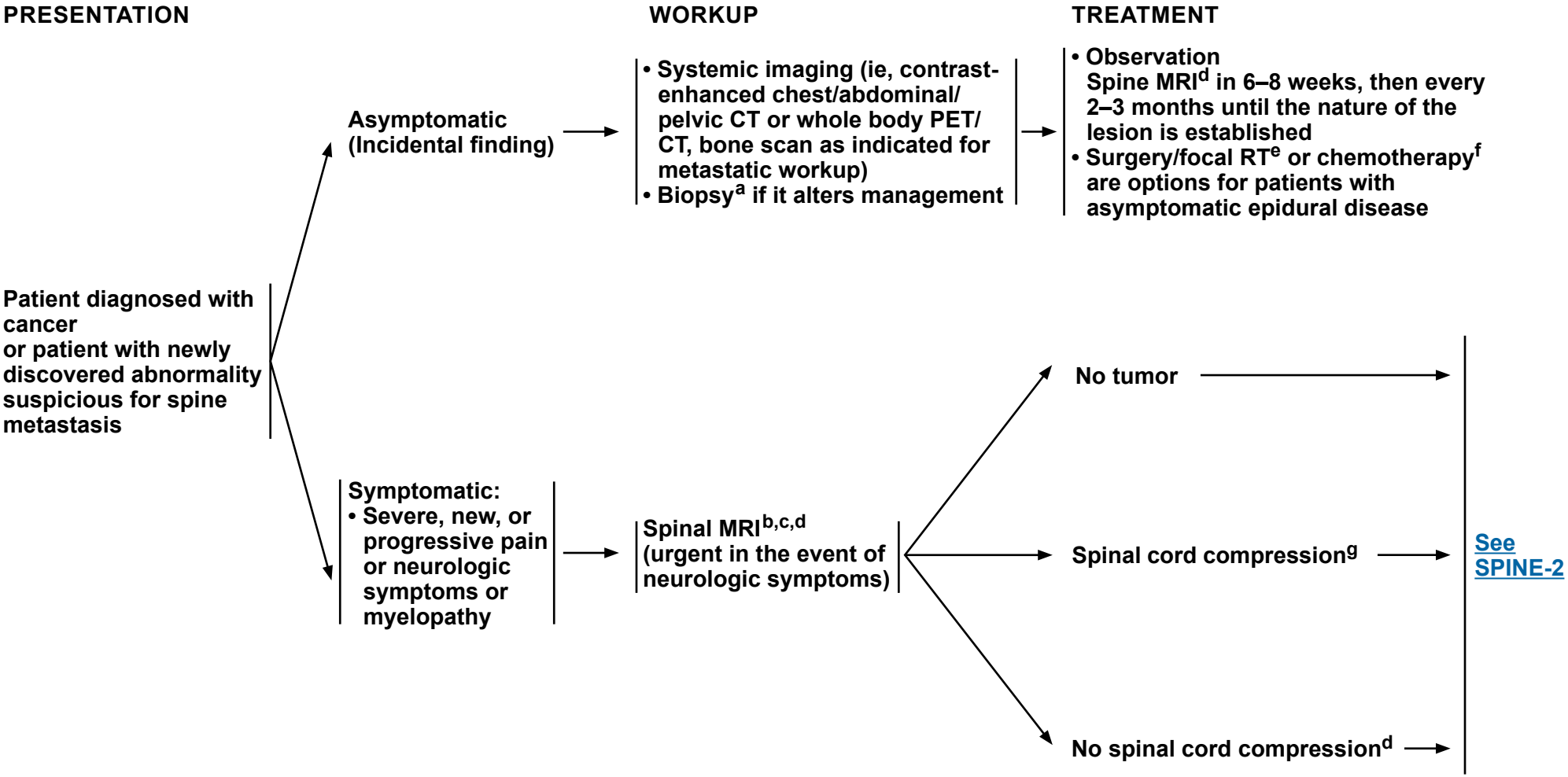

[a]Biopsy if remote history of cancer.
[b]If the patient is unable to have an MRI, then a CT myelogram is recommended, which may also be useful for SRT planning.
[c]15%–20% of patients have additional lesions. Highly recommend complete spine imaging.
[d]See Principles of Brain and Spine Tumor Imaging (BRAIN-A).
[e]See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C).
[f]See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).
[g]Includes cauda equina syndrome.

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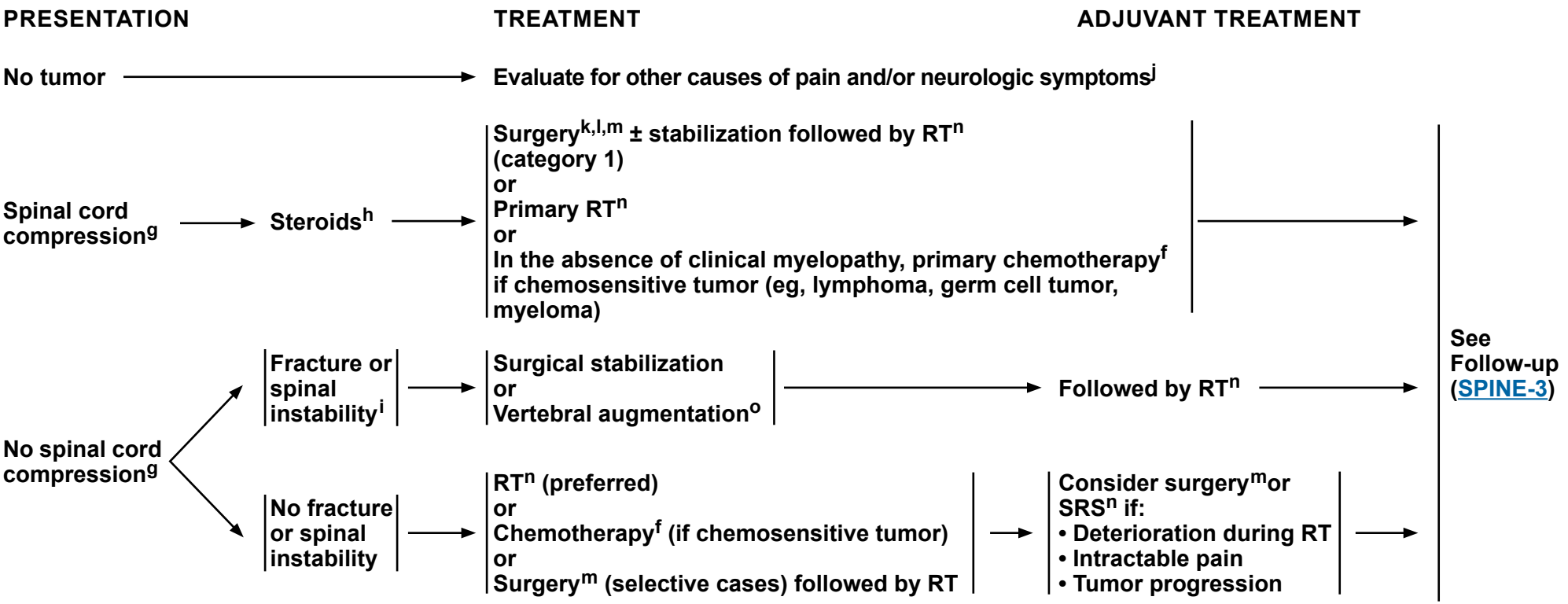

[f] See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).

[g] Includes cauda equina syndrome.

[h] The recommended minimum dose of steroids is 4 mg of dexamethasone every 6 hours, although dose of steroids may vary (10–100 mg). A randomized trial supported the use of high-dose steroids (Sorensen PS, et al. Eur J Cancer 1994;30A:22-27).

[i] Spinal instability is grossly defined as the presence of significant kyphosis or subluxation (deformity), or of significantly retropulsed bone fragment.

[j] Consider alternative diagnosis of leptomeningeal disease (See LEPT-1).

[k] Tumor resection with or without spinal stabilization. Surgery should be focused on anatomic pathology.

[l] Regarding surgery, note the following:
- Category 1 evidence supports the role of surgery in patients with a solitary epidural spinal cord compression by a tumor not known to be radiosensitive and who are willing to undergo surgery. (Patchell RA, et al. Lancet 2005;366(9486):643-648)
- For surgery, patients with hematologic tumors (ie, lymphoma, myeloma, leukemia) should be excluded, life expectancy should be ≥3 mo, and the patient should not be paraplegic for >24 h.
- Surgery is especially indicated if the patient has any of the following: spinal instability, no history of cancer, rapid neurologic deterioration during RT, previous RT to site, and single-site spinal cord compression.

[m] Postoperative spine MRI should be delayed by at least 2–3 weeks to avoid post-surgical artifacts. See Principles of Brain Tumor Surgery (BRAIN-B).

[n] Recommend SRS if oligometastases and radioresistant. See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C).

[o] Vertebral augmentation: vertebroplasty, kyphoplasty.

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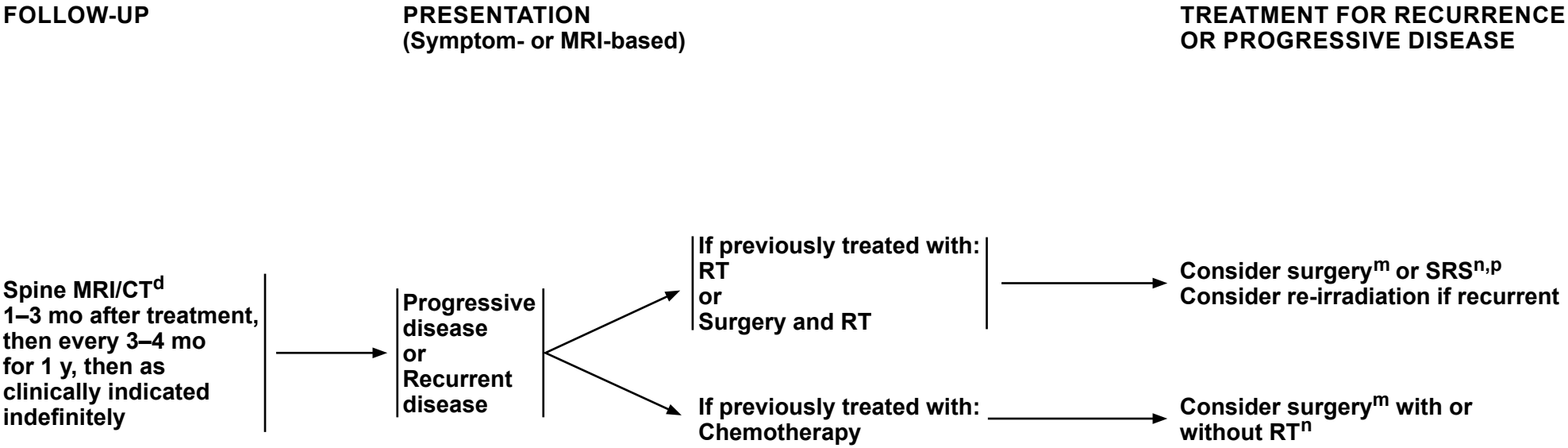

[d] See Principles of Brain and Spine Tumor Imaging (BRAIN-A).
[m] Postoperative spine MRI should be delayed by at least 2–3 weeks to avoid post-surgical artifacts. See Principles of Brain Tumor Surgery (BRAIN-B).
[n] Recommend SRS if oligometastases and radioresistant. See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C).
[p] Gary AK, et al. Prospective evaluation of spinal reirradiation by using stereotactic body radiation therapy: The University of Texas MD Anderson Cancer Center experience. Cancer 2011;117:3509-3516.

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PRINCIPLES OF BRAIN AND SPINE TUMOR IMAGING[1]

This is a list of imaging modalities available and used in neuro-oncology primarily to make treatment decisions. The most common use for MR spectroscopy, MR perfusion, and PET scanning is to differentiate radiation necrosis from active tumor, as this might obviate the need for surgery or the discontinuation of an effective therapy. Imaging is always recommended to investigate emergent signs or symptoms.

- **MRI[2] of the brain and spine (with and without contrast):**
  - **Gold standard**
  - **Provides a "static" picture of tumors**
  - **Benefits: Provides a reasonably good delineation of tumors; higher grade tumors and brain leptomeningeal metastasis usually enhance; lower grade tumors usually do not enhance**
  - **Limitations: Sensitive to movement, metallic objects cause artifact, patients with implantable devices cannot have an MRI, claustrophobia may be an issue, or renal insufficiency**
  - **Postoperative brain MRI should be performed within 48 hours for gliomas and other brain tumors to determine extent of resection.**
  - **Postoperative spine MRI should be delayed by at least 2–3 weeks to avoid post-surgical artifacts.**
  - **Follow-up brain MRI should be performed at the frequency and intervals stated in the treatment algorithms. More frequent imaging may be done as clinically indicated by the treating physician, such as in the event of a clinical change such as development of seizures or neurologic deterioration.**

- **CT of the brain and spine (with and without contrast):**
  - **Should be used in patients who cannot have an MRI**
  - **Benefits: Claustrophobia or implantable devices are not an issue, can be done faster than an MRI**
  - **Limitations: Lacks resolution of MRI, especially in posterior fossa, or renal insufficiency**

- **MR spectroscopy: Assess metabolites within tumors and normal tissue**
  - **May be useful in differentiating tumor from radiation necrosis; may be helpful in grading tumors or assessing response**
  - **Area most abnormal would be the best place to target for a biopsy**
  - **Limitations: Tumors near vessels, air spaces, or bone. Extra time in MRI and others as noted under MRI**

- **MR perfusion: Measures cerebral blood volume in tumors**
  - **May be useful in differentiating grade of tumor or tumor versus radiation necrosis. Area of highest perfusion would be the best place to biopsy.**
  - **Limitations: Tumors near vessels, air spaces, bone, small-volume lesions, or tumors in the spinal cord. Extra time in MRI and others as noted under MRI.**

- **Brain PET scanning: Assess metabolism within tumor and normal tissue by using radiolabeled tracers**
  - **May be useful in differentiating tumor from radiation necrosis but has some limitations; may also correlate with tumor grade or provide the optimal area for biopsy**
  - **Limitations: Accuracy of interpretations, availability of equipment and isotopes**

[1]The imaging modalities listed may not be available at every institution.

[2]Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment for high-grade gliomas: Response assessment in neuro-oncology working group. J Clin Oncol 2010;28:1963-1972.

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PRINCIPLES OF BRAIN TUMOR SURGERY

Guiding Principles
- Gross total resection (GTR) when appropriate
- Minimal surgical morbidity
- Accurate diagnosis

Factors
- Age
- Performance status (PS)
- Feasibility of decreasing the mass effect with surgery
- Resectability, including number of lesions, location of lesions, time since last surgery (recurrent patients)
- New versus recurrent tumor
- Suspected pathology – benign vs. malignant, possibility of other non-cancer diagnoses, projected natural history
- For patients with IDH1 mutations, there is evidence to suggest that a supramarginal resection is most appropriate, which would include not only enhancing areas but also T2/flair areas when appropriate in terms of a safe surgical approach, with the use of any and all surgical adjuncts possible.[a]

Options[a]
- GTR where feasible
- Stereotactic biopsy
- Open biopsy/debulking followed by planned observation or adjuvant therapy
- Chemotherapy implants, when indicated (See footnote h on GLIO-1)
- Carmustine polymer wafer may be placed in the tumor resection cavity of patients.[b,c]

Tissue
- Sufficient tissue to pathologist for neuropathology evaluation and molecular correlates
- Frozen section analysis when possible to help with intraoperative decision-making
- Review by experienced neuropathologist
- Postoperative brain MRI should be performed within 48 hours for gliomas and other brain tumors to determine the extent of resection. Postoperative spine MRI should be delayed by at least 2–3 weeks to avoid post-surgical artifacts.
- The extent of resection should be judged on the postoperative study and used as a baseline to assess further therapeutic efficacy or tumor progression.

[a]A number of surgical adjuncts can be considered to facilitate safe brain tumor surgery, including use of an intraoperative microscope, frameless stereotactic image guidance, preoperative functional MRI and/or DTI fiber tracking, awake craniotomy, motor and/or speech mapping, intraoperative MRI, and intraoperative fluorescence-guided surgery with 5-ALA.

[b]Ewend MG, Brem S, Gilbert M, et al. Treatment of single brain metastasis with resection, intracavity carmustine polymer wafers, and radiation therapy is safe and provides excellent local control. Clin Cancer Res 2007;13:3637-3641.
[c]Brandes AA, Tosoni A, Amista P, et al. How effective is BCNU in recurrent glioblastoma in the modern era? A phase II trial. Neurology 2004;63:1281-1284.

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PRINCIPLES OF RADIATION THERAPY FOR BRAIN AND SPINAL CORD

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

- Tumor volumes are best defined using pre- and postoperative MRI imaging, usually fluid-attenuated inversion recovery (FLAIR)/T2 and, occasionally, enhanced T1 sequences to define gross tumor volume (GTV). Clinical target volume (CTV) (GTV plus 1–2 cm margin) should receive 45–54 Gy in 1.8–2.0 Gy fractions.[1-3] Consider RT dose escalation to 59.4–60 Gy for IDH-wild-type low-grade gliomas, as these patients have a more aggressive course of disease.

Anaplastic Gliomas/Glioblastoma High-Grade (Grades III/IV)

Simulation and Treatment Planning

- Tumor volumes are best defined using pre- and postoperative MRI imaging using enhanced T1 with/without FLAIR/T2 sequences to define GTV. To account for sub-diagnostic tumor infiltration, the GTV is expanded 1–2 cm (CTV) for grade III, and up to 2–2.5 cm (CTV) for grade IV. Although trials in glioblastoma have historically used CTV expansion in the range of 2 cm, smaller CTV expansions are supported in the literature and can be appropriate. A planning target volume (PTV) of margin of 3–5 mm is typically added to the CTV to account for daily setup errors and image registration. Daily image guidance is required if smaller PTV margins are used (3 mm or less). When edema as assessed by T2/FLAIR is included in the initial phase of treatment, fields are usually reduced for the last phase of the treatment (boost). The boost target volume will typically encompass only the gross residual tumor and the resection cavity. A range of acceptable clinical target volume margins exists. Both strategies appear to produce similar outcomes.[4]

RT Dosing Information

- The recommended dose is 60 Gy in 2.0 Gy fractions or 59.4 Gy in 1.8 Gy fractions.
- A slightly lower dose, such as 54–55.8 Gy in 1.8 Gy or 57 Gy in 1.9 Gy fractions, can be applied when the tumor volume is very large (gliomatosis), there is brainstem/spinal cord involvement, or for grade III astrocytoma.
- If a boost volume is used, the initial phase of the RT plan will receive 46 Gy in 2 Gy fractions or 45–50.4 Gy in 1.8 Gy fractions. The boost plan will typically then receive 14 Gy in 2 Gy fractions or 9–14.4 Gy in 1.8 Gy fractions.[4]
- In poorly performing patients or elderly patients, a hypofractionated accelerated course should be considered with the goal of completing the treatment in 2–4 weeks. Typical fractionation schedules are 34 Gy/10 fx, 40.05 Gy/15 fx, or 50 Gy/20 fx.[5,6] Alternatively, a shorter fractionation schedule of 25 Gy/5 fx may be considered for elderly and/or frail patients with smaller tumors for whom a longer course of treatment would not be tolerable.[7]

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PRINCIPLES OF RADIATION THERAPY FOR BRAIN AND SPINAL CORD

Adult Intracranial and Spinal Ependymoma

- **Limited Fields:**
  - **Intracranial tumor volumes are best defined using pre- and postoperative MRI imaging, usually enhanced T1 and/or FLAIR/T2. GTV is defined as anatomic areas that are touched by preoperative tumor volume plus postoperative signal abnormality as seen on MRI.**
  - **RT Dosing Information:**
    - ◊ **CTV (GTV plus 1–2 cm margin) should receive 54–59.4 Gy in 1.8–2.0 Gy fractions. PTV of margin of 3–5 mm is typically added to the CTV to account for daily setup errors and image registration.**
- **Craniospinal:**
  - **To reduce toxicity from craniospinal irradiation (CSI) in adults, consider the use of intensity-modulated radiotherapy or protons if available.**
  - **RT Dosing Information:**
    - ◊ **Whole brain and spine (to bottom of thecal sac) receive 36 Gy in 1.8 Gy fractions, followed by limited field to spine lesions to 45 Gy. (Gross metastatic lesions below the conus could receive higher doses of 54–60 Gy).[8,9]**
    - ◊ **Primary intracranial site should receive total dose of 54–59.4 Gy in 1.8–2.0 Gy fractions.**
    - ◊ **Consider boosting any gross intracranial metastatic sites to a higher dose while respecting normal tissue tolerances.**
- **Spine Ependymoma:**
  - **For spine ependymomas, see section on primary spinal cord tumors (BRAIN-C 3 of 8).[10,11]**
  - **CTV margins of 1–2 cm in the superior and inferior directions are recommended.**
  - **PTV of margin of 3–5 mm is typically added to the CTV to account for daily setup errors and image registration.**

Adult Medulloblastoma

- **Standard Risk for Recurrence:**
  - **Conventional dose: 30–36 Gy CSI[12,†] and boosting the primary brain site to 54–55.8 Gy with or without adjuvant chemotherapy.**
  - **Reduced dose: May consider reduced dose radiation with adjuvant chemotherapy: 23.4 Gy CSI[12,13,††] and boosting the primary brain site to 54–55.8 Gy.[1]**
- **High Risk for Recurrence:**
  - **36 Gy CSI[3,†] with boosting primary brain site to 54–55.8 Gy with adjuvant chemotherapy.**

†To reduce toxicity from craniospinal irradiation in adults, consider the use of intensity-modulated radiotherapy or protons if available.
††Regimen supported by data from pediatric trials only.

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PRINCIPLES OF RADIATION THERAPY FOR BRAIN AND SPINAL CORD

Primary CNS Lymphoma

- **WBRT may be withheld in the primary setting in patients treated with chemotherapy.**

  - **RT Dosing:**
    - ◊ **When used, low-dose WBRT should be limited to 23.4 Gy in 1.8 Gy fractions following a complete response (CR) to chemotherapy.[14]**
    - ◊ **For less than CR, consider WBRT to 30–36 Gy followed by a limited field to gross disease to 45 Gy or focal radiation to residual disease only.[15-18]**

  - **For patients who are not candidates for chemotherapy:**
    - ◊ **WBRT doses of 24–36 Gy followed by a boost to gross disease for a total dose of 45 Gy.**

Primary Spinal Cord Tumors

- **RT Dosing:**
  - ◊ **Doses of 45–54 Gy are recommended using fractions of 1.8 Gy.**
  - ◊ **In tumors below the conus medullaris higher doses up to 60 Gy may be delivered.**
  - ◊ **CTV margins of 1–2 cm in the superior and inferior directions are recommended.**
  - ◊ **PTV margins of 3–5 mm are typically added to the CTV to account for daily setup errors and image registration.**

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PRINCIPLES OF RADIATION THERAPY FOR BRAIN AND SPINAL CORD

Meningiomas

- **General Treatment Information**
  - If appropriate, may be treated using SRS or fractionated SRS.
  - Highly conformal fractionated RT techniques (eg, 3D-CRT, IMRT, VMAT, proton therapy) are recommended to spare critical structures and uninvolved tissue.
  - Stereotactic or image-guided therapy is recommended when using tight margins or when close to critical structures.

- WHO Grade I Meningiomas:
  - RT Dosing:
    - ◊ 45–54 Gy.
    - ◊ WHO grade I meningiomas may also be treated with SRS doses of 12–16 Gy in a single fraction when appropriate, or consider hypofractionated SRT (25 Gy in 5 fractions) if near critical structures. Optimal dosing has not been determined.

- WHO Grade II Meningiomas:
  - General Treatment Information
    - ◊ Treatment should be directed to gross tumor (if present), surgical bed, and a margin (1–2 cm) to account for microscopic disease.
    - ◊ Limit margin expansion into the brain parenchyma if there is no evidence of brain invasion.
  - RT Dosing:
    - ◊ 54–60 Gy in 1.8–2.0 Gy fractions.

- WHO Grade III Meningiomas:
  - General Treatment Information
    - ◊ Treat as malignant tumors with treatment directed to gross tumor (if present), surgical bed, and a margin (2–3 cm).
  - RT Dosing:
    - ◊ 59.4–60 Gy in 1.8–2.0 Gy fractions.

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PRINCIPLES OF RADIATION THERAPY FOR BRAIN AND SPINAL CORD

Brain Metastases

- **WBRT: Doses vary between 20 and 40 Gy delivered in 5–20 fractions.**
  - **The standard regimens include 30 Gy in 10 fractions or 37.5 Gy in 15 fractions.**
  - **Nevertheless, 20 Gy in 5 fractions is a good option for patients with poor predicted prognosis.[19]**
  - **For patients with a better prognosis, consider memantine during and after WBRT for a total of 6 months.[20]**
  - **For patients with a better prognosis (4 months or greater), consider hippocampal-sparing WBRT. [21-22]**

  - **SRS: Maximum marginal doses from 15–24 Gy based on tumor volume is recommended.[23-26]**
    - **Consider fractionated SRS for brain tumor >3 cm.**
      – Most common fractionated SRT doses include: 27 Gy in 3 fx and 30 Gy in 5 fx.
    - **Postoperative SRS or SRT: Local recurrence rates after brain metastasis resections remain high (in the range of 50% at 1–2 years) even in the setting of a radiographic GTR. Postoperative SRS or SRT to the surgical cavity is supported by randomized data to improve local control over observation and to offer similar overall survival and superior cognitive preservation to postoperative WBRT.[27,28] A consensus statement regarding radiation target delineation has been published.[29] Fractionated SRT may be preferred for larger cavities.[30] Common dose-fractionation schedules include 16–20 Gy in 1 fraction, 27 Gy in 3 fractions, and 30 Gy in 5 fractions.**

    - **SRS is generally preferred over WBRT for limited brain metastases.**

Leptomeningeal Metastases

- **Volumes and dose depend on primary source and sites requiring palliation.**

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PRINCIPLES OF RADIATION THERAPY FOR BRAIN AND SPINAL CORD

Metastatic Spine Tumors

- **General Treatment Information**
  - Doses to vertebral body metastases will depend on patient's PS, spine stability, location in relationship to spinal cord, primary histology, presence of epidural disease, and overall treatment intent (pain relief, long-term local control, or cure).
  - Stereotactic radiation approaches (SRS/stereotactic body radiotherapy [SBRT]) for spinal cases may be preferred for patients with oligometastatic disease where tumor ablation is a goal of treatment and in tumors considered radioresistant (eg, renal cell, melanoma, sarcoma, hepatocellular, and some colorectal and NSCLC cases). Stereotactic radiation approaches may also be preferred in the setting of tumor recurrence after prior radiation as a strategy to limit radiation dose to the spinal cord or other critical structures. Careful adherence to consensus guidelines for radiosurgery planning and delivery is recommended.[31-33]

- **RT Dosing:**
  - Generally, conventional external beam radiation doses of 8 Gy/1 fx, 20 Gy/5 fx, or 30 Gy/10 fx can be used. It is critical to consider tolerance at the spine and/or nerve root. In selected cases, or recurrences after previous radiation, SBRT is appropriate.

  - Common recommended doses for spine SRS/SBRT may include:
    - ◊ 16–24 Gy x 1 fx;
    - ◊ 24 Gy in 2 fx;
    - ◊ 24–27 Gy in 3 fx;
    - ◊ 30–35 Gy in 5 fx

  - In patients with uncomplicated spine metastases that are treated primarily for pain relief, 8 Gy in 1 fraction has been shown to provide equivalent pain control to longer fractionation schedules. Single fraction treatment is more convenient for patients and an important consideration for patients with poor prognoses. This treatment may be associated with higher rates of retreatment, and a consideration for patients with a prognosis that exceeds 6 months or greater.

  - When lower BED regimens are utilized upfront (ie, BED ≤60 Gy_2, which includes up to 20 Gy in 5 fractions but does not include 30 Gy in 10 fractions), retreatment with similar BED regimens, such as 20 Gy in 5 fractions or 8 Gy in 1 fraction, can safely be considered as early as 4 weeks from initial treatment for pain relief.

  - In other cases of retreatment, doses ranging from 15 Gy in 1 fraction to 40 Gy in 20 fractions have been utilized for tumor control, with careful consideration of tolerance of the spinal cord and/or nerve roots. In these instances, it is generally recommended that 6 months or more of time between treatments is required.

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PRINCIPLES OF BRAIN AND SPINAL CORD TUMOR RADIATION THERAPY
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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] (category 2B)	• Temozolomide[b,3-4] • PCV[b]	▸ mTOR inhibitor (eg, everolimus)[6-7] for patients with SEGA
Recurrent or Progressive Disease[a]	• None	• RT + adjuvant PCV • RT + adjuvant temozolomide • RT+ concurrent and adjuvant temozolomide • Temozolomide[c,4,8,9] • Lomustine or carmustine • PCV[10] • Platinum-based regimens[d,11-13]	• None

See Evidence Blocks on BRAIN-D (EB-1)

[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.

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EVIDENCE BLOCKS FOR ADULT LOW-GRADE GLIOMA/PILOCYTIC AND INFILTRATIVE SUPRANTENTORIAL ASTROCYTOMA/OLIGODENDROGLIOMA

ADJUVANT TREATMENT (ASTR-2)	
Preferred regimens	
RT + adjuvant PCV	
RT + concurrent and adjuvant temozolomide	
RT + adjuvant temozolomide	
Other recommended regimens	
Temozolomide	
PCV	

RECURRENT OR PROGRESSIVE DISEASE (ASTR-3)		
Other recommended regimens		
	Resected	**Unresectable**
Patients with or without prior fractionated external beam RT		
Temozolomide[d]		
Lomustine		
Carmustine		
PCV		
Patients with no prior fractionated external beam RT		
RT + adjuvant PCV		
RT + adjuvant temozolomide		
RT + concurrent and adjuvant temozolomide		

[d]For patients not previously treated.

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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,14] • RT with neoadjuvant PCV (category 1)[e,15]	• RT with concurrent and adjuvant TMZ[16] • RT with adjuvant TMZ[17,18]	• None
Adjuvant Treatment Anaplastic astrocytoma/anaplastic oligoastrocytoma, NOS[f] (KPS ≥60)	• RT with concurrent and adjuvant TMZ[19,20] • RT followed by adjuvant TMZ (12 cycles)[20]	• RT with adjuvant PCV[e,21,22] • RT with neoadjuvant PCV[e]	• None
Adjuvant Treatment Anaplastic gliomas (KPS <60)	• None	• TMZ[g] (category 2B)[23]	• None
Recurrence Therapy[h]	• TMZ[8,9,24,25] • Lomustine or carmustine[26] • PCV[27] • Bevacizumab[i, 28-30]	• Bevacizumab + chemotherapy[j] (carmustine or lomustine,[31,32] TMZ,[33,34] carboplatin [category 2B][35,36])	• If failure or intolerance to the preferred or other recommended regimens ▸ Etoposide[37,38] (category 2B) ▸ Platinum-based regimens[d,39-41] (category 3)

See Evidence Blocks on BRAIN-D (EB-2) and BRAIN-D (EB-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.

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EVIDENCE BLOCKS FOR ANAPLASTIC GLIOMAS

ADJUVANT TREATMENT (GLIO-2)	
Anaplastic oligodendroglioma (1p19q co-deleted) (KPS ≥60)	
Preferred regimens	
Fractionated RT + adjuvant PCV	
Fractionated RT + neoadjuvant PCV	
Other recommended regimens	
Fractionated RT + concurrent and adjuvant TMZ	
Fractionated RT + adjuvant TMZ	

Anaplastic astrocytoma/anaplastic oligoastrocytoma, NOS[f] (KPS ≥60)	
Preferred regimens	
Fractionated RT + concurrent and adjuvant TMZ	
Fractionated RT + adjuvant TMZ	
Other recommended regimens	
Fractionated RT + adjuvant PCV	
Fractionated RT + neoadjuvant PCV	

Anaplastic gliomas (KPS <60)	
Other recommended regimens	
TMZ	

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Continued on BRAIN-D (EB-3)

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RECURRENCE THERAPY (GLIO-5)			
	Diffuse or multiple	Local resected	Local unresectable or resection not recommended/ elected
Preferred regimens			
TMZ			
Lomustine			
Carmustine			
PCV			
Bevacizumab			
Other recommended regimens			
Bevacizumab/ carmustine			
Bevacizumab/ lomustine			
Bevacizumab/TMZ			
Bevacizumab/ carboplatin			
Useful in certain circumstances (if failure or intolerance to the preferred or other recommended regimens)			
Etoposide			

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PRINCIPLES OF BRAIN AND SPINAL CORD TUMOR SYSTEMIC THERAPY

GLIOBLASTOMA

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Adjuvant or Concurrent Treatment	• RT with concurrent and adjuvant TMZ[42, 43]	• None	• RT with concurrent or adjuvant TMZ (for patients age 70 or younger and KPS <60)[44] • TMZ (for patients with MGMT promoter-methylated tumors and KPS <60 or age >70 years and KPS ≥60)[42,45]
Recurrence Therapy[h,l]	• Bevacizumab[i,k, 46-49] • Temozolomide[9,25,50,51] • Lomustine or carmustine[52-55] • PCV[56,57]	• Bevacizumab + chemotherapy[j] (carmustine or lomustine,[58,59] TMZ,[60,61] carboplatin [category 2B][62,63])	• If failure or intolerance to the preferred or other recommended regimens ▸ Etoposide (category 2B)[37] ▸ Platinum-based regimens[d] (category 3)[62,63]

See Evidence Blocks on BRAIN-D (EB-4) and BRAIN-D (EB-5)

[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.
[k]An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[l]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.

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EVIDENCE BLOCKS FOR GLIOBLASTOMA

ADJUVANT TREATMENT			
Performance Status	**Good (KPS ≥60)**		**Poor (KPS <60)**
MGMT promoter methylation	**Yes**	**Unmethylated or Indeterminate**	**Any**
Age ≤ 70 years (GLIO-3)			
Preferred regimens			
Standard brain RT + concurrent temozolomide and adjuvant temozolomide + alternating electric field therapy			—
Standard brain RT + concurrent temozolomide and adjuvant temozolomide			—
Useful in certain circumstances			
Hypofractionated RT + concurrent temozolomide	—	—	
Hypofractionated RT + adjuvant temozolomide	—	—	
Temozolomide	—	—	
Age >70 years (GLIO-4)			
Preferred regimens			
Standard brain RT + concurrent temozolomide and adjuvant temozolomide + alternating electric field therapy			—
Standard brain RT + concurrent temozolomide and adjuvant temozolomide			—
Hypofractionated brain RT + concurrent temozolomide and adjuvant temozolomide			—
Useful in certain circumstances			
Temozolomide		—	

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Continued on BRAIN-D (EB-5)

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EVIDENCE BLOCKS FOR GLIOBLASTOMA

RECURRENCE THERAPY (GLIO-5)			
	Diffuse or multiple	Local resected	Local unresectable or resection not recommended/ elected
Preferred regimens			
Bevacizumab			
Temozolomide			
Lomustine			
Carmustine			
PCV			
Other recommended regimens			
Bevacizumab/carmustine			
Bevacizumab/lomustine			
Bevacizumab/temozolomide			
Bevacizumab/carboplatin			
Useful in certain circumstances (if failure or intolerance to the preferred or other recommended regimens)			
Etoposide			

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PRINCIPLES OF BRAIN AND SPINAL CORD TUMOR SYSTEMIC THERAPY

ADULT INTRACRANIAL AND SPINAL EPENDYMOMA (EXCLUDING SUBEPENDYMOMA)

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Recurrence Therapy	• None	• Platinum-based regimens:[d] Single agent or combination[64,65] • Etoposide[66,67] • Lomustine or carmustine[64] • Bevacizumab[i,68] • TMZ[69] • Lapatinib + TMZ (category 2B)[70]	• None

ADULT MEDULLOBLASTOMA

Regimens following weekly vincristine[m] during craniospinal radiation therapy	• Cisplatin, cyclophosphamide, and vincristine[m,71] • Cisplatin, lomustine, and vincristine[m,71]	• None	• None
Recurrence Therapy	• None	• No prior chemotherapy ▸ High-dose cyclophosphamide ± etoposide ▸ Carboplatin, etoposide, and cyclophosphamide ▸ Cisplatin, etoposide, and cyclophosphamide • Prior chemotherapy ▸ High-dose cyclophosphamide ± etoposide ▸ Oral etoposide[72,73] ▸ TMZ[8,74]	• Consider high-dose chemotherapy with autologous stem cell reinfusion[75] in patients who achieve a CR with conventional doses of chemotherapy or have no residual disease after re-resection • Vismodegib (for mutations in the sonic hedgehog pathway and if prior chemotherapy)[76]

See Evidence Blocks on BRAIN-D (EB-6)

[d]Platinum-based regimens include cisplatin or carboplatin.
[i]Patients who have evidence of radiographic progression may benefit from continuation of bevacizumab to prevent rapid neurologic deterioration.
[m]Omission of vincristine during radiotherapy phase of therapy or dose modification may be required for adults because they do not tolerate this regimen as well. Data supporting vincristine's use have been found in pediatric trials only. Patients should be closely monitored for neurologic toxicity with periodic exams.

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EVIDENCE BLOCKS FOR ADULT MEDULLOBLASTOMA

Postoperative Adjuvant Treatment for Newly Diagnosed Disease (AMED-2)	Standard Risk for Recurrence	High Risk for Recurrence
Preferred regimens		
Craniospinal RT with weekly vincristine followed by post-radiation cisplatin, cyclophosphamide, and vincristine		
Craniospinal RT with weekly vincristine followed by post-radiation cisplatin, lomustine, and vincristine		

Treatment of Recurrence (AMED-3)	Resected Localized Recurrence	Disseminated Recurrence
Other recommended regimens		
No prior chemotherapy		
High-dose cyclophosphamide		
High-dose cyclophosphamide/etoposide		
Carboplatin, etoposide, and cyclophosphamide		
Cisplatin, etoposide, and cyclophosphamide		
Prior chemotherapy		
High-dose cyclophosphamide		
High-dose cyclophosphamide/etoposide		
Oral etoposide		
Temozolomide		
Useful in certain circumstances		
Vismodegib (if prior chemotherapy and mutation in the sonic hedgehog pathway)		

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PRINCIPLES OF BRAIN AND SPINAL CORD TUMOR SYSTEMIC THERAPY

PRIMARY CNS LYMPHOMA

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Induction Therapy ▸ Systemic therapy ◊ High-dose methotrexate 8 g/m^2 combined with the following:[n,77] – Rituximab[o,78-81] – Rituximab and TMZ[o,82] ◊ High-dose methotrexate 3.5 g/m^2 combined with the following, and consider WBRT:[n,p] – Vincristine, procarbazine, and rituximab (R-MPV)[83-86] – TMZ + rituximab followed by post-RT TMZ[87] • Consolidation Therapy ▸ High-dose chemotherapy with stem cell rescue ◊ Carmustine + thiotepa[88,89] ◊ Thiotepa, busulfan, and cyclophosphamide (TBC)[90] ▸ High-dose cytarabine + etoposide (EA)[91] ▸ High-dose cytarabine[83-85]	• Relapsed or Refractory Disease ▸ Retreat with high-dose methotrexate with or without rituximab[n, 77] ▸ Ibrutinib[q, 92] ▸ TMZ[93] ▸ Rituximab ± TMZ[94-96] ▸ Lenalidomide with or without rituximab[97] ▸ Topotecan[98,99] ▸ Consider high-dose chemotherapy with autologous stem cell reinfusion in eligible patients[88,100,101] ▸ High-dose cytarabine[102] ▸ Dexamethasone, high-dose cytarabine, cisplatin[103] ▸ Pemetrexed[104] ▸ Pomalidomide[105]	• Intra-CSF therapy as induction therapy ▸ If CSF positive or spinal MRI positive ◊ Methotrexate ◊ Cytarabine ◊ Rituximab[106]

See Evidence Blocks on BRAIN-D (EB-7)

[n]Consider glucarpidase (carboxypeptidase G2) for prolonged methotrexate clearance due to methotrexate-induced renal toxicity. Ramsey LB, Balis FM, O'Brien MM, et al. Consensus guideline for use of glucarpidase in patients with high-dose methotrexate induced acute kidney injury and delayed methotrexate clearance. Oncologist 2018;23:52-61.

[o]Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist. The NCCN Guidelines for B-Cell Lymphomas (NHODG-B, 2 of 4) also has information about HBV testing for patients considering rituximab.

[p]Other combinations with methotrexate may be used.

[q]Ibrutinib is associated with risk of aspergillus infection.

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EVIDENCE BLOCKS FOR PRIMARY CNS LYMPHOMA
(PCNS-2)

Preferred regimens	
Induction Therapy	
High-dose methotrexate 8 g/m^2/rituximab	
High-dose methotrexate 8 g/m^2/rituximab/TMZ	
High-dose methotrexate 3.5 g/m^2/vincristine/ procarbazine/rituximab, with WBRT	
High-dose methotrexate 3.5 g/m^2/vincristine/ procarbazine/rituximab	
High-dose methotrexate 3.5 g/m^2/TMZ/rituximab, with RT followed by post-RT TMZ	

Consolidation therapy following induction therapy	Complete response or complete response unconfirmed	Residual disease
Carmustine/thiotepa (as high-dose chemotherapy with stem cell rescue)		—
Thiotepa/busulfan/cyclophosphamide (as high-dose chemotherapy with stem cell rescue)		—
High-dose cytarabine/etoposide		
High-dose cytarabine		

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PRINCIPLES OF BRAIN AND SPINAL CORD TUMOR SYSTEMIC THERAPY

MENINGIOMAS

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• None	• Interferon alfa (category 2B)[107] • Somatostatin analogue, if octreotide scan positive[108] • Sunitinib (category 2B)[109] • Bevacizumab[i,110,111] • Bevacizumab[i] + everolimus (category 2B)[112]	• None

See Evidence Blocks on BRAIN-D (EB-8)

[i]Patients who have evidence of radiographic progression may benefit from continuation of bevacizumab to prevent rapid neurologic deterioration.

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EVIDENCE BLOCKS FOR MENINGIOMAS

Treatment for Recurrent or Progressive Disease[h] (MENI-2)	
Other recommended regimens	
Interferon alfa	
Somatostatin analogue[i]	
Sunitinib	
Bevacizumab/everolimus	
Bevacizumab	

[h]Not surgically accessible and RT not possible
[i]If octreotide scan positive

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PRINCIPLES OF BRAIN AND SPINAL CORD TUMOR SYSTEMIC THERAPY
BRAIN METASTASES

Newly Diagnosed[r]

- Treatment as per the regimens of the primary tumor[s]
- Melanoma
  - ◊ Ipilimumab + nivolumab[113,114]
  - ◊ Nivolumab[114]
  - ◊ Pembrolizumab[115]
  - ◊ BRAF/MEK inhibitor combination:
    - – Dabrafenib[116-118]/trametinib[119]
    - – Vemurafenib[120]/cobimetinib[s] (category 2B)
- Non-Small Cell Lung Cancer
  - ◊ Pembrolizumab (PD-L1 positive)[115]
  - ◊ Alectinib (ALK rearrangement-positive)[121]
  - ◊ Osimertinib (EGFR mutation-positive)[122]
  - ◊ Nivolumab (category 2B)[123-125]
  - ◊ Brigatinib (ALK rearrangement-positive)[126]
  - ◊ Ceritinib (ALK rearrangement-positive) (category 2B)[127]
- NTRK gene-fusion tumors
  - ▸ Larotrectinib[128,129]
  - ▸ Entrectinib[130,131]

Recurrent Disease[u]

- Treatment as per the regimens of the primary tumor
- Temozolomide 5/28 schedule
- Breast Cancer
  - ◊ Capecitabine[132-136]
  - ◊ Capecitabine + lapatinib (*HER2* positive)[137,138]
  - ◊ Capecitabine + neratinib (*HER2* positive) (category 2B)[139]
  - ◊ Paclitaxel + neratinib (*HER2* positive) (category 2B)[140]
  - ◊ Cisplatin[141,142]
  - ◊ Etoposide[141,142]
  - ◊ Cisplatin + etoposide (category 2B)[142,143]
  - ◊ High-dose methotrexate [n,144]
- Lymphoma
  - ◊ High-dose methotrexate[n,145]
- Small Cell Lung Cancer
  - ◊ Topotecan
- Melanoma
  - ◊ Ipilimumab[146]
  - ◊ Nivolumab
  - ◊ Ipilimumab + nivolumab[113,147]
  - ◊ Pembrolizumab[115]
  - ◊ BRAF/MEK inhibitor combination:
    - – Dabrafenib[116,118]/trametinib[119]
    - – Vemurafenib[120,148]/cobimetinib[t] (category 2B)
- Non-Small Cell Lung Cancer
  - ◊ Pembrolizumab (PD-L1 positive)[115,149]
  - ◊ Ceritinib,[127] alectinib,[150] brigatinib[151] (ALK rearrangement-positive)
  - ◊ Erlotinib,[152,153] afatinib,[154] gefitinib[155,156] (EGFR-sensitizing mutation-positive)
  - ◊ Osimertinib (EGFR T790M mutation-positive)[157,158]
  - ◊ Crizotinib (ALK rearrangement-positive or ROS1 positive)[159]
- NTRK gene-fusion tumors
  - ▸ Larotrectinib[128,129]
  - ▸ Entrectinib[130,131]

See Evidence Blocks on BRAIN-D (EB-9)

[n]Consider glucarpidase (carboxypeptidase G2) for prolonged methotrexate clearance due to methotrexate-induced renal toxicity. Ramsey LB, Balis FM, O'Brien MM, et al. Consensus guideline for use of glucarpidase in patients with high-dose methotrexate induced acute kidney injury and delayed methotrexate clearance. Oncologist 2018;23:52-61.

[r]For patients with asymptomatic brain metastases, it is reasonable to treat with these systemic therapies in lieu of upfront WBRT or SRS.

[s]See the appropriate NCCN treatment guidelines for systemic therapy recommendations for newly diagnosed brain metastases for any cancers not listed here.

[t]Although there are no published prospective studies on the combination of vemurafenib and cobimetinib for melanoma patients with brain metastases, there is high-quality evidence that for melanoma with distant metastasis, combination therapy with vemurafenib and cobimetinib is associated with improved outcomes and safety compared with single-agent vemurafenib.

[u]Use agents active against primary tumor.

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NCCN Guidelines Version 3.2019
Central Nervous System Cancers
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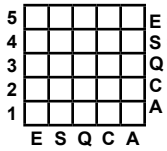

E = Efficacy of Regimen/Agent
S = Safety of Regimen/Agent
Q = Quality of Evidence
C = Consistency of Evidence
A = Affordability of Regimen/Agent

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EVIDENCE BLOCKS FOR BRAIN METASTASES

Newly Diagnosed Limited Brain Metastases (LTD-2)

Melanoma
Dabrafenib/trametinib
Ipilimumab/nivolumab
Nivolumab
Pembrolizumab
Vemurafenib/cobimetinib
Non-Small Cell Lung Cancer
Alectinib (ALK rearrangement-positive)
Brigatinib (ALK rearrangement positive)
Ceritinib (ALK rearrangement positive)
Nivolumab
Osimertinib (EGFR mutation positive)
Pembrolizumab (PD-L1 positive)
NTRK gene-fusion tumors
Larotrectinib
Entrectinib

Recurrent Limited or Extensive Brain Metastases (LTD-3, MU-2)

Temozolomide 5/28 schedule
Breast Cancer
Capecitabine
Capecitabine/lapatinib (HER2-positive)
Capecitabine/neratinib (HER2-positive)
Cisplatin
Cisplatin/etoposide
Etoposide
High-dose methotrexate
Paclitaxel/neratinib (HER2-positive)
Lymphoma
High-dose methotrexate
Small Cell Lung Cancer
Topotecan
Melanoma
Dabrafenib + trametinib
Ipilimumab
Ipilimumab + nivolumab

Melanoma (continued)
Nivolumab
Pembrolizumab
Vemurafenib/cobimetinib
Non-Small Cell Lung Cancer
Afatinib (EGFR-sensitizing mutation-positive)
Alectinib (ALK rearrangement-positive)
Brigatinib (ALK rearrangement-positive)
Ceritinib (ALK rearrangement-positive)
Crizotinib (ALK rearrangement-positive or ROS1 rearrangement-positive)
Erlotinib (EGFR-sensitizing mutation-positive)
Gefitinib (EGFR-sensitizing mutation-positive)
Osimertinib (EGFR T790M mutation-positive)
Pembrolizumab (PD-L1 positive)
NTRK gene-fusion tumors
Larotrectinib
Entrectinib

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PRINCIPLES OF BRAIN AND SPINAL CORD TUMOR SYSTEMIC THERAPY

LEPTOMENINGEAL AND SPINE METASTASES

- **Treatment**
  - **Systemic therapy specific to primary cancer type; emphasizing drugs with good CNS penetration**
  - **Intra-CSF chemotherapy[160]**
    - ◊ **Thiotepa[161]**
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    - ◊ **Intra-CSF chemotherapy**
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    - ◊ **High-dose methotrexate[n,144]**
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    - ◊ **Osimertinib (EGFR mutation positive)[173]**
    - ◊ **Weekly pulse erlotinib for (EGFR exon 19 deletion or exon 21 L858R mutation) (category 2B)[152]**

Metastatic Spine Tumors
- **Use regimen for disease-specific site**

[n]Consider glucarpidase (carboxypeptidase G2) for prolonged methotrexate clearance due to methotrexate-induced renal toxicity. Ramsey LB, Balis FM, O'Brien MM, et al. Consensus guideline for use of glucarpidase in patients with high-dose methotrexate induced acute kidney injury and delayed methotrexate clearance. Oncologist 2018;23:52-61.

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PRINCIPLES OF BRAIN AND SPINAL CORD TUMOR SYSTEMIC THERAPY
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PRINCIPLES OF BRAIN AND SPINAL CORD TUMOR SYSTEMIC THERAPY
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PRINCIPLES OF BRAIN AND SPINE TUMOR MANAGEMENT

General

Patients diagnosed with a tumor involving the brain, spinal cord, and related support structures should be referred to practitioners who are experienced in the diagnosis and management of these lesions.[1] The patient may (and should) be presented with options for care, which may include procedures or treatments best done by other specialists. The care options should then be discussed with the patient and their chosen supports in a manner that is understandable and culturally and educationally sensitive. It is strongly encouraged to discuss goals of care with the patient.

Multidisciplinary Care

- **During the course of their treatment, most patients will be seen by multiple subspecialists. Close and regular communication among all providers across disciplines is essential. Brain tumor board or multidisciplinary clinic care models are strongly recommended. These models facilitate interactions among multiple subspecialists, ideally including allied health services (ie, physical, occupational and speech therapies, nursing, psychology, social work) for optimizing treatment plan recommendations.**
- **As treatment proceeds, it is important that the patient and family understand the role of each team member. One practitioner should be identified early on as the main point of contact for follow-up care questions. This individual can facilitate referral to the appropriate specialist.**
- **Offering patients the option of participation in a clinical trial is strongly encouraged. Practitioners should discuss any local, regional, and national options for which the patient may be eligible and the advantages and disadvantages of participation. Centers treating neuro-oncology patients are encouraged to participate in large collaborative trials in order to have local options to offer patients.**
- **Patients should be educated on the importance of informed consent and side effects when receiving chemotherapy.**
- **Throughout treatment the patient's quality of life should remain the highest priority and guide clinical decision-making. While responses on imaging are benchmarks of successful therapy, other indicators of success such as overall well-being, function in day-to-day activities, social and family interactions, nutrition, pain control, long-term consequences of treatment, and psychological issues must be considered.**
- **Patients should be informed of the possibility of pseudoprogression, its approximate incidence, and potential investigations that may be needed in the event that pseudoprogression is suspected. Close follow-up imaging, MR perfusion, MR spectroscopy, PET/CT imaging, and repeat surgery may be necessary if clinically indicated. Educate patients on the uncertainty of imaging as a whole, and the potential need for corollary testing to interpret scans.**
- **For patients with spine tumors, it is important to assemble a multidisciplinary team to integrate diagnosis, treatment, symptom management, and rehabilitation. Patients with spine tumors have complex physical, psychological, and social care needs.**
- **Optimal managment requires a multidisciplinary team including the following expertise: neuro-oncology/medical and radiation oncology; surgery (ie, neurosurgery, orthopedic surgery, surgical oncology); radiology; interventional pain specialties; physical and rehabilitation medicine; physiatrists; experts in bowel and bladder care, back care, and ambulation support; physical therapy; occupational therapy; psychological and/or social services; and nutritional support.**
- **Practitioners should become familiar with palliative and hospice care resources that are available in their community in order to help educate patients and families that involvement of these services does not indicate a state of hopelessness, no further treatment, or abandonment. Palliative and pain management care should be integrated into management of neuro-oncology patients early in the course of their treatment.**
  See NCCN Guidelines for Palliative Care and Ferrell BR, Temel JS, Temin S, et al. Integration of Palliative Care Into Standard Oncology Care: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 2017;35:96-112.

[1]Depending on local referral patterns and available expertise, this physician may be a neurosurgeon, neurologist, medical oncologist, or radiation oncologist.

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PRINCIPLES OF BRAIN AND SPINE TUMOR MANAGEMENT

Medical Management

1. Mass Effect, Brain Edema, Radiation Necrosis

- **Steroid therapy should be carefully monitored. If a patient is asymptomatic, steroids may be unnecessary. Careful questioning for subtle symptoms should be undertaken if edema is extensive on imaging. In general, the lowest dose of steroids should be used for the shortest time possible.[2] Downward titration of the dose should be attempted whenever possible. Patients with extensive mass effect should receive steroids for at least 24 hours before radiation therapy. Patients with a high risk of GI side effects (ie, perioperative patients, prior history of ulcers/GI bleed, receiving NSAIDS or anticoagulation) should receive H_2 blockers or proton pump inhibitors. Care should be taken to watch for development of steroid side effects.[3] Consider prophylactic treatment of pneumocystis jiroveci pneumonia for patients undergoing long-term steroid therapy. Consider short-course bevacizumab for management of symptoms driven by RT necrosis,[4,5] poorly controlled vasogenic edema, or mass effect in patients with brain metastases and primary brain tumors, particularly those with deep-seated unresectable tumors, as it may allow overall quality-of-life improvements by reducing steroid dose and improving functional status.[6]**

2. Seizures

- **Seizures are frequent in patients with primary or metastatic brain tumors. Despite this, studies have shown that the use of older, "traditional" anti-seizure medications, including phenytoin, phenobarbital, and valproic acid as prophylaxis against seizures in patients who have never had a seizure or who are undergoing neurosurgical procedures, is ineffective and is not recommended. Newer agents (ie, levetiracetam, topiramate, lamotrigine, pregabalin) have not yet been systematically studied.**
- **Seizure prophylaxis is not recommended as routine in asymptomatic patients but is reasonable to consider perioperatively.**
- **Many anti-seizure medications have significant effects on the cytochrome P450 system, and may have effects on the metabolism of numerous chemotherapeutic agents such as irinotecan, gefitinib, erlotinib, and temsirolimus among others. Where possible, such enzyme-inducing anti-seizure medications (EIAEDs) should be avoided (ie, phenytoin, phenobarbital, carbamazepine), and non-EIAEDs should be used instead (ie, levetiracetam, topiramate, valproic acid, lacosamide). Patients should be closely monitored for any adverse effects of the anti-seizure medications or chemotherapeutic agents.**

3. Endocrine Disorders

- **Endocrinopathies are common with brain tumor patients. This may be affected by concomitant steroid use as well as by radiotherapy, surgery, and certain medical therapies. Patients who present with a declining sense of well-being or quality of life should be evaluated not only for abnormalities related to their hypothalamic pituitary and adrenal axis, but also with regard to thyroid and gonad function. For patients who received prior RT, long-term monitoring of the hypothalamic pituitary and adrenal axis may be considered (eg, ACTH stimulation test, thyroid monitoring).**

4. Fatigue (Also see the NCCN Guidelines for Cancer-Related Fatigue)

- **Fatigue is commonly experienced by brain tumor patients. This symptom can be severe, persistent, emotionally overwhelming, and not related to the degree or duration of physical activity. Screening should be initiated to identify any underlying medical sources of this symptom, after which patients can be taught energy conservation and organizational skills to help manage this effect. Supervised, moderate exercise may be of assistance for those in otherwise good general medical condition. More data are needed on the use of CNS stimulants and these agents are not routinely recommended.**

[2]An exception to this rule is in the case of suspected CNS lymphoma. Steroids should be avoided where possible (see PCNS-1) prior to biopsy to allow best chance of diagnosis.

[3]Refractory hyperglycemia, skin changes, visual changes, fluid retention, and myopathy. If any of these changes occur, it is imperative to evaluate potential palliative treatments for them and also to evaluate the current dose of steroids to see if it can be reduced in an attempt to mitigate these side effects. Clinical monitoring for adrenal insufficiency is recommended when weaning steroids for patients who have been on long-term steroid therapy.

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PRINCIPLES OF BRAIN AND SPINE TUMOR MANAGEMENT

Medical Management—continued

5. Psychiatric Disorders (Also see the NCCN Guidelines for Distress Management including NCCN Distress Thermometer [DIS-A])

- **Depression and/or anxiety is common in neuro-oncology patients. These symptoms are greater than simple sadness or anxiety associated with the diagnosis of a tumor. The vegetative symptoms associated with depression or severe anxiety may become very disabling for the patient and distressing for the family. These symptoms will respond to psychotropic medications as they do in non-tumor patients. If less severe, strong support from behavioral health allies and other qualified counselors is also extremely beneficial. Physicians, and other members of their health care teams, should be sensitive to these symptoms and inquire about them in follow-up visits in order to determine if the patient may be a candidate for psychological or psychiatric treatment. Communication between members of the patient's health care team regarding the patient's response to treatment is important. See Andersen BL, DeRubeis RJ, Berman BS, et al. Screening, assessment, and care of anxiety and depressive symptoms in adults with cancer: an American Society of Clinical Oncology guideline adaptation. J Clin Oncol 2014;32:1605-1619.**
- **Anti-seizure medications, anxiolytics, some chemotherapy agents, antiemetics, and other agents used directly in cancer therapy may affect mental status, alertness, and mood. Alterations in thought processes should trigger an investigation for any treatable causes, including endocrine disorders, infection, side effects of medication, or tumor progression.**

6. Venous Thromboembolism (VTE)

- **See the NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease.**

Allied Services

- **Physical therapy, occupational therapy, and speech therapy may be helpful for many patients with CNS tumors, either benign or malignant. Surgical intervention is not a prerequisite for referral, and these therapies should not be withheld from patients because of the uncertain course of certain malignant tumors. Many patients with aggressive, malignant primary brain tumors or CNS metastases can benefit from inpatient rehabilitation.**
- **Practitioners are encouraged to serve as a resource and to refer patients to social services, support groups, and cancer patient advocacy organizations. Institutional or community resources that can assist patients and families in dealing with financial, insurance, and legal issues are important.**
- **Practitioners should be familiar with their state laws concerning seizures and driving so that they can advise patients and families appropriately.**

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PRINCIPLES OF BRAIN TUMOR PATHOLOGY

- **Incorporation of relevant diagnostic markers, including histopathologic and molecular information, as per the WHO 2016 Classification of Tumors of the Central Nervous System should be considered standard practice for tumor classification.**
- **Molecular/genetic characterization complements standard histologic analysis, providing additional diagnostic and prognostic information that can greatly improve diagnostic accuracy, influence treatment selection, and possibly improve management decision-making.**

Standard Histopathologic Examination and Classification

- **Histologic subgrouping of CNS neoplasms provides valuable prognostic information, as is described in the WHO Classification of Tumors of the Central Nervous System.[1]**
- **Inter-observer discrepancies in histologic diagnosis and grading are a recognized issue, due to the inherently subjective nature of certain aspects of histopathologic interpretation (eg, astrocytic vs. oligodendroglial morphology). Also, surgical sampling does not always capture all the relevant diagnostic features in morphologically heterogeneous tumors.**
- **Even so, the traditional histologic classification of CNS neoplasms into primary neuroectodermal neoplasms (eg, glial, neuronal, embryonal), other primary CNS neoplasms (eg, lymphoma, germ cell, meningeal), metastatic neoplasms, and non-neoplastic conditions mimicking tumors remains fundamental to any pathologic assessment.**

Molecular Characterization

- **With the use of genetic and molecular testing, histologically similar CNS neoplasms can be differentiated more accurately in terms of prognosis and, in some instances, response to different therapies.[2-6]**
- **Molecular characterization of primary CNS tumors has substantially impacted clinical trial eligibility and risk stratification in the past 10 years, thereby evolving the standard of care towards an integrated tumor diagnosis in neuro-oncology.**
- **Molecular/genetic characterization does not replace standard histologic assessment, but serves as a complementary approach to provide additional diagnostic and prognostic information that often enhances treatment selection.**
- **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.**

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PRINCIPLES OF BRAIN TUMOR PATHOLOGY MOLECULAR MARKERS

The following molecular markers are often used by neuropathologists to facilitate characterization of gliomas and/or by neuro-oncologists to guide treatment decisions:

Isocitrate Dehydrogenase 1 and 2 (IDH1 and IDH2) Mutation

- **Recommendation: IDH mutation testing is required for the workup of glioma.**
- **Description: IDH1 and IDH2 are metabolic enzymes. Specific mutations in genes encoding these enzymes lead to the aberrant production of D-2-hydroxyglutarate, an oncometabolite that causes epigenetic modifications in affected cells.[7]**
- **Detection: The most common IDH1 mutation (R132H) is reliably screened by mutation-specific immunohistochemistry, which is recommended for all glioma patients. If the R132H immunostain result is negative, in the appropriate clinical context, sequencing of IDH1 and IDH2 is highly recommended to detect less common IDH1 and IDH2 mutations. Prior to age 55 years, sequencing of IDH1 and IDH2 is required if the R132H immunostain result is negative. Standard sequencing methods include Sanger sequencing, pyrosequencing, and next-generation sequencing, and should be performed on formalin-fixed, paraffin-embedded tissue.[7]**
- **Diagnostic value:**
  - **IDH mutations define WHO grade II and III astrocytomas and oligodendrogliomas, and the secondary grade IV glioblastomas into which astrocytomas often evolve. Their presence distinguishes lower-grade gliomas from primary glioblastomas, which are IDH-wild type.[8,9] Detection of these mutations in a specimen that is otherwise equivocal for tumor may also be regarded as evidence that a diffusely infiltrative glioma is present.[7]**
  - **True grade I non-infiltrative gliomas, such as pilocytic astrocytomas and gangliogliomas, do not contain IDH mutations. In such cases, detection of an IDH mutation indicates that the tumor is at least a grade II diffusely infiltrative glioma.[7]**
- **Prognostic value:**
  - **IDH mutations are commonly associated with MGMT promoter methylation.[4]**
  - **IDH1 or 2 mutations are associated with a relatively favorable prognosis and are important in stratification for clinical trials.[10]**
  - **In grade II or III infiltrative gliomas, wild-type IDH1 or 2 is associated with increased risk of aggressive disease.[4]**
  - **IDH1 or 2 mutations are associated with a survival benefit for patients treated with radiation or alkylating chemotherapy.[11,12]**

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PRINCIPLES OF BRAIN TUMOR PATHOLOGY MOLECULAR MARKERS

The following molecular markers are often used by neuropathologists to facilitate characterization of gliomas and/or by neuro-oncologists to guide treatment decisions:

Codeletion of 1p and 19q

- Recommendation: 1p19q testing is an essential part of molecular diagnostics for oligodendroglioma.
- Description: This codeletion represents an unbalanced translocation (1;19)(q10;p10), leading to whole-arm deletion of 1p and 19q.[13]
- Detection: The codeletion of 1p and 19q is detectable by fluorescence in situ hybridization (FISH) or polymerase chain reaction (PCR). Additional methods, including array-based genomic copy number testing and next-generation sequencing, may also be employed.
- Diagnostic value: It is strongly associated with oligodendroglial histology and helps confirm the oligodendroglial character of tumors with equivocal or mixed histologic features.[14]
  - IDH-mutated gliomas that do NOT show loss of ATRX (for example, by IHC) should be strongly considered for 1p19q testing, even if not clearly oligodendroglial by histology. Conversely, IDH1 wild-type gliomas do not contain true whole-arm 1p/19q codeletion.[15] Therefore, 1p/19q testing is unnecessary if a glioma is not IDH-mutant, and a glioma should not be regarded as 1p/19q-codeleted without an accompanying IDH mutation, regardless of test results.
  - A tumor should only be diagnosed as an oligodendroglioma if it contains both an IDH mutation and 1p/19q codeletion. Furthermore, the term “oligoastrocytoma” should no longer be used, as such morphologically ambiguous tumors can reliably be resolved into astrocytomas and oligodendrogliomas with molecular testing.[16]
- Prognostic value: The codeletion confers a favorable prognosis and is predictive of response to alkylating chemotherapy and combination therapy with radiation and alkylating chemotherapy.[17,18]

MGMT Promoter Methylation

- Recommendation: MGMT promoter methylation is an essential part of molecular diagnostics for all high-grade gliomas (grade III and IV).
- Description: MGMT (O^6-methylguanine-DNA methyltransferase) is a DNA repair enzyme that reverses the DNA damage caused by alkylating agents, resulting in tumor resistance to temozolomide and nitrosourea-based chemotherapy. Methylation of the MGMT promoter silences MGMT, making the tumor more sensitive to treatment with alkylating agents.[19]
- Detection: Methylation of the MGMT promoter is detectable by methylation-specific PCR,[20] pyrosequencing,[21] or array-based technologies.[22]
- Prognostic value:
  - MGMT promoter methylation is strongly associated with IDH mutations and genome-wide epigenetic changes (G-CIMP phenotype).[4]
  - MGMT promoter methylation confers a survival advantage in glioblastoma and is used for risk stratification in clinical trials.[23]
  - MGMT promoter methylation is particularly useful in treatment decisions for elderly patients with high-grade gliomas (grades III-IV).[24,25]
  - Patients with glioblastoma that are not MGMT promoter methylated derive less benefit from treatment with temozolomide compared to those whose tumors are methylated.[23]

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PRINCIPLES OF BRAIN TUMOR PATHOLOGY MOLECULAR MARKERS

The following molecular markers are often used by neuropathologists to facilitate characterization of gliomas and/or by neuro-oncologists to guide treatment decisions:

ATRX Mutation

- **Recommendation: ATRX mutation testing is strongly recommended but not required for glioma.**
- **Description: ATRX encodes a chromatin regulator protein. Loss of function mutations enable alternative lengthening of telomeres (ALT).[26]**
- **Detection: ATRX mutations can be detected by IHC for wild-type ATRX (loss of wild-type expression) and/or sequencing.[27]**
- **Diagnostic value: ATRX mutations in glioma are strongly associated with IDH mutations, and are nearly always mutually exclusive with 1p/19q codeletion.[27] ATRX deficiency, coupled with IDH mutation, is typical of astrocytoma. A lack of ATRX immunostaining in glioblastoma should trigger IDH1/2 sequencing if IDH1 R132H immunostaining is negative, due to the frequent co-occurrence of ATRX and IDH mutations.[5,27]**

TERT Mutation

- **Recommendation: TERT mutation testing is recommended but not required for gliomas.**
- **Description: TERT encodes the catalytic active site of telomerase, the enzyme responsible for maintaining telomere length in dividing cells. TERT mutations found in gliomas are located in its noncoding promoter region, and cause increased expression of the TERT protein.[28]**
- **Detection: TERT mutations can be detected by sequencing of the promoter region.[29]**
- **Diagnostic value: TERT mutations are almost invariably present in 1p/19q codeleted oligodendroglioma, and are found in most glioblastomas. TERT mutation, in combination with IDH mutation and 1p/19q codeletion, is characteristic of oligodendroglioma. Absence of TERT mutation, coupled with IDH mutation, designates astrocytoma.**
- **Prognostic value: In the absence of an IDH mutation, TERT mutations in diffusely infiltrative gliomas are associated with reduced overall survival compared to gliomas lacking TERT mutations.[4,30,31]**
  Combined TERT and IDH mutations in the absence of 1p/19q codeletion is an uncommon event, but such tumors have a prognosis as favorable as gliomas with all three molecular alterations.[4,30]

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PRINCIPLES OF BRAIN TUMOR PATHOLOGY MOLECULAR MARKERS

The following molecular markers are often used by neuropathologists to facilitate characterization of gliomas and/or by neuro-oncologists to guide treatment decisions:

H3F3A Mutation

- **Recommendation: *H3F3A* and *HIST1H3B* mutation testing is recommended in the appropriate clinical context.**
- **Description: The most common histone mutation in brain tumors, *H3K27M*, is caused by a lysine-to-methionine substitution in the *H3F3A* gene and inhibits the trimethylation of *H3.3* histone. *G34* mutations are more common in cortical gliomas in children.[32-34]**
- **Detection: Although a *K27M* histone antibody is available,[35] it is not 100% specific and interpretation can be difficult for non-experts. Therefore, screening by *H3F3A* and *HIST1H3B* sequencing is a viable alternative and the preferred approach, especially since it will also detect mutations in *G34*.**
- **Diagnostic value: Histone mutations most commonly occur in pediatric midline gliomas (eg, diffuse intrinsic pontine gliomas [DIPG]), although midline gliomas in adults can also contain histone mutations.[36] Their presence can be considered solid evidence of an infiltrative glioma, which is often helpful in small biopsies of midline lesions that may not be fully diagnostic with light microscopy or do not fully resemble infiltrative gliomas.[32,33,36]**
- **Prognostic value: *K27M* gliomas typically do not have MGMT promoter methylation, and the mutation is an adverse prognostic marker in children and adults. The *G34* mutation does not appear to have any prognostic significance once the diagnosis of a glioblastoma has been established.[33,36,37]**

BRAF Mutation

- **Recommendation: *BRAF* fusion and/or mutation testing is recommended in the appropriate clinical context.**
- **Description: Activating mutations in *BRAF*, most commonly the V600E variant seen in other cancers (eg, melanoma), are present in 60%–80% of supratentorial grade II-III pleomorphic xanthoastrocytomas (PXA), 30% of dysembryoplastic neuroepithelial tumors, 20% of grade I gangliogliomas, and 5% of grade I pilocytic astrocytomas (PA). Diffusely infiltrative gliomas can also harbor a *BRAF* mutation, especially in children. *BRAF* V600E has even been found in nonneoplastic cortical dysplasia. In contrast, activating *BRAF* fusions occur predominately in PA of the posterior fossa, although some supratentorial PA also have this fusion.[38-40]**
- **Detection: *BRAF* V600E is best detected by sequencing, and *BRAF* fusions can be detected with RNA-Seq or other PCR-based breakpoint methods that capture the main 16-9, 15-9, and 16-11 breakpoints between *BRAF* and its main fusion partner, *KIAA1549*. FISH is too unreliable to detect *BRAF* fusions.[38]**
- **Diagnostic value: The presence of a *BRAF* fusion is reliable evidence that the tumor is a pilocytic astrocytoma, provided the histology is compatible. *BRAF* V600E is more complicated, as it can occur in a variety of tumors over all four WHO grades and requires integration with histology.[38]**
- **Prognostic value: Tumors with *BRAF* fusions tend to be indolent, with occasional recurrence but only rare progression to lethality. *BRAF* V600E tumors show a much greater range of outcomes and need to be considered in context with other mutations and clinicopathologic findings (eg, CDKN2A/B deletion). *BRAF* V600E tumors may respond to BRAF inhibitors such as vemurafenib, but comprehensive clinical trials are still ongoing.[41-43]**

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PRINCIPLES OF BRAIN TUMOR PATHOLOGY MOLECULAR MARKERS

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RELA fusion

- **Recommendation: RELA fusion testing is recommended in the appropriate clinical context.**
- **Description: Ependymomas arising in the supratentorium often contain activating fusions of RELA. Increased RELA activity leads to increased NF-kappa-B signaling and more aggressive behavior. This event is more common in children than in adults, and occurs only in the supratentorium, not the posterior fossa or spine.[44,45]**
- **Detection: The most common RELA fusion partner is C11orf95. This can be detected with RNA-Seq or a break-apart FISH probe set.[46]**
- **Diagnostic value: Detection of RELA fusion is not required for the diagnosis of ependymoma, as this entity is still diagnosed by light microscopy.**
- **Prognostic value: RELA fusion-positive ependymomas are now a distinct entity in the WHO classification of CNS tumors, as this subset of ependymomas tends to be far more aggressive than other supratentorial ependymomas.[1,44,45,47]**

Medulloblastoma Molecular Subtyping

- **Recommendation: Medulloblastoma testing should be referred to academic tertiary centers with expertise in this area.**
- **Description: Medulloblastomas are WHO grade IV tumors that predominantly arise from the cerebellum in pediatric patients, but can also occur in adults. The WHO committee on CNS tumors now recommends subclassification of these tumors into four distinct groups: i) WNT-activated; ii) SHH-activated and TP53-mutant; iii) SHH-activated and TP53-wildtype; and iv) non-WNT/non-SHH.[1,48]**
- **Detection: Virtually all WNT-driven medulloblastomas will contain mutations in either CTNNB1 or, less commonly, APC (the latter mutation may be germline if the patient has Turcot syndrome). WNT-driven tumors will also usually contain monosomy 6. Nuclear immunoreactivity for beta-catenin is a very useful way to identify WNT medulloblastomas, in conjunction with CTNNB1 sequencing and chromosome 6 FISH. Differentiating between WNT-activated, SHH-activated, and non-WNT/non-SHH tumors is best classified by expression arrays, DNA methylation arrays, or an immunohistochemistry panel composed of beta-catenin, GAB1, and YAP1. Because there are a variety of hotspots in TP53, gene sequencing is recommended in SHH-activated medulloblastomas.[49-52]**
- **Diagnostic value: None of the molecular markers associated with each medulloblastoma subtype is specific to medulloblastomas; the diagnosis of medulloblastoma is still made on the basis of light microscopy.**
- **Prognostic value: The most important aspect of medulloblastoma molecular diagnostics is that the WNT-activated subset has a markedly better prognosis relative to the other three subtypes, regardless of age at diagnosis. Among SHH-activated medulloblastomas, detection of TP53 mutations is associated with more aggressive behavior, whereas TP53-wildtype SHH-activated medulloblastomas have a variable course. Non-WNT/non-SHH medulloblastomas also show a variable course.[1,48,53]**

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Continued

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PRINCIPLES OF BRAIN TUMOR PATHOLOGY
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Discussion

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 indicated.

NCCN Categories of Preference

Preferred intervention: Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.

Other recommended intervention: Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.

Useful in certain circumstances: Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

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Overview

In the year 2019, an estimated 23,820 people in the United States will be diagnosed with a malignant primary central nervous system (CNS) tumor, and these tumors will be responsible for approximately 17,760 deaths.[1] The incidence of primary brain tumors has been increasing over recent decades,[2] especially in older adults.[3,4] However, this growth in incidence rates may be explained by increased use of CT and MRI and changes in WHO classification of CNS tumors.[2,5,6]

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Central Nervous System Cancers, an electronic search of the PubMed database was performed to obtain key literature in the field of neuro-oncology, using the following search terms: {[(brain OR spine OR spinal OR supratentorial OR cranial OR intracranial OR leptomeningeal) AND (cancer OR carcinoma OR tumor OR metastases OR lesion)] OR glioma OR astrocytoma OR oligodendroglioma OR glioblastoma OR ependymoma OR medulloblastoma OR (primary central nervous system lymphoma) OR meningioma}. The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[7]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Practice Guideline; Guidelines; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The data from key PubMed articles and articles from additional sources deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN website (www.NCCN.org).

Tumor Types

The NCCN Guidelines for CNS Cancers focus on management of the following adult CNS cancers: pilocytic and infiltrative supratentorial astrocytomas, oligodendrogliomas, anaplastic gliomas and glioblastoma, ependymomas, medulloblastoma, brain metastases, leptomeningeal metastases, non–AIDS-related primary CNS lymphomas (PCNSLs), metastatic spinal tumors, meningiomas, and primary spinal cord tumors. These guidelines are updated annually to include new information or treatment philosophies as they become available. However, because this field continually evolves, practitioners should use all of the available information to determine the best clinical options for their patients.

Principles of Management

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 dozens of 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

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basis and sensitively communicated to each patient. In addition, these CNS tumors are associated with a range of symptoms such as seizures, fatigue, psychiatric disorders, impaired mobility, neuro-cognitive dysfunction, difficulty speaking, and short-term memory problems, as well as complications such as intracerebral edema, endocrinopathies, and venous thromboembolism that can seriously impact patients' quality of life.

The involvement of an interdisciplinary team, including neurosurgeons, RT therapists, oncologists, neurologists, and neuroradiologists, is a key factor in the appropriate management of these patients. For any subtype of malignant brain tumors, the NCCN Panel strongly recommends brain tumor board or multidisciplinary review of each patient's case once the pathology is available. Further discussion of multidisciplinary care and allied services, as well as guidelines on medical management of various disease complications, can be found in the section, *Principles of Brain and Spine Tumor Management*.

Treatment Principles

Several important principles guide surgical management and treatment with RT and systemic therapy for adults with brain tumors. Regardless of tumor histology, neurosurgeons generally provide the best outcome for their patients if they remove as much tumor as safely possible (ideally achieving a gross total resection [GTR]) and thereby providing sufficient representative tumor tissue to ensure an accurate diagnosis. Decisions regarding aggressiveness of surgery for primary brain tumors are complex and depend on the: 1) age and performance status (PS) of the patient; 2) proximity to "eloquent" areas of the brain; 3) feasibility of decreasing the mass effect with aggressive surgery; 4) resectability of the tumor (including the number and location of lesions); and 5) time since last surgery in patients with recurrent disease.[8] Further discussion can be found in the *Principles of Brain Tumor Surgery.* It is recommended to consult neurosurgeons with extensive experience in the management of intracranial and spine neoplasms.

The surgical options include stereotactic biopsy, open biopsy, subtotal resection (STR), or GTR. The pathologic diagnosis is critical and may be difficult to accurately determine without sufficient tumor tissue. Review of the tumor tissue by an experienced neuropathologist is highly recommended. *Principles of Brain Tumor Pathology* describes guiding principles for diagnosis of CNS tumor pathology, given the relatively recent addition of molecular parameters to the WHO classification of CNS tumors.[9]

Radiation oncologists use several different treatment modalities in patients with primary brain tumors, including fractionated stereotactic RT, and stereotactic radiosurgery (SRS). Standard fractionated external beam RT (EBRT) is the most common approach. Hypofractionated radiation is an appropriate option for select patients (ie, older adults and patients with a poor PS). RT for patients with primary brain tumors is administered within a limited field (covering tumor or surgical cavity and a small margin of adjacent brain tissue), while whole-brain RT (WBRT) and SRS are used primarily for treatment of brain metastases. The dose of RT administered varies depending on the pathology as seen in *Principles of Brain and Spinal Cord Tumor Radiation Therapy*.

The information contained in the algorithms and principles of management sections are designed to help clinicians to navigate through the complex management of patients with CNS tumors. Standard systemic therapy options for each tumor subtype are listed in the *Principles of Brain and Spinal Cord Tumor Systemic Therapy*; however, enrollment in a clinical trial is the preferred treatment for eligible patients.

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Gliomas

The NCCN Guidelines for CNS Cancers include recommendations for management of the following gliomas:[9]

- Grade I: pilocytic astrocytoma, pleomorphic xanthoastrocytoma, ganglioglioma, subependymal giant cell astrocytoma
- Grade II: diffuse astrocytomas and oligodendrogliomas
- 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 information that improves diagnostic accuracy and aids in treatment selection.

Updated Classification of Gliomas Based on Histology and Molecular Features

Key changes to the WHO classification system for version 2016 for grade II–III gliomas are as follows: 1) oligodendrogliomas are 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 are further subdivided according to *IDH* mutation status; and 3) oligoastrocytoma is no longer a valid designation unless molecular data (1p19q deletion and *IDH* mutation status) are not available and cannot be obtained, or in very rare cases of concurrent, spatially distinct oligodendroglioma (1p19q codeleted) and astrocytoma (1p19q intact) components in the same tumor.[9] Such tumors should be described as "oligoastrocytoma, not otherwise specified (NOS)" to indicate that the characterization of the tumor is incomplete. 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.[10-13] Thus, the change from 2007 WHO to 2016 WHO reclassifies a significant proportion of gliomas.

Multiple independent studies on glioma tissue removed from the brain 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.[12,14-17] Unsupervised clustering analyses, an unbiased method for identifying molecularly similar tumors, have been used to identify subgroups of gliomas with distinct molecular profiles.[12,14,15,17] 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.[10-13,15,16,18-27] Using these markers alone, the majority of grade II–III tumors can be divided into 3 molecular subtypes: 1) mutation of either *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).[12] 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 rare.[10,11,23,25,28,29] In a tumor that is equivocal, the presence of an *IDH* mutation indicates at least a grade II diffusely infiltrative glioma.[30] Grade I non-infiltrative gliomas do not have *IDH* mutations.[30]

Beginning with the 2017 version of the NCCN Guidelines, "anaplastic oligodendroglioma" was limited to patients with 1p19q-codeleted tumors, and "anaplastic astrocytoma" to those lacking whole-arm codeletion of

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both 1p and 19q. "Anaplastic oligoastrocytoma" corresponds to the 2016 WHO category "anaplastic oligoastrocytoma, NOS" and should include only: 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; and 2) rare instances in which the tumor has region(s) with histologic features of oligoastrocytoma with 1p19q codeletion, and distinct region(s) with histologic features of anaplastic astrocytoma and no 1p19q codeletion.[9]

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.[31,32] *ATRX* mutation is robustly associated with *IDH* mutations, and this combination is strongly suggestive of astrocytoma.[33] 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 transcriptase* (*TERT*) gene occur frequently in glioblastomas and oligodendrogliomas.[34,35] *TERT* promoter mutations in gliomas are associated with 1p19q codeletion and *IDH* mutations in oligodendrogliomas. Interestingly, they are also highly characteristic of *IDH*-wt, *ATRX* wild-type glioblastomas, especially those that contain amplification of epidermal growth factor receptor (EGFR).[34,35] *H3K27M* mutations in the histone-encoding *H3F3A* gene are mostly found in diffuse midline gliomas in both children and adults.[36] 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.[36]

Analyses of large databases have also suggested a number of other molecular markers as being potential characteristic/prognostic features of specific subgroups.[11,13,15,16,23,28,33] Molecular features suggested as markers for subtyping grade II–III gliomas include: mutations in *NOTCH1*, *CIC*, *FUBP1*; mutation in or overexpression of *TP53*; *PTEN* loss or promoter methylation; loss/deletion of *CDKN2A/B*; amplification of EGFR; and chromosome 7 gain, chromosome 10 loss.[10,12-14,16,24] However, due to variability in results across studies, many of these molecular markers are not yet widely used to subclassify gliomas.

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).[11,15,19,21,25,37-40] Likewise, the presence of an *IDH* mutation is a strong favorable prognostic marker for OS in grade II–III gliomas,[10-16,21,23,25,28,37-43] although a few analyses did not find a significant correlation with PFS.[11,21] 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 (TTF), 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).[38]

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,[12,14,15,37] as well as smaller studies limited to 1—2 grades or histologic subtypes.[11,16,18,42,44] 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.[11-14,25,37-39] Analyses within single treatment arms have

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confirmed this trend in prognosis across a variety of postoperative adjuvant treatment options.[11,38,39,44] *TERT* mutations in patients with high-grade *IDH*-wt glioma are associated with shorter OS, compared to *IDH*-wt tumors without a *TERT* mutation.[13,35,45] 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 to patients with *TERT*-mut oligodendrogliomas (HR, 2.72; 95% CI, 1.05–7.04; *P* = .04).[46]

MGMT (O-6-methylguanine-DNA methyltransferase) is a DNA repair enzyme that can cause resistance to DNA-alkylating drugs.[47] *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,[48-51] even in older adult patients.[52,53] Tumors with *H3K27M* mutations are far less likely to be *MGMT* promoter methylated[36] and are associated with worse prognosis.[54,55] 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.[55,56]

Most pilocytic astrocytomas in pediatric patients contain *BRAF* fusions, especially those arising in the posterior fossa; such tumors are rarely high grade.[57] *BRAF* fusion is associated with better prognosis in pediatric low-grade astrocytoma.[57-59] The likelihood of a *BRAF* fusion in a pilocytic astrocytoma decreases with age.[57] 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,[57,60] as well as a small proportion of glioblastomas.[61] Retrospective studies have shown that *BRAF* V600E may be associated with increased risk of progression in pediatric low-grade gliomas,[62] but one study found that this association was not quite statistically significant (*N* = 198; *P* = .07).[59] Some have shown that tumors with a *BRAF* V600E mutation may respond to BRAF inhibitors such as vemurafenib,[63-65] but ongoing trials will further clarify targeted treatment options in the presence of a *BRAF* fusion or 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. Based on studies showing that *IDH* status is associated with better prognosis in patients with grade II–III glioma,[28,37,38,41] the panel recommends *IDH* mutation testing in patients with glioma. Patients with oligodendroglioma should also undergo 1p19q testing. However, since 1p19q codeletion is strongly associated with *IDH* mutation,[25,28,29] 1p19q testing is not necessary in tumors that are *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.[31,33-35] 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, since *MGMT* promoter-methylated tumors may respond better to alkylating chemotherapy, compared to unmethylated tumors.[48,52,53] To date, there are no targeted agents that have shown efficacy in the treatment of glioblastoma. Nevertheless, molecular testing of glioblastoma tumors 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 prognostic stratification. Detection of a mutation could also expand clinical trial options.

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Low-Grade Pilocytic and Infiltrative Astrocytomas and Oligodendrogliomas

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.[9] Seizure is a common symptom (81%) of low-grade gliomas, and is more frequently associated with oligodendrogliomas.[66] The median duration from onset of symptoms to diagnosis ranges from 6 to 17 months. Factors prognostic for PFS or OS in patients with grade II gliomas include age, tumor diameter, tumor crossing midline, neurologic or PS prior to surgery, and the presence of certain molecular markers (see section above on *Molecular Profiling for Gliomas)*.[11,21,67-74]

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 5 years in approximately half of patients.[75,76] The most common non-infiltrative astrocytomas are pilocytic astrocytomas. Other grade I gliomas in which treatment recommendations are included in the NCCN Guidelines for Central Nervous System 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,[77,78] though mitotic index is associated with survival outcomes.[78,79] Gangliogliomas are commonly located in the temporal lobe, and the most significant predictors of survival are low tumor grade and younger age.[80]

SEGAs are typically located at the caudothalamic groove adjacent to the foramen of Monro. Though they are generally slow-growing and benign, they can also be associated with symptoms such as hydrocephalus, intracranial pressure, and seizures.[81] SEGAs can be distinguished from subependymal nodules by their characteristic serial growth.[82] These tumors occur in 5% to 20% of individuals with tuberous sclerosis complex (TSC).[83-86]

Oligodendrogliomas are thought to arise from oligodendrocytes. Radiographically, low-grade oligodendrogliomas appear well demarcated, occasionally contain calcifications, and do not enhance with contrast. The typical “fried egg” appearance of these tumors is evident in paraffin but not in frozen sections. Grade II oligodendrogliomas have a much better 5-year survival rate (70%) than mixed gliomas (56%) and astrocytomas (37%).[87]

Treatment Overview

Surgery

Surgery remains an important diagnostic and therapeutic modality. The primary surgical goals are maximal safe resection of tumor and to provide 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 a lower histologic grade.

Though grade I gliomas are usually curable by surgery alone, the role of maximal tumor resection in low-grade astrocytomas remains unresolved. 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. Multivariate analyses from a number of studies in patients with primary low-grade gliomas show that extent of resection is a significant prognostic

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factor for PFS and/or OS.[69-74,88-92] Maximal safe resection may also delay or prevent malignant progression[93-95] and recurrence.[96] Patients who undergo an STR, open biopsy, or stereotactic biopsy are, therefore, considered to be at higher risk for progression.

Biological 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 reflected in a small specimen. Second, complete excision may decrease the risk of future dedifferentiation to a more malignant tumor.[93] Third, a large tumor burden is removed, which also may enhance the effect 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. Low-grade oligodendrogliomas are often amenable to total excision due to their location in the frontal lobes and distinct tumor margins. However, for tumors that involve eloquent areas, a total removal may not be feasible and an aggressive approach could result in neurologic deficits. There are also data suggesting that resection of all fluid-attenuated inversion recovery (FLAIR) signal abnormality in *IDH*-mut gliomas is associated with improved survival.[97]

Indication for treatment of SEGAs is based on development of new symptoms or radiologic evidence of tumor growth.[82] Though surgery is a recommended option for SEGAs, recurrence following resection can occur, or tumors may be located in an area not amenable to surgical resection.[98] Postoperative complications are also common.[99] Reducing or stabilizing the volume of these tumors 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 to 39 patients who received a placebo (35% vs. 0%; $P < .001$), and 6-month PFS was 100% versus 86%, respectively ($P < .001$).[100] 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.[101] 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%.[102]

Adjuvant Therapy

A large meta-analysis, including data from phase 3 trials (EORTC 22844 and 22845,[69,103] and NCCTG 86-72-51[71]), confirmed that surgery followed by RT significantly improves PFS but not OS in patients with low-grade gliomas.[104] 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.[103]

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)[105] showed significant improvements in both PFS and OS with the addition of PCV. [106] 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.[105] Exploratory analyses based on histologic subgroups showed a statistically significant improvement in OS for all subgroups except for patients with astrocytoma.[106] Given that the study participants treated with PCV after RT experienced a significantly higher incidence of grade 3 or 4 adverse

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events (specifically neutropenia, gastrointestinal disorder, and fatigue),[105,106] PCV may be difficult to tolerate in patients who are older or with poor PS.

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, bi-hemispherical, tumor diameter ≥6 cm, neurologic function status >1).[107] 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).[22] 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). 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,[69,71] and on several retrospective analyses showing similar results.[70,72,108] Because higher doses offer no clear advantages, the CNS Panel recommends low-dose RT (45–54 Gy) for treatment of low-grade gliomas (grades I/II), including high-risk cases. However, whole genome sequencing analysis of 1122 diffuse grade II–IV gliomas showed that low-grade gliomas that are *IDH*-wt have similar survival outcomes compared to glioblastomas that are *IDH*-wt.[109] Therefore, an RT dose of 59.4 to 60 Gy may be considered for this subset of patients with low-grade glioma.

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.[110-114] There are very little data to inform treatment of patients with recurrent or progressive low-grade glioma who have not had prior RT treatment, as most of the studies of recurrent or progressive low-grade gliomas include those who have had prior RT. Results of the RTOG 9802 trial[105,106] support use of RT with chemotherapy for these patients. Data from phase II trials inform recommendations for chemotherapy treatment of patients with recurrent or progressive low-grade glioma.[115-120]

NCCN Recommendations

Primary and Adjuvant Treatment

When possible, maximal safe resection is recommended for low-grade gliomas,[121,122] and the actual extent of resection should be documented with a T2-weighted or FLAIR MRI scan within 48 hours after surgery. Treatment with an mTOR inhibitor (eg, everolimus) should be considered for patients with SEGA,[100,101] though institutional expertise and patient preference should guide treatment decision-making for these rare tumors.[82]

For treatment recommendations for newly diagnosed grade II gliomas, the panel used the RTOG 9802[105,106] criteria for determining if a patient is

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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,[122] such as tumor size, presence of neurologic deficits, or the *IDH* mutation status of the tumor.[22,67] In the event that these other risk factors are considered, and treatment of a patient is warranted, the panel recommends that the patient be treated as high risk.

Patients with low-risk and low-grade glioma, particularly grade I gliomas (ie, pilocytic astrocytoma, pleomorphic xanthoastrocytoma, ganglioglioma), may be observed following surgery. For patients with grade II infiltrative or supratentorial astrocytoma or oligodendroglioma, close follow-up is essential as over half of these patients will develop tumor progression within 5 years.[74] If patients with a grade I glioma (ie, pilocytic astrocytoma, pleomorphic xanthoastrocytoma, ganglioglioma) had an 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.

Following surgery, RT followed by PCV is a category 1 recommendation for patients with low-grade glioma who are considered to be at high risk for tumor progression, based on the practice-changing results from the RTOG 9802 study,[105,106] 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 non-codeleted anaplastic gliomas.[123] Data from EORTC and NCIC studies, which included patients with glioblastoma, support RT with concurrent and adjuvant TMZ as an evidence-based regimen.[124,125] Therefore, this is a category 2A option, while RT followed by adjuvant TMZ is a category 2B option, based on panel consensus. 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[105,106] 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 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.

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 undergo transformation to higher-grade gliomas over time. Therefore, documenting histopathologically the 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

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chemotherapy; and 3) palliative/best supportive care. Reirradiation is a good choice if the patient had been progression-free for more than 2 years after prior RT, the new lesion is outside the target of previous RT, or 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,[105,106] 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 (TMZ, PCV, carmustine/lomustine, or a platinum-based regimen) is also a treatment option for these patients, though this is a category 2B option based on less panel consensus.

Anaplastic Gliomas and Glioblastomas

High-grade gliomas are the most common type of brain cancer, accounting for more than half of all malignant primary tumors of the CNS.[126] 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.[126]

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. These tumors usually do not have associated hemorrhage or calcification but produce considerable edema and mass effect, and they enhance after the administration of intravenous contrast. Tumor cells have been found in the peritumoral edema, which corresponds to the T2-weighted MRI abnormalities. As a result, this volume is frequently used to define RT portals.

It can be difficult to assess the results of therapy by MRI scans, because the extent and distribution of contrast enhancement, edema, and mass effect are a function of blood-brain barrier (BBB) integrity. Thus, other 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.

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 to incomplete resection and biopsy.[127] Unfortunately, the infiltrative nature of high-grade astrocytomas frequently renders GTR difficult. On the other hand, GTR is often possible for oligodendrogliomas, because most occur in the frontal lobes, and the tumors are frequently well demarcated.

Unfortunately, nearly all high-grade gliomas recur. At recurrence, reoperation may improve the outcome for select patients.[128] According to an analysis by Park et al,[129] tumor involvement in specific critical brain areas, poor KPS score, and large tumor volume were associated with unfavorable re-resection outcomes.

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Radiation Therapy

Conformal RT (CRT) techniques including 3-dimensional CRT (3D-CRT) and IMRT for performing focal brain irradiation are recommended. 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.[130,131] 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.[132] 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.[132]

Anaplastic oligodendrogliomas are conventionally treated to a similar dose. Given the improved prognosis in these patients, 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 recent trials such as RTOG 9813,[41] 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. The CTV is an expansion on the GTV (consisting of the addition of a 1- to 2-cm margin for grade III gliomas and a 2- to 2.5-cm margin for grade IV gliomas, although smaller CTV expansions for glioblastoma are supported in the literature and can be appropriate) to account for subclinical disease. The CTV is then expanded to a PTV to account for setup error. 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 boost target volume will typically encompass only the gross residual tumor and the resection cavity. There is a range of acceptable CTV margins. Both strategies appear to produce similar outcomes.[132]

Special attention has been given to determine the optimal therapy in older adults, given their especially poor prognosis and limited functional status. Overall, the approach in these patients has been to reduce treatment time while attempting to maintain treatment efficacy. Roa et al randomized patients 60 years or older with a poor PS (KPS < 70) to 60 Gy given over 6 weeks versus 40 Gy given over 3 weeks and found no difference in survival between these two regimens.[133] However, fewer patients who received 40 Gy over 3 weeks required a posttreatment increase in corticosteroid dose, compared to the patients who received 60 Gy over 6 weeks (23% vs. 49%, respectively; $P = .02$). Subsequent studies in older adult patients have confirmed dose-fractionation regimens of 40 Gy in 15 fractions and 34 Gy in 10 fractions, all showing non-inferiority compared to the standard 60 Gy regimen.[52] Interestingly, more recent data from Roa et al suggest that an even more hypofractionated regimen of 25 Gy in 5 fractions may be no less inferior to the previously mentioned hypofractionated regimen (40 Gy in 15 fractions) in a particularly poor prognosis subgroup of patients.[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.[135] The largest benefit was noted in patients with MGMT promoter methylation (see discussion of *Systemic Therapy* for *Glioblastoma*, below). 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

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patients has not been performed in patients 65 years and older. Therefore, standard radiation (60 Gy given over 6 weeks) with concurrent and adjuvant temozolomide (with or without alternating electric field therapy; see discussion of this treatment option below) 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

Anaplastic oligodendrogliomas are relatively rare; they are characterized by high cellularity, nuclear pleomorphism, frequent mitosis, endothelial proliferation, and necrosis, and have a distinct molecular signature. While these tumors can be confused with glioblastoma histopathologically, if molecular analysis detects that the tumor is 1p19q codeleted and *IDH1*-mut or *IDH2*-mut, then the tumor is an anaplastic oligodendroglioma.[9] This distinct subtype has a much better prognosis compared to other high-grade gliomas (anaplastic astrocytomas and glioblastomas). In the revised 2016 WHO Classification of Tumors of the CNS,[9] oligoastrocytoma is no longer a valid diagnosis; however, “oligoastrocytoma, NOS” may continue to be used if a tumor has features of mixed histology and molecular testing is not possible or in the rare instance that the tumor has distinct histologic regions of oligodendroglioma that are 1p19q codeleted and astrocytoma that are not 1p19q codeleted.[9]

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[39,138,139]). 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).[28,136,137]

RTOG 9402 randomized 291 patients with histopathologically diagnosed anaplastic oligodendroglioma or anaplastic oligoastrocytoma to PCV followed by immediate 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 in the intense PCV arm followed by RT.[138,139]

The phase III CODEL study was designed to assess the efficacy of TMZ for the treatment of newly diagnosed anaplastic oligodendrogliomas. The

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initial treatment arms were RT alone, RT + TMZ, and TMZ alone.[140] However, 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 results in similar outcomes as RT with concurrent nitrosourea 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).[41] The toxicity of nitrosourea was far 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 anaplastic astrocytoma. A recently published 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).[123] 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 *IDH*-mut anaplastic astrocytomas benefit from treatment with adjuvant TMZ (HR, 0.41; 95% CI, 0.27–0.64), but not anaplastic astrocytomas that are *IDH*-wt (HR, 1.05; 95% CI, 0.73–1.52).[141] There was also no benefit to administering concurrent TMZ in patients with *IDH*-mut anaplastic astrocytomas (HR, 0.71; 95% CI, 0.35–1.42; P = .32). However, these analyses are currently available in abstract form only. Further follow-up and molecular analyses are ongoing.

Glioblastoma

TMZ is recommended in conjunction with postoperative RT for patients with glioblastoma and good PS. Stupp et al[125] conducted the phase III, randomized EORTC-NCIC study that assessed the drug in 573 patients with glioblastoma with age ≤70 years with a WHO PS of 2 or less. 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 post-irradiation on a 5-day schedule every 28 days. Alternate schedules such as a 21/28 dose-dense regimen or a 50 mg/m^2 continuous daily schedule 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 post-radiation dose-dense TMZ, compared to the standard post-radiation TMZ dose.[143] A pooled analysis of individual patient data from 4 randomized trials[125,143-145] of patients with newly diagnosed glioblastoma determined that treating with post-radiation TMZ beyond 6 cycles does not improve OS, even for patients whose tumors are MGMT promoter methylated.[146]

Building on the findings that hypofractionated RT alone has similar efficacy and is better tolerated compared to 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

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RT with concurrent and adjuvant TMZ to hypofractionated radiation alone. Patients in the combination therapy arm had greater 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 to patients treated with hypofractionated RT alone.[124] 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.[52,53] The Nordic trial randomized 291 patients aged 60 years and older with good PS across 3 treatment groups: TMZ, hypofractionated RT, or standard RT.[52] Patients older than 70 years had better survival with TMZ or hypofractionated RT compared to standard RT, and patients whose tumors were MGMT promoter-methylated benefitted more from treatment with TMZ compared to 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 to standard RT in 373 patients aged 65 years and older.[53] TMZ was found to be non-inferior 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* (non-inferiority) = .033). For patients whose tumors were MGMT promoter methylated, event-free survival was longer with TMZ treatment compared to standard RT (8.4 months vs. 4.6 months). 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.[52,53]

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 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 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.[147] 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.[148] 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.[149] There was no increased frequency of seizures.[150,151] Based on the results of this study, concurrent treatment with adjuvant temozolomide 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 temozolomide.

Therapy for Recurrence

Patients with malignant gliomas eventually develop tumor recurrence or progression. Surgical resection of locally recurrent disease is reasonable

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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 temozolomide and development of tumor progression, it is reasonable to restart a patient on temozolomide,[152] particularly if the patient's tumor is MGMT methylated. Similarly, a nitrosourea, such as carmustine or lomustine,[153-156] 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.[157,158] 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 anti-tumor effect.[159,160]

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).[161] However, 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.[162] 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 non-inferiority 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, re-irradiation may be reasonable to consider for some recurrent glioblastoma patients, but the panel is also divided about this option.

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. One exception is when CNS lymphoma is suspected; a biopsy should be performed first 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.

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 1p19q codeleted anaplastic oligodendroglioma, RT plus PCV, given before or after RT, is preferred, based on the results of the RTOG 9402[39,139] 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.

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Fractionated RT, with or without concurrent TMZ, followed by adjuvant TMZ is also a reasonable option,[163] particularly if it is predicted that the patient might have significant difficulty tolerating PCV due to age or coexisting medical conditions.

In the case of patients with anaplastic astrocytoma and anaplastic oligoastrocytoma (NOS) and good PS, RT, with or without concurrent TMZ, followed by adjuvant TMZ is preferred based on the interim analysis results of the CATNON trial showing improvement in survival with RT followed by 12 cycles of TMZ compared to RT alone.[123] However, for newly diagnosed anaplastic oligoastrocytoma patients, RT with PCV administered before or afterwards is also an acceptable treatment option.[164,165]

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.

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.[48,52,135,166] Category 1 recommendations for patients aged 70 years and younger with a good PS, regardless of the tumor's MGMT methylation status, include fractionated standard brain RT plus concurrent and adjuvant TMZ with or without alternating electric field therapy. Since patients with newly diagnosed glioblastoma whose MGMT promoter-unmethylated tumors are likely to experience less clinical benefit from treatment with 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[124] 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[124] is preferred, but standard brain RT plus concurrent and adjuvant TMZ and alternating electric field therapy is also a reasonable option (category 1 option)[147,148] 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 2–6 weeks post-irradiation, then every 2–4 months for 3 years, then every 3–6 months indefinitely) after the completion of treatment for newly diagnosed disease. Because RT can produce additional BBB dysfunction, scans may appear worse during the first 3 months after completion of RT even though there may be no actual tumor progression. 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.

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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 RT-induced necrosis (also called "pseudoprogression") versus actual disease progression.[167,168]

Management of recurrent tumors depends on the extent of disease and patient condition. 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 re-treatment with TMZ (if there has been a long interval between completion of adjuvant temozolomide and development of recurrent disease),[116,152,169-172] carmustine/lomustine[153-156,173], bevacizumab,[157,174-179] and PCV.[117,180,181] A patient with a poor PS should receive palliative/best supportive care.

Intracranial and Spinal Ependymomas

Ependymomas constitute up to 4% of adult CNS tumors and 10% of pediatric CNS tumors.[182] In adults, ependymomas occur more often in the spinal canal than in the intracranial compartment (supratentorial and posterior fossa). These tumors can cause hydrocephalus and increased intracranial pressure, mimic brainstem lesions, cause multiple cranial nerve palsies, produce localizing cerebellar deficits, and cause neck stiffness and head tilt if they infiltrate the upper portion of the cervical cord.[183,184]

RELA activating fusions occur in about 19% of patients with ependymomas.[185] They occur only in supratentorial ependymomas and not in those in the posterior fossa or spinal canal; they are also more likely to occur in children than in adults.[185] Ependymomas with RELA activating fusions are more likely to be advanced and aggressive than RELA fusion-negative ependymomas, with a greater likelihood of being grade II or III, and with shorter PFS and OS.[185,186] In the revised 2016 WHO classification system, RELA fusion-positive ependymoma is now designated as a subtype,[9] raising the potential for RELA fusion testing of ependymomas based on the clinical context.

This section focuses on adult ependymal tumors including spinal and intracranial grade I (termed subependymomas or myxopapillary ependymomas), grade II differentiated (termed ependymomas), and grade III (termed anaplastic ependymomas) tumors. Grade I subependymomas are non-infiltrative and can often be cured by resection alone.

Treatment Overview

Surgery

There is a paucity of robust studies addressing the role of surgery in this uncommon disease, but multiple case series have reported that patients with totally resected tumors tend to have the best survival for both low- and high-grade ependymomas.[187-191] In a retrospective analysis by Rodriguez et al,[192] patients who underwent surgery had a better outcome than those who did not (HR, 1.99; $P < .001$). Supratentorial ependymomas generally have a poorer prognosis than their infratentorial counterparts, because a greater proportion of supratentorial lesions are of high grade.

Radiation Therapy

The survival benefits of RT following surgery have been established for anaplastic ependymomas and suboptimally resected tumors, although much of the data are derived from pediatric patients. Rodriguez et al[192] reviewed over 2400 cases of ependymomas in the SEER database and reported that patients with partially resected tumors who do not receive RT have a poorer prognosis than those who are treated with RT (HR, 1.75; $P = .024$). The short-term and 10-year survival rate after RT reached over 70% and 50%, respectively.[193-195] The value of RT is more controversial for

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differentiated ependymomas,[188,196] with data demonstrating improved survival mainly for subtotally resected tumors.[189,192] Emerging data show poor survival rates in patients with supratentorial non-anaplastic ependymoma who do not receive RT following GTR.[197] Further, much of the data supporting observation following surgical resection are based on retrospective studies.[198-200] Given the availability of highly CRT modalities and the relatively lower level of concerns for late effects of RT in adults (vs. children), RT is recommended as the standard adjuvant treatment approach in these patients until high-quality evidence supporting observation alone becomes available.

In the past, the standard practice was to irradiate the entire craniospinal axis or administer WBRT. However, studies have demonstrated that: 1) local recurrence is the primary pattern of failure; 2) spinal seeding is uncommon in the absence of local failure; 3) the patterns of failure are similar in patients with high-grade tumors who are treated with local fields or craniospinal axis irradiation; and 4) spinal metastases may not be prevented by prophylactic treatment.[201-203] Prophylactic craniospinal RT or WBRT does not lead to improvement in survival compared to conformal regional RT with higher doses in modern studies of non-disseminated disease.[190,196,204]

Typical craniospinal irradiation scheme includes 36 Gy in 1.8 Gy fractions to the whole brain and spine, followed by limited-field irradiation to spine lesions to 45 Gy. For intracranial ependymomas, the primary brain site should receive a total of 54 to 59.4 Gy in 1.8 to 2.0 Gy fractions. PTV of margin of 3 to 5mm is typically added to the CTV. Tolerance of the cauda equina is in the range of 54 to 60 Gy.[205,206] Therefore, a boost to gross intracranial metastatic sites (respecting normal tissue tolerances) may be considered.

For spinal ependymomas, patients could receive local RT to 45 to 54 Gy in 1.8 Gy fractions, with higher doses up to 60 Gy being reasonable for spinal tumors below the conus medullaris. These dosing recommendations are consistent with those for primary spinal cord tumors. However, it is important to note that retrospective analyses have shown that adjuvant RT does not improve disease outcomes in patients with these tumors.[207,208]

Proton beam craniospinal irradiation may be considered when clinically appropriate and when toxicity is a concern. SRS has been used as a boost after EBRT or to treat recurrence with some success, although data on long-term results are still lacking.[209-211]

Systemic Therapy

Studies regarding the role of chemotherapy have largely been in the setting of pediatric ependymomas; the role of chemotherapy in the treatment of ependymomas in adult patients remains poorly defined. No study has demonstrated a survival advantage with the addition of chemotherapy to RT in newly diagnosed tumors. However, chemotherapy is sometimes considered as an alternative to palliative/best supportive care or RT in the recurrence setting. Possible options include platinum-based regimens (cisplatin or carboplatin),[212,213] etoposide,[214,215] lomustine or carmustine,[213] bevacizumab,[216] and temozolomide.[217] The combination of lapatinib, a tyrosine kinase inhibitor (TKI), and dose-dense TMZ has been evaluated in a phase II trial in patients with recurrent grade I–III ependymoma, with preliminary results reported only in abstract form.[218]

NCCN Recommendations

Primary and Adjuvant Treatment

Whenever possible, maximal safe resection should be attempted with contrast-enhanced brain image verification within 48 hours after surgery. Spine MRI should be delayed by at least 2 to 3 weeks after surgery to avoid post-surgical artifacts. If maximal resection is not feasible at diagnosis, STR or biopsy (stereotactic or open) should be performed. Due

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to the established relationship between the extent of resection and outcome, multidisciplinary review and re-resection (if possible) should be considered if MRI shows that initial resection is incomplete. For spinal myxopapillary ependymomas, en bloc resection without capsule violation is recommended whenever feasible.

The adjuvant treatment algorithm depends on the extent of surgical resection, histology, and staging by craniospinal MRI and cerebrospinal fluid (CSF) cytology. For spinal ependymomas, brain MRI should be obtained to determine if these are drop metastases from a primary brain lesion. CSF dissemination develops in up to 15% of intracranial ependymomas. Lumbar puncture for CSF cytology should be done following spine MRI and should be delayed at least 2 weeks after surgery and to avoid a false-positive result. Lumbar puncture may be contraindicated in some cases (for example, if there is increased intracranial pressure and risk of herniation).

Limited-field fractionated EBRT is the appropriate postoperative management for patients with negative findings for tumor dissemination on MRI scans and CSF analysis. Patients with grade I spinal ependymomas that have been totally resected may not require adjuvant RT, as the recurrence rate tends to be low. For patients who have undergone maximum safe resection for low-grade intracranial ependymoma with no signs of dissemination on MRI and CSF analysis, adjuvant limited-field fractionated EBRT may be considered. Limited-field fractionated EBRT is also an adjuvant treatment option for patients with myxopapillary ependymoma who had an STR or if capsule violation occurred, even if CSF cytology is negative. Craniospinal RT is mandatory when MRI spine or CSF results reveal metastatic disease, regardless of histology and extent of resection.

Follow-up and Recurrence

Follow-up of ependymoma depends on tumor grade and the location and extent of the disease. For localized disease, contrast-enhanced brain and spine MRI (if initially positive) should be done 2 to 3 weeks postoperatively and then every 3 to 4 months for one year. The interval can then be extended to every 4 to 6 months in the years 2 through 4, every 6 to 12 months for years 5 through 10, then as clinically indicated depending on the physician's concern regarding the extent of disease, histology, and other relevant factors. If tumor recurrence in the brain or spine is noted on one of these scans, restaging by brain and spine MRI as well as CSF analysis is necessary. More frequent MRI scans may also be indicated for close follow-up in this setting. Resection is recommended if possible.

Upon disease progression or recurrence, treatment options depend on extent of disease, imaging and CSF findings, and prior treatment. For patients not previously irradiated, treatment with limited-field EBRT or consideration of SRS in appropriate cases for localized recurrence (negative MRI scan and CSF results), and craniospinal RT is recommended when there is evidence of neuraxis metastasis. For patients who have received prior RT treatment, clinical trials, chemotherapy, or palliative/best supportive care (in the setting of poor functional status) are the treatment options for those with evidence of metastasis based on imaging and CSF findings. Patients who have received prior RT, are in good functional status, and do not show evidence of neuraxis metastatic disease should be considered for enrollment in a clinical trial. Reirradiation and chemotherapy may also be considered for these patients, as clinically appropriate.

Adult Medulloblastoma

Though medulloblastoma is the most common brain tumor in children, it also can occur in adults,[219] though it makes up only 1% of CNS tumors in adults.[220] These tumors are often located in the cerebellar hemisphere[221]

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and can be broken into distinct molecular subtypes: WNT-activated, SHH-activated, and non-WNT/non-SHH (ie, Group 3 and Group 4).[9,219,222] Subtype analysis continues to evolve.[223] Tumors activated by SHH signaling are the most common in adult medulloblastoma.[219,224] Metastatic disease is less common in adult medulloblastoma than in children. It tends to occur in patients with non-WNT, non-SHH disease.[225] Tumors activated by WNT signaling are associated with good OS outcomes ($P < .001$), based on a sample of patients with medulloblastoma that included children, infants, and adults, though trends were not statistically significant in analysis including only adults ($n = 65$).[219] In patients with tumors activated by SHH signaling, prognosis is poor for those with tumors that are *TP53*-mut, compared to those with SHH-activated tumors that are not *TP53*-mut, even when controlling for histology, sex, presence of distantly metastatic disease, and age.[226] Therefore, the WHO further classifies SHH-mut medulloblastoma as *TP53*-mut and *TP53*-wt.[9]

Treatment Overview

Surgery

Evidence in adult patients is meager for this rare disease and there are no randomized trial data, but there is general consensus that surgical resection should be the routine initial treatment to establish diagnosis, relieve symptoms, and maximize local control. Complete resection can be achieved in half of the patients[227-229] and is associated with improved survival.[227,230] When viewed by molecular subtype, near-total resection (<1.5 cm residual) and GTR produced equivalent OS for SHH, WNT, and Group 3 patients.[231] In addition, surgical placement of a ventriculoperitoneal shunt can be used to treat hydrocephalus.

Radiation Therapy

Adjuvant RT following surgery is the current standard of care, although most studies are based on the pediatric population. The conventional dose is 30 to 36 Gy of craniospinal irradiation and a boost to a total of 54 to 55.8 Gy to the primary brain site.[227,230] Data from pediatric trials support use of a lower craniospinal dose of 23.4 Gy, combined with chemotherapy, while maintaining 54 to 55.8 Gy to the posterior fossa.[232-234] A randomized pediatric trial for standard-risk patients treated with radiation alone found an increased relapse risk with dose reduction.[235] A multicenter study including 70 adults with nonmetastatic medulloblastoma showed that reduced-dose craniospinal irradiation (23.4 or 35.2 Gy with a boost of 55.2 Gy to the fossa posterior) with maintenance chemotherapy is feasible.[236] It is reasonable to consider proton beam for craniospinal irradiation where available, as it is associated with less toxicity.[237] SRS demonstrated safety and efficacy in a small series of 12 adult patients with residual or recurrent disease.[238]

Systemic Therapy

The use of post-irradiation chemotherapy to allow RT dose reduction is becoming increasingly common especially for children,[232,233] but optimal use of adjuvant chemotherapy is still unclear for adult patients.[229,239-242] Neoadjuvant therapy has not shown a benefit in pediatric or adult patients.[243-245] It is used in infants to defer radiation. A phase III study that enrolled more than 400 patients between 3 and 21 years of age with average-risk disease to receive post-irradiation cisplatin-based chemotherapy regimens recorded an encouraging 86% 5-year survival.[234]

In the setting of recurrence, several regimens are in use in the recurrence setting, most of which include etoposide.[246-248] Temozolomide has also been used in this setting.[116,249] High-dose chemotherapy in combination with autologous stem cell transplantation is a feasible strategy for patients who have had good response with conventional-dose chemotherapy, although long-term control is rarely achieved.[248,250] SHH-pathway inhibitors that have been evaluated in phase II trials including adults with recurrent medulloblastoma include vismodegib[251] and sonidegib.[252] Patients in these

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trials with SHH-activated disease were more likely to respond than patients with non-SHH disease.[251,252]

NCCN Recommendations

Primary Treatment

MRI scan is the gold standard in the assessment of medulloblastoma. The typical tumor shows enhancement and heterogeneity. Diffusion-weighted abnormalities are also characteristic of medulloblastoma. Fourth ventricular floor infiltration is a common finding related to worse prognosis.[239,241,242] Multidisciplinary consultation before treatment initiation is advised. Maximal safe resection is recommended wherever possible. Contrast-enhanced brain MRI should be performed within 48 hours following surgery, but spinal MRI should be delayed by 2 to 3 weeks. Because of the propensity of medulloblastoma to CSF seeding, CSF sampling after spine imaging via lumbar puncture is also necessary for staging. Molecular profiling is recommended, as identification of clinically relevant medulloblastoma subtypes (eg, SHH-activated) may encourage opportunities for clinical trial enrollment. Medulloblastoma should be staged according to the modified Chang system using information from both imaging and surgery.[253,254]

Adjuvant Therapy

Patients should be stratified according to recurrence risk for planning of adjuvant therapy (reviewed by Brandes et al[255]). The NCCN Panel agrees that patients with large cell or anaplastic medulloblastoma, disease dissemination, unresectable tumors, or residual tumors greater than 1.5 cm^2 postsurgery are at heightened risk. These patients should undergo irradiation of the neuraxis and chemotherapy. Collection of stem cells before RT may be considered on the condition that RT is not delayed for potential future autologous stem cell reinfusion at disease progression. For patients at average risk, craniospinal RT with or without chemotherapy or reduced-dose craniospinal RT with chemotherapy followed by post-irradiation chemotherapy are viable options.

Recurrence and Progression

There are no robust data supporting an optimal follow-up schedule for medulloblastoma. General guidelines include brain MRI every 3 months for the first 2 years, every 6 to 12 months for 5 to 10 years, then as clinically indicated. If recurrent disease is detected on these scans, CSF sampling is also required, and concurrent spine imaging should also be performed. Bone scans, contrast-enhanced CT scans, and bone marrow biopsies may be considered as indicated.

Maximal safe resection should be attempted for recurrent medulloblastoma if symptomatic and there is no evidence of dissemination. Additional options include systemic therapy alone, RT alone (including SRS), and chemoradiation. High-dose chemotherapy with autologous stem cell rescue may be considered for patients showing no evidence of disease after conventional reinduction chemotherapy. Patients with metastases should be managed by systemic therapy, in very selected cases of intrathecal chemotherapy, or best supportive care, which can include palliative RT.

Primary CNS Lymphomas

PCNSL accounts for approximately 3% of all primary CNS tumors. It is an aggressive form of non-Hodgkin's lymphoma that develops within the brain, spinal cord, eye, or leptomeninges without evidence of systemic involvement. Its age-adjusted incidence has seen a three-fold increase over the past 20 years from 0.15 to 0.48 per 100,000, in part due to the impact of HIV infections.[256] Non-immunosuppressed patients have a better prognosis than AIDS-related cases,[257] and survival of this group has improved over the years with treatment advances.[258] For more guidance on treatment of patients with PCNSL who are living with HIV, see the

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NCCN Guidelines for Cancer in People Living with HIV (available at www.NCCN.org).

Pathologically, PCNSL is an angiocentric neoplasm composed of a dense monoclonal proliferation of lymphocytes, usually diffuse large B cells.[259] More than 90% of these primary CNS diffuse large B-cell lymphoma cases are of the activated B-cell–like (ABC) subtype.[260] The tumor is infiltrative and typically extends beyond the primary lesion, as shown by CT or MRI scans, into regions of the brain with an intact BBB.[260] The brain parenchyma is involved in more than 90% of all PCNSL patients, and the condition can be multifocal in more than 50% of cases. Leptomeningeal involvement may occur, either localized to adjacent parenchymal sites or in diffuse form (that is, positive cytology) in up to 30% of patients. Ocular involvement may develop independently in 10% to 20% of patients. Patients with PCNSL can present with various symptoms because of the multifocal nature of the disease. In a retrospective review of 248 immunocompetent patients, 43% had mental status changes, 33% showed signs of elevated intracranial pressure, 14% had seizures, and 4% suffered visual symptoms at diagnosis.[261]

PCNSL occurs in about 7% to 15% of patients with post-transplant lymphoproliferative disorders (PTLD)[262-265] and is associated with poor prognosis.[264,266,267] PTLDs are a heterogeneous group of lymphoid neoplasms associated with immunosuppression following solid organ transplantation (SOT) or allogeneic hematopoietic stem cell transplantation (HSCT).[268-270] For guidance on managing transplant recipients, see the Post-Transplant Lymphoproliferative Disorders sub-algorithm in the NCCN Guidelines for Diffuse Large B-Cell Lymphoma (available at www.NCCN.org).

Treatment Overview

Steroid Administration

Steroids can rapidly alleviate signs and symptoms of PCNSL and improve PS. However, as these drugs are cytolytic, they can significantly decrease enhancement and size of tumors on CT and MRI scans as well as affect the histologic appearance. In the absence of significant mass effect, it is recommended that steroids be withheld or used judiciously until diagnostic tissue can be obtained if PCNSL is suspected.

Stereotactic Biopsy

In contrast to the principles previously outlined for invasive astrocytomas and other gliomas, the surgical goals for PCNSL are more modest, with the goal of obtaining diagnostic tissue under minimal risk of morbidity. Currently, most authors recommend biopsy rather than resection.[271] This approach stems from the fact that data do not demonstrate a survival advantage for patients who have had a complete resection or extensive STR when compared with those who have had only a stereotactic biopsy. In addition, STR is associated with risk for postoperative neurologic deficits.[261]

Systemic Therapy

Methotrexate is the most effective agent against PCNSL. It is commonly used in combination with other drugs such as vincristine, procarbazine, cytarabine, rituximab, and temozolomide.[272-284] High doses of intravenous methotrexate are necessary (3.5 g/m^2 or higher) to overcome the BBB and achieve therapeutic levels in the CSF. Intrathecal methotrexate can be useful where CSF cytology yields positive findings. Other intrathecal chemotherapy options in this setting include cytarabine[284] and rituximab.[285] Phase II trials in the United States and Europe have shown that high-dose chemotherapy with autologous stem cell rescue following high-dose methotrexate-based chemotherapy is feasible and well-tolerated, with very little evidence of neurotoxicity.[281,286-293]

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Renal dysfunction induced by high-dose methotrexate therapy is a potentially lethal medical emergency due to heightened toxicities resulting from a delay in methotrexate excretion. Early intervention with glucarpidase, a recombinant bacterial enzyme that provides an alternative route for methotrexate clearance, has shown efficacy in rapidly reducing plasma concentrations of methotrexate and preventing severe toxicity.[294,295]

Because patients older than 60 years often suffer from significant and sometimes lethal neurotoxic effects from consolidation RT,[275,296,297] a number of phase II trials have adopted the approach of chemotherapy without planned RT.[272,275,298-302] Complete response to chemotherapy ranged from 42% to 61%, with OS ranging between 14 and 55 months. However, a high fraction of patients who have forgone initial RT—typically older or with significant comorbidities—may fail to achieve complete response to chemotherapy. Studies investigating the efficacy of methotrexate-based regimens as induction therapy for patients with PCNSL have utilized WBRT, including reduced WBRT following cytarabine as consolidation treatment.[274-276]

Cytarabine combined with etoposide as high-dose consolidation therapy following induction treatment with methotrexate, temozolomide, and rituximab was evaluated in the multicenter Alliance 50202 trial.[303] This protocol was feasible and generally well-tolerated, with one treatment-related death.

Unfortunately, even for patients who initially achieved complete response, half will eventually relapse. Re-treatment with high-dose methotrexate may produce a second response in patients who achieved complete response with prior exposure.[304] Rituximab may be used in combination with high-dose methotrexate retreatment. Several other regimens, including ibrutinib,[305] temozolomide,[306-308] rituximab,[285,309] rituximab plus temozolomide,[310,311] lenalidomide with or without rituximab,[312] topotecan,[313,314] high-dose cytarabine,[315] dexamethasone plus high-dose cytarabine and cisplatin,[316] pomalidomide,[317] and pemetrexed[318] have also shown activity in the relapsed/refractory disease setting, but none has been established as a standard of care.

High-dose chemotherapy with autologous stem cell transplantation in the relapsed/refractory setting has been tested with some success in two phase 2 European trials,[319,320] although evidence of its advantage over conventional treatment is lacking. The German Cooperative PCNSL Study Group evaluated the safety and efficacy of rituximab, high-dose cytarabine, and thiotepa followed by autologous stem cell transplantation in 39 patients with relapsed or refractory PCNSL with previous high-dose methotrexate-based treatment.[320] A complete response was achieved in 56% of the patients. Out of the remaining patients, only one had progressive disease (18% of the patients had a partial response or stable disease). However, median OS was not reached, with a 2-year OS rate of 56.4%. Median PFS was 12.4 months, with a 2-year PFS rate of 46%. A phase 2 trial from France evaluated the efficacy of high-dose cytarabine and etoposide followed by autologous stem cell transplantation in 43 patients with relapsed or refractory PCNSL with previous high-dose methotrexate-based treatment.[319] Out of the 27 patients who completed autologous stem-cell rescue, median OS was 58.6 months (2-year OS was 69%) and median PFS was 41.1 months (2-year PFS was 58%).

Radiation Therapy

Historically, WBRT was the treatment standard to cover the multifocal nature of the disease. The majority of studies demonstrated the limitation of high-dose RT and led to the recommended dose of 24 to 36 Gy in 1.8 to 2.0 Gy fractions to the whole brain, without a boost.[274,276,321-324] Although RT alone is useful for initial tumor control, frequent and rapid relapse of the disease led to a short OS of 12 to 17 months.[257,323] This dismal outcome has prompted the addition of pre-irradiation methotrexate-based

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combination chemotherapy in later studies. This approach yields impressive response rates of up to 94% and improved OS ranging from 33 to 60 months.[274-276,284,296,297,321,325,326] However, excessive grade 3 and 4 hematologic toxicity (up to 78%) as well as RT-induced delayed neurotoxicity (up to 32%) sometimes leading to deaths are primary concerns, although most of these studies utilized a high RT dose of greater than or equal to 40 Gy. Of note, younger patients (aged <60 years) consistently fare better, and there is a higher incidence of late neurotoxic effects in older patients, but significant neurotoxicity can also occur in younger adults.

Thiel and colleagues[327] conducted a randomized, phase III, non-inferiority trial of high-dose methotrexate plus ifosfamide with or without WBRT in 318 patients with PCNSL. There was no difference in OS (HR, 1.06; 95% CI, 0.80–1.40; *P* = .71), but the primary hypothesis (0.9 non-inferiority margin) was not proven. Patients who received WBRT had a higher rate of neurotoxicity than those who did not (49% vs. 26%). The panel currently recommends that patients receiving WBRT because they are not candidates for chemotherapy should receive a dose of 24 to 36 Gy with a boost to gross disease, for a total dose of 45 Gy.

Although WBRT alone is seldom sufficient as primary treatment and is primarily reserved for patients who cannot tolerate multimodal treatment, it can be effective as second-line therapy. Results from a phase II trial showed that reduced-dose WBRT (23.4 Gy in 1.8 Gy/fraction) following a complete response to induction chemotherapy was associated with disease response and long-term control, as well as low neurotoxicity.[328] When administered after chemotherapy failure, WBRT has shown response rates reaching nearly 75%.[329] Median PFS was 9.7 months overall, 57.6 months in patients who had achieved a CR with WBRT, and 9.7 months in patients with a PR. For patients who had a less than complete response to chemotherapy, a dosing schedule consistent with that used for induction treatment may be used, followed by a limited field to gross disease, or focal RT to residual disease.

NCCN Recommendations

Initial Evaluation

Neuroradiologic evaluation is important in the diagnosis of PCNSL and to evaluate the effectiveness of subsequent therapy. With MRI, the tumor is often isointense or hypointense on T1- and T2-weighted images and enhances frequently.[330] In addition, restricted diffusion can be seen in the area of the enhancing abnormality on diffusion-weighted imaging sequences. On a CT scan, PCNSL is usually isodense or hyperdense compared to the brain and enhances in most cases. Hallmark features include a periventricular distribution, ring enhancement, multiple lesions, and a smaller amount of edema than might otherwise be expected from a similar-sized metastatic tumor or glioma. If contrast-enhanced brain MRI (or contrast-enhanced CT if MRI is contraindicated) suggests PCNSL, clinicians are advised to hold the use of steroids if possible before diagnosis is established, since the imaging and histologic features of PCNSL can be profoundly affected by these drugs.

Patients with an enhancing brain lesion consistent with PCNSL should receive a biopsy (if lesion is amenable to biopsy), as this is the most direct and rapid route to achieve a pathologic diagnosis. Because the role of maximal surgical resection is limited to alleviating symptoms of raised intracranial pressure or preventing herniation,[261] stereotactic biopsy is generally preferred to minimize invasiveness.[271] Even with molecular marker testing, however, a biopsy can occasionally be falsely negative, particularly if the patient had been treated previously with steroids. Thus, if a biopsy is nondiagnostic, the panel recommends that the steroids be tapered and that the patient be followed closely, both clinically and radiographically. If and when the lesion recurs, there should be a prompt repeat CSF evaluation or rebiopsy before the initiation of steroids. If, on

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the other hand, no definitive diagnosis of lymphoma is made from biopsy and the patient has not received steroid therapy, workup for other diagnoses (for example, inflammatory processes) or repeat CSF evaluation/rebiopsy is recommended.

Evaluation for Extent of Disease

Once the diagnosis of PCNSL is established, the patient should undergo a thorough staging workup detailed by The International PCNSL Collaborative Group.[271] This workup involves a complete CNS evaluation including imaging of the entire neuraxis (MRI of the spine with contrast). If possible, this should be done before CSF analysis is attempted to avoid post-lumbar puncture artifacts that can be mistaken for leptomeningeal disease on imaging.

A lumbar puncture with evaluation of CSF (15–20 mL of spinal fluid) should be considered, if it can be done safely and without concern for herniation from increased intracranial pressure, and if it will not delay diagnosis and treatment. A delay in treatment may compromise patient outcomes.[303] Caution should be taken in patients who are anticoagulated, thrombocytopenic, or who have a bulky intracranial mass. CSF analysis should include flow cytometric analysis. The yield for a positive diagnostic test can be increased by the use of molecular markers of monoclonality, such as an immunoglobulin gene rearrangement.

Since disease is sometimes detected in the retina and optic nerve, a full ophthalmologic exam should be done, which should include a slit-lamp eye examination. In some cases, the diagnosis of lymphoma is made by vitrectomy; in this case, flow cytometric analysis is recommended. In addition, blood work (CBC and chemistry panel) and a contrast-enhanced body CT or PET/CT[331] are required to rule out systemic involvement. Bone marrow biopsy is a category 2B option that may be considered. In men older than 60 years of age, testicular ultrasound may be considered (category 2B). In these patients, regular testicular examination is encouraged. If both testicular examination and CT or PET/CT imaging are negative, then testicular ultrasound may not be necessary.

An HIV blood test should also be performed, because both prognosis and treatment of patients with HIV-related PCNSL may be different than that of patients who are otherwise immunocompetent. HIV-positive patients should consider highly active retroviral therapy.

Newly Diagnosed Disease

Induction treatment should be initiated as soon as possible following confirmation of diagnosis. The International PCNSL Collaborative Group has published treatment response criteria for complete response, unconfirmed complete response, partial response, progressive disease, and relapsed disease.[271] Given the dramatic effect of steroids on symptom relief, they are commonly administered concurrently with workup. A high-dose methotrexate-containing regimen is the recommended induction treatment. In the case of methotrexate-induced renal dysfunction, consider glucarpidase to aid clearance. Non–methotrexate-based regimens, including intra-CSF chemotherapy (category 2B), may be used if the patient cannot tolerate methotrexate.

If a patient is found to have malignant uveitis, orbital RT may be considered because of poor penetration of systemic chemotherapy into the uveal fluid. However, there are reports of clearance of ocular lymphoma in patients who were treated with systemic high-dose methotrexate.[272] Therefore, for a patient with PCNSL who has asymptomatic ocular involvement, a reasonable strategy is to delay RT to the globe in order to see if high-dose methotrexate is effective. Referral to a neuro-ophthalmologist for intraocular injection of chemotherapy (category 2B) is also an option.

WBRT may be used in patients who are not candidates for chemotherapy. For a patient treated with WBRT, consideration of intra-CSF

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chemotherapy plus focal spinal RT are treatment options if the lumbar puncture or spinal MRI are positive. Intrathecal chemotherapy options include methotrexate, cytarabine, and rituximab.

Treatment following induction high-dose methotrexate-based therapy depends on disease response.[271] Given the rarity of this disease, there are few high-quality studies to inform treatment decision-making. For patients who have a complete or unconfirmed complete response, consolidation therapy options that may be considered include high-dose chemotherapy (carmustine/thiotepa or thiotepa/busulfan/cyclophosphamide [TBC]) with stem cell rescue[281,286-292] or low-dose WBRT. However, WBRT in this setting may increase neurotoxicity,[327,332] especially in patients older than 60 years.[275,296,297] High-dose cytarabine with or without etoposide is also a consolidation treatment option for patients who had a complete response to induction high-dose methotrexate-based therapy (this regimen may also be considered in patients who do not have a complete response).[274-276,303] If there is not a complete or unconfirmed complete disease response following induction therapy, it is recommended to pursue WBRT or another systemic therapy in order to rapidly induce a response, diminish neurologic morbidity, and optimize quality of life. Best supportive care is another option for patients with residual disease following methotrexate-based treatment who are not candidates for other reasonable rescue therapies.

Relapsed or Refractory Disease

Patients should be followed using brain MRI. Imaging of the spine and CSF sampling may be done as clinically indicated for patients with spine disease. If ocular involvement, ophthalmologic exams may also be carried out.

For patients who are treated with prior WBRT and ultimately relapse, they may consider further chemotherapy (systemic and/or intrathecal), focal reirradiation, or palliative/best supportive care.

For patients who were initially treated with high-dose methotrexate-based chemotherapy but did not receive WBRT, the decision about whether to use more chemotherapy or proceed to RT at the time of relapse depends on the duration of response to initial chemotherapy. If a patient had experienced a relatively long-term response of one year or more, then treating either with the same or another regimen is reasonable. However, for patients who either have no response or relapsed within a very short time after systemic therapy, recommendations include WBRT, switching to a different chemotherapy regimen, or involved-field RT with or without chemotherapy.[329] In either case, palliative/best supportive care remains an option.

High-dose chemotherapy with stem cell rescue may also be considered as treatment for relapsed/refractory disease in patients who did not previously receive this treatment (ie, patients who were treated with high-dose methotrexate-based therapy or with WBRT) (category 2B). Regardless of primary treatment received, stem cell rescue should only be used for relapsed/refractory disease if there is a complete or partial response to reinduction high-dose chemotherapy.

For patients previously treated with high-dose chemotherapy with stem cell rescue, retreatment may be considered if there was a previous disease response and if time to relapse was at least one year. For patients who did not have a response to high-dose chemotherapy with stem cell rescue, and the time to relapse was less than one year, treatment options include RT to the whole brain or to the involved field. Regardless of time to relapse, using a different systemic therapy regimen (without stem cell rescue) and best supportive care are also options.

Primary Spinal Cord Tumors

Spinal tumors are classified according to their anatomic location as extradural, intradural-extramedullary, and intradural-intramedullary.

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Extradural tumors are primarily due to metastatic disease and are discussed in the section *Metastatic Spinal Tumors*. This section focuses on intradural primary spinal tumors.

Primary spinal cord tumors are a histologically diverse set of disease that represents 2% to 4% of all primary CNS tumors. The overall incidence is 0.74 per 100,000 person-years with a 10-year survival rate of 64%.[333] Extramedullary lesions, most commonly benign meningiomas, account for 70% to 80% of spinal cord tumors.[334] Astrocytomas (more prevalent in children) and ependymomas (more prevalent in adults) are the most common intramedullary tumors. Clinicians are advised to refer to the corresponding sections in these guidelines for further details regarding these subtypes, as intracranial and spinal lesions are biologically similar.

Individuals with type I neurofibromatosis, type II neurofibromatosis, and von Hippel-Lindau syndrome are predisposed to form, respectively, spinal astrocytomas, spinal peripheral nerve sheath tumors, spinal ependymomas, and intramedullary hemangioblastomas.

Since 70% of primary spinal cord tumors are low-grade and slow-growing,[333] it is common for patients to suffer from pain for months to years before diagnosis. Pain that worsens at night is a classic symptom for intramedullary lesions. Progressive motor weakness occurs in half of the patients, and patients may experience sensory loss with late autonomic dysfunction (incontinence).

Treatment Overview

Observation

Many asymptomatic primary tumors of the spinal cord, especially grade I meningiomas and peripheral nerve sheath tumors, follow an indolent course and can be followed by observation without immediate intervention.

Surgery

Surgery is the preferred treatment when the tumor is symptomatic. For lesions that are radiographically well defined, such as ependymoma, WHO grade I astrocytoma, hemangioblastoma, schwannoma, and WHO grade I meningioma, potentially curative, maximal, safe resection is the goal. En bloc total resection yielded excellent local control rates of more than 90%.[335-338]

GTR is seldom feasible with grade II or higher astrocytomas because they are infiltrative and poorly circumscribed. In a study of 202 patients with intramedullary tumors, over 80% of grade I astrocytomas were completely resected, while total resection was achieved in only 12% of grade II tumors.[339] Nevertheless, Benes et al[340] conducted a review of 38 studies on spinal astrocytomas and concluded that maximal safe resection should be attempted whenever possible based on reports of survival benefit.

Radiation Therapy

RT is not recommended as primary therapy because of limited response, unknown histology without surgery, and low RT tolerance of the spinal cord. It is also not advisable following GTR, as tumors that can be excised completely have a low local recurrence rate.

A large retrospective analysis including over 1700 patients with primary spinal gliomas found an association between RT and worse cause-specific and overall survival, although there may be a bias that patients who received RT had more adverse factors.[341] The role of adjuvant RT following incomplete excision or biopsy remains controversial.[340,342,343] One exception is primary spinal myxopapillary ependymoma, for which postoperative RT has been demonstrated to reduce the rate of tumor progression.[344,345] On the other hand, EBRT is considered a viable option at disease progression or recurrence. SRS has also shown safety and efficacy in several patient series.[346-348]

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Systemic Therapy

Unfortunately, evidence on efficacious chemotherapeutic agents for primary spinal cord tumors is too scant for specific recommendations. The panel agrees that chemotherapy should be an option where surgery and RT fail, but there is no consensus on the best regimen. Chemotherapy is best given in the setting of a clinical trial.

NCCN Recommendations

MRI imaging is the gold standard for diagnosis of spinal cord lesions. However, CT myelogram may be used for diagnosis in patients for whom MRI is contraindicated. Asymptomatic patients may be observed (especially for suspected low-grade) or resected, while all symptomatic patients should undergo some form of surgery. The surgical plan and outcome is influenced by whether a clear surgical plane is available.[349] Whenever possible, maximal safe resection should be attempted, with a spine MRI 2-3 weeks following surgery to assess the extent of the resection. Postoperative adjuvant RT is appropriate if symptoms persist after incomplete resection or biopsy, or for patients with myxopapillary ependymoma that has been incompletely resected. Patients should be managed according to the pathology results (see *Low-Grade Infiltrative Astrocytomas & Oligodendrogliomas*, *Anaplastic Gliomas and Glioblastomas*, and *Intracranial and Spinal Ependymomas*). Those diagnosed with hemangioblastoma should consider screening for von Hippel-Lindau syndrome including neuraxis imaging.[350]

All patients should be followed by sequential MRI scans, with a greater frequency in patients with high-grade tumors. At progression or recurrence, re-resection is the first choice. If this is not feasible, conventional EBRT or SRS is the next option. Chemotherapy is reserved for cases where both surgery and RT are contraindicated.

Meningiomas

Meningiomas are extra-axial CNS tumors arising from the arachnoid cap cells in the meninges. They are most often discovered in middle-to-late adult life, and have a female predominance. The annual incidence for males and females reported by the Central Brain Tumor Registry of the United States (CBTRUS) are 1.8 and 3.4 per 100,000 people, respectively.[351] In a review of 319 cases using the WHO grading scale, 92% of meningiomas are grade I (benign), 6% are grade II (atypical), and 2% are grade III (malignant).[352] Small tumors are often asymptomatic, incidental findings.[353] Seizure is a common presenting symptom occurring in 27% of patients.[354]

Imaging

Brain imaging with contrast-enhanced CT or MRI is the most common method of diagnosing, monitoring, and evaluating response to treatment (review by Campbell et al[355]). The CT scan best reveals the chronic effects of slowly growing mass lesions on bone remodeling. Calcification in the tumor (seen in 25%) and hyperostosis of the surrounding skull are features of an intracranial meningioma that can be easily identified on a non-contrast CT scan. Nonetheless, MR imaging reveals a number of imaging characteristics highly suggestive of meningioma, and in stereotactic RT articles, MR has been used to operationally define pathology. These MR findings include a tumor that is dural-based and isointense with gray matter, demonstrates prominent and homogeneous enhancement (>95%), has frequent CSF/vascular cleft(s), and often has an enhancing dural tail (60%). However, approximately 10% to 15% of meningiomas have an atypical MRI appearance mimicking metastases or malignant gliomas. In particular, secretory meningiomas may have a significant amount of peritumoral edema. Cerebral angiography is occasionally performed, often for surgical planning, as meningiomas are vascular tumors prone to intraoperative bleeding. In some instances preoperative embolization is helpful for operative hemostasis

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management. Angiographic findings consistent with a meningioma include a dual vascular supply with dural arteries supplying the central tumor and pial arteries supplying the tumor periphery. A “sunburst effect” may be seen due to enlarged and multiple dural arteries, and a prolonged vascular stain or so-called “blushing” can be seen, which results from intratumoral venous stasis and expanded intratumoral blood volume.

Meningiomas are also known to have high somatostatin receptor density, which allows for the use of octreotide brain scintigraphy to help delineate extent of disease and to pathologically define an extra-axial lesion.[356-358] Octreotide imaging with radiolabeled indium or, more recently, gallium may be particularly useful in distinguishing residual tumor from postoperative scarring in subtotally resected/recurrent tumors.

Treatment Overview

Observation

Studies that examined the growth rate of incidental meningiomas in otherwise asymptomatic patients suggested that many asymptomatic meningiomas may be followed safely with serial brain imaging until either the tumor enlarges significantly or becomes symptomatic.[359,360] These studies confirm the tenet that many meningiomas grow very slowly and that a decision not to operate is justified in selected asymptomatic patients. As the growth rate is unpredictable in any individual, repeat brain imaging is mandatory to monitor an incidental asymptomatic meningioma.

Surgery

The treatment of meningiomas is dependent upon both patient-related factors (ie, age, PS, medical comorbidities) and treatment-related factors (ie, reasons for symptoms, resectability, goals of surgery). Most patients diagnosed with surgically accessible symptomatic meningioma undergo surgical resection to relieve neurologic symptoms. Complete surgical resection may be curative and is therefore the treatment of choice, if feasible. Both the tumor grade and the extent of resection impact the rate of recurrence. In a cohort of 581 patients, 10-year PFS was 75% following GTR but dropped to 39% for patients receiving STR.[361] Short-term recurrences reported for grade I, II, and III meningiomas were 1% to 16%, 20% to 41%, and 56% to 63%, respectively.[362-364] The Simpson classification scheme that evaluates meningioma surgery based on extent of resection of the tumor and its dural attachment (grades I–V in decreasing degree of completeness) correlates with local recurrence rates.[365] First proposed in 1957, it is still being widely used by surgeons today.

Radiation Therapy

Safe GTR is sometimes not feasible due to tumor location. In this case, STR followed by adjuvant EBRT has been shown to result in long-term survival comparable to GTR (86% vs. 88%, respectively), compared to only 51% with incomplete resection alone.[366] Of 92 patients with grade I tumors, Soyuer and colleagues found that RT following STR reduced progression compared to incomplete resection alone, but has no effect on OS.[367] Conformal fractionated RT (eg, 3D-CRT, IMRT, VMAT, proton therapy) may be used in patients with grade I meningiomas to spare critical structures and uninvolved tissue.[368]

Because high-grade meningiomas have a significant probability of recurrence even following GTR,[369] postoperative high-dose EBRT (>54 Gy) has become the accepted standard of care for these tumors to improve local control.[370] A review of 74 patients showed that adjuvant RT improves survival in patients with grade III meningioma and in those with grade II disease with brain invasion.[371] The role of post-GTR RT in benign cases remains controversial.

Technical advances have enabled stereotactic administration of RT by linear accelerator (LINAC), Leksell Gamma Knife™, or CyberKnife™ radiosurgery. The use of stereotactic RT (either single fraction or

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fractionated) in the management of meningiomas continues to evolve. Advocates have suggested this therapy in lieu of EBRT for small (<35 mm), recurrent, or partially resected tumors. In addition, it has been used as primary therapy in surgically inaccessible tumors (ie, base-of-skull meningiomas) or in patients deemed poor surgical candidates because of advanced age or medical comorbidities. Nonrandomized and retrospective studies show that stereotactic RT is associated with excellent tumor control and good survival outcomes, particularly in grade I tumors, indicating that this treatment is effective as primary and second-line treatment for meningiomas smaller than 3.5 cm.[372-376] However, optimal dosing has not been determined.

Systemic Therapy

For meningiomas that recur despite surgery and/or RT, or are not amenable to treatment with surgery or RT, systemic therapies are often considered. Due to the rarity of these patients requiring systemic therapy, large randomized trials are lacking. Historical estimates of 6-month PFS rates in these patients range from 0% to 29%.[377] Smaller studies support the use of targeted therapy including somatostatin analogues,[378,379] as well as alpha interferon.[380] Recently, studies investigating anti-angiogenic therapies in meningioma have demonstrated improved results.

A prospective, multicenter, nonrandomized, phase II trial evaluating the safety and efficacy of sunitinib in 36 heavily pretreated patients with refractory meningioma showed a 6-month PFS rate of 42%, with a median PFS rate of 5.2 months and a median OS rate of 24.6 months.[381] However, toxicities were considerable, with 60% of patients experiencing grade 3 or higher toxicity.

Retrospective data support the use of bevacizumab for patients with recurrent meningioma, especially for patients with symptoms driven by RT necrosis, with a 6-month PFS rate of 43.8% for recurrent surgery and radiation-refractory grade II and III meningioma with bevacizumab monotherapy.[382,383] In a phase II trial evaluating the efficacy and safety of bevacizumab combined with everolimus for recurrent meningioma (*N* = 17), stable disease was reported in 88% of patients, with no complete or partial responses reported.[384] The median PFS and OS rates were 22.0 months and 23.8 months, respectively, with 18-month PFS and OS rates of 57% and 69%, respectively. Treatment was discontinued in 22% of patients due to toxicity.

NCCN Recommendations

Initial Treatment

Meningiomas are typically diagnosed by brain MRI. Surgery or octreotide scan may be considered for confirmation. For treatment planning, multidisciplinary panel consultation is encouraged. Patients are stratified by the presence or absence of symptoms and the tumor size. Most asymptomatic patients with small tumors (≤3 cm) are best managed by observation; else, patients should undergo surgical resection whenever possible. Non-surgical candidates should undergo RT (EBRT or SRS).

Regardless of tumor size and symptom status, all patients with surgically resected grade III meningioma (even after GTR) should receive adjuvant RT to enhance local control. For patients with grade II meningioma, postoperative RT is recommended for incomplete resection; in the case of complete resection in these patients, postoperative RT may be considered. Patients with grade I meningioma may be observed following surgery, though postoperative RT may be considered in patients with symptomatic disease. SRS may be used in lieu of conventional RT as adjuvant or primary therapy in asymptomatic cases.

Follow-up and Recurrence

In the absence of data, panelists have varying opinions on the best surveillance scheme and clinicians should follow patients based on individual clinical conditions. Generally, malignant or recurrent

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meningiomas are followed more closely than grade I and II tumors. A typical schedule for low-grade tumors is MRI every 3 months in year 1, then every 6 to 12 months for another 5 years. After 5 years, imaging may be done every 1 to 3 years as clinically indicated.

Upon detection of recurrence, the lesion should be resected whenever possible, followed by RT. Non-surgical candidates should receive RT. Chemotherapy is reserved for patients with an unresectable recurrence refractory to RT. Observation is an option if there is no clinical indication for treatment at recurrence.

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% to 10% of patients with cancer are affected by symptomatic metastatic tumors in the brain.[385,386] A much higher incidence based on autopsy has been reported. 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, accounting for half of intracranial metastases, although melanoma has been documented to have the highest predilection to spread to the brain. Diagnosis of CNS involvement is now more common in patients with breast cancer as therapy for metastatic disease is improving.[387]

Nearly 80% of brain metastases occur in the cerebral hemispheres, an additional 15% occur in the cerebellum, and 5% occur in the brainstem.[388] 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.[389,390] The objectives of surgery for brain metastasis include retrieval of tissue for diagnosis, removal of mass effect, and resolution of edema.[391] 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[392] 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 to WBRT alone in another randomized study by Vecht and colleagues (n = 63).[393] 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.[394]

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.[391] Late side effects of SRS such as symptomatic edema and RT necrosis are relatively

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uncommon, but may be observed at higher rates when treating larger lesions.[395]

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.[396-399] Collectively, these studies demonstrate comparable OS and superior cognitive preservation and quality of life with SRS alone compared to 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.[400] 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. [401-405] 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.[406,407] Some brain metastases of radio-resistant primary tumors such as melanoma and renal cell carcinoma have also been shown to achieve good local control with SRS.[408] Other predictors of longer survival with SRS include younger age, good PS, and primary tumor control.[401,406,407,409]

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.[396,400,410] Multi-fraction SRS may be considered for larger tumors, with the most common doses being 27 Gy in 3 fractions and 30 Gy in 5 fractions.[411-413] Contouring guidelines have been published elsewhere.[414] 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.[415-420]

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 to no postoperative treatment (72% vs. 43%, respectively; HR, 0.46; 95% CI, 0.24–0.88; P = .015).[389] A separate randomized phase III trial comparing postoperative SRS with postoperative WBRT demonstrated similar OS and improved cognitive preservation with a strategy of postoperative SRS, despite superior CNS control outcomes with WBRT.[421]

Whole-Brain Radiation Therapy

Historically, WBRT was the mainstay of treatment for 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[396-399,422,423] and in two meta-analyses. Both meta-analyses found no OS improvement but improved local control with the addition of WBRT to SRS.[424,425] One meta-analysis found that distant brain control was improved by the combination therapy, but treatment with SRS alone was associated with greater preservation of neurocognitive functioning and fewer serious adverse effects.[424] The second meta-

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analysis showed a median survival benefit with the combination therapy in patients with one brain metastasis (*P* = .04). This study also found an improvement in PS and a decrease in steroid use, though these findings were based on low-quality evidence.[425] The randomized phase III EORTC 22952 trial failed to show an OS benefit from WBRT following resection or SRS, compared to observation,[399] even in subgroup analyses including only patients with controlled extracranial disease and a favorable prognostic score.[426] 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 non-inferiority QUARTZ trial compared WBRT to optimal supportive care in patients with non-small 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. Moreover, a number of retrospective studies support SRS for older patients and those with poor prognosis who have historically received WBRT.[427-429] 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,[397,398,421] a number of trials have evaluated strategies to promote cognitive preservation in patients with brain metastases including investigation of neuroprotective agents, anatomical 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.[430] There was less decline in episodic memory (HVLT-R Delayed Recall) in the memantine arm compared to placebo at 24 weeks (*P* = .059), but the difference was not statistically significant, possibly due to lack of statistical power. 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. For all cognitive endpoints, the memantine arm was either superior to or was no different from the placebo. For patients with a good prognosis, memantine may be considered during WBRT, as well as after treatment for 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 to a historical control.[431] Based on these results, the phase III NRG-CC001 trial evaluated WBRT with memantine with or without hippocampal avoidance.[432] At 6-month follow-up, time to failure of neurocognitive function was significantly less for patients in the hippocampal avoidance arm (58.0%) than in the control arm (69.1%). Study results are currently only available in abstract form. Hippocampal-sparing WBRT may be considered in patients with good prognosis.

In the postoperative setting, two 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.[433] Postoperative RT was associated with a dramatic reduction in tumor recurrence (18% vs. 70%; *P*

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< .001) and likelihood of neurologic deaths (14% vs. 44%; *P* = .003). OS, a secondary endpoint, showed no difference between the arms. The NCCTG N107C/CEC-3 randomized phase III trial included 194 patients with resected brain metastases randomized to either postoperative SRS or WBRT.[421] 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 to WBRT (median 3.7 months vs. median 3.0 months; HR, 0.47; 95% CI, 0.35–0.63; *P* < .001).

Systemic Therapy

Many tumors that metastasize to the brain are not very chemosensitive or have already been heavily pretreated with organ-specific effective agents. Poor penetration through the BBB is an additional concern.[434] However, there are now an increasing number 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, NSCLC, and breast cancer. 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.

Melanoma

Rapid advancements in melanoma have produced effective systemic options for metastatic disease.[435,436] These include multiple immunotherapy options. Two phase II trials support the use of a combination of the immunotherapy agents ipilimumab and nivolumab for patients with asymptomatic untreated brain metastases from melanoma.[437,438] In one of these trials, which was conducted in Australia, intracranial responses were observed in 46% of patients who received this combination, with a complete response observed in 17% (*n* = 79).[437] In the second trial, CheckMate 204, the intracranial response was 57%, with a complete response of 26% (*N* = 94).[438] In both of these trials, grade 3 or 4 treatment-related adverse events occurred in just over half of the patients evaluated.[437,438] Results from the Australian trial also suggest there may be a role for nivolumab monotherapy for patients with asymptomatic untreated brain metastases (*n* = 27), with an intracranial response rate of 20%.[437] For patients with asymptomatic untreated lesions, the response rate for patients who received ipilimumab/nivolumab was better than for nivolumab monotherapy. This trial also evaluated nivolumab monotherapy for a small number of patients for whom local therapy failed (*n* = 16), but the intracranial response rate was low (6%). A nonrandomized phase II study supports ipilimumab monotherapy for patients with small asymptomatic brain metastases from melanoma (*n* = 51), with a CNS disease control rate of 24% (no complete responses).[439] Most of the patients in this study had received previous systemic or local treatment. Nivolumab monotherapy is a reasonable treatment option for a carefully monitored patient whose goal is to avoid radiation.

The anti-PD-1 antibody pembrolizumab is also supported for treatment of both untreated and progressive brain metastases from melanoma, based on early results of a phase II trial showing a CNS ORR of 22% (*n* = 18).[440] Long-term follow-up from this trial showed a CNS response in 26% of the sample (*N* = 23), with 4 complete responses.[441] In patients who had a

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CNS response, these responses were ongoing at 24 months in all of the patients. Median PFS and OS were 2 months and 17 months, respectively. Grade 3–4 treatment-related adverse events were minimal. Despite data showing that brain metastases can respond to immune checkpoint inhibitors, the data do not yet provide any robust comparison of these agents from treatment of brain metastases from melanoma.

There is also evidence that brain metastases from melanoma can respond to BRAF/MEK inhibitor combination therapy. The nonrandomized phase II COMBI-MB trial demonstrated clinical benefit and acceptable toxicity for the combination of the BRAF inhibitor dabrafenib with the MEK inhibitor trametinib in 125 patients with brain metastases from *BRAF* V600-mut melanoma.[442] Among the patients with asymptomatic brain metastases, an intracranial response was observed in 58% of those with untreated metastases and in 56% of those with previously treated metastases. In patients with symptomatic brain metastases, an intracranial response was observed in 59%. Use of the BRAF inhibitor vemurafenib for patients with both newly diagnosed and previously treated brain metastases from *BRAF* V600-mut melanoma is supported by nonrandomized studies.[443,444] Although there are no published prospective studies on the combination of vemurafenib and cobimetinib for patients with brain metastases from melanoma, there is high-quality evidence that, for distantly metastatic melanoma, combination therapy with vemurafenib and cobimetinib is associated with improved outcomes, compared with vemurafenib monotherapy.[445,446] Prospective randomized trials are needed to determine which *BRAF*-directed therapy options provide the best results in patients with brain metastases from melanoma.

Lung Cancer

Systemic treatment options for patients with brain metastases from NSCLC include immunotherapy agents and targeted therapies for cancer that is anaplastic lymphoma kinase (ALK) rearrangement-positive and EGFR mutation-positive.

PD-1/PD-L1 Inhibitors

A phase II trial showed a 33% response rate for pembrolizumab in 18 patients with brain metastases from PD-L1-positive NSCLC.[440] Pooled analyses from a phase II trial[447] and two phase III trials[448,449] showed that nivolumab for patients with previously treated brain metastases from NSCLC is well-tolerated, though results from these analyses are currently only reported in abstract form.[450] Nivolumab for patients with brain metastases from NSCLC is also supported by results from a retrospective multi-institutional study.[451]

ALK Inhibitors

At time of diagnosis, brain metastases are present in 24% of patients with ALK rearrangement-positive NSCLC.[452] Crizotinib inhibits *ALK* rearrangements, *ROS1* rearrangements, and some MET TKIs. Crizotinib does demonstrate some CNS activity,[453] but the response and control rates appear to be clearly lower than newer generation ALK inhibitors.

In a randomized phase III trial, the ALK inhibitor alectinib was compared to crizotinib in 303 patients with advanced ALK rearrangement-positive NSCLC and no previous systemic therapy treatment.[454] Brain metastases were reported in 40.3% of the sample. Among these patients, a CNS response was observed in 81% of patients in the alectinib arm (8 complete responses) and 50% of patients in the crizotinib arm (1 complete response). The median duration of intracranial response in these 122 patients was 17.3 months in the alectinib arm and 5.5 months in the crizotinib arm. Pooled analyses from two phase II studies[455,456] including patients with ALK rearrangement-positive NSCLC that progressed on crizotinib showed that alectinib was associated with a good objective response rate and excellent disease control in patients with brain

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metastases.[457] Patients who did not receive previous brain RT seemed to have a better response to alectinib than patients with previous RT, but the sample size for these analyses was small.

In a similar randomized phase III trial, brigatinib, another ALK inhibitor, was compared to crizotinib in 275 patients with locally advanced or metastatic ALK rearrangement-positive NSCLC and no previous systemic therapy treatment.[458] Among patients with brain metastases (*n* = 90), an intracranial response was more likely in the brigatinib arm than in the crizotinib arm (67% vs. 17%, respectively; OR, 13.00; 95% CI, 4.38–38.61). Complete intracranial responses were observed in 16 patients who received brigatinib and 2 patients who received crizotinib. Twelve-month survival without intracranial disease progression was greater in the brigatinib arm than in the crizotinib arm (67% vs. 21%, respectively; HR, 0.27; 95% CI, 0.13–0.54). Brigatinib treatment in patients with brain metastases from ALK rearrangement-positive NSCLC and disease progression on crizotinib is supported by the phase II ALTA trial, which showed an intracranial response rate of 67%.[459] Median intracranial PFS was 12.8 months in these patients. A dosing schedule of 180 mg once daily with a 7-day lead-in at 90 mg was used to reduce the chance of early-onset moderate to severe pulmonary adverse events.

The ALK inhibitor ceritinib was evaluated in a phase I trial including 246 patients with ALK rearrangement-positive NSCLC.[460] About half the sample had brain metastases (*n* = 124). Retrospective analyses were used to evaluate intracranial response in these patients. Disease control rate was 78.9% in patients not previously treated with an ALK inhibitor and 65.3% in patients with previous ALK inhibitor treatment. However, most of these patients had received RT to the brain. Therefore, it is difficult to draw conclusions regarding the contribution of RT versus ceritinib to disease control rates in these patients.

In general, the panel prefers second- and third-generation ALK inhibitors for patients with brain metastases from ALK rearrangement-positive NSCLC, based on better activity profiles.

Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors

Some treatment options for patients with advanced NSCLC that harbor EGFR-TKI–sensitizing mutations have been evaluated and are now available.

Older-generation EGFR-TKIs have demonstrated some CNS activity. Gefitinib for treatment of patients with CNS metastases from NSCLC is supported by phase II studies.[461,462] Erlotinib following another EGFR-TKI for patients with CNS metastases from EGFR-sensitizing mutation-positive NSCLC is supported by two small retrospective studies.[463,464] Afatinib treatment was evaluated in patients with CNS metastasis from NSCLC and with disease progression following platinum-based chemotherapy and either erlotinib or gefitinib (*n* = 100).[465] Cerebral response was observed in 35% of these patients, and disease control was observed in 66%.

In a randomized phase III FLAURA trial, the EGFR-TKI osimertinib was compared to a different EGFR-TKI (gefitinib or erlotinib) in 556 patients with previously untreated EGFR-sensitizing mutation-positive NSCLC.[466] CNS metastases were reported in 20.9% of the sample. Median PFS was greater for these patients in the osimertinib arm than in the standard EGFR-TKI arm (15.2 months vs. 9.6 months, respectively; HR, 0.47; 95% CI, 0.30–0.74; *P* < .001). Preplanned exploratory analyses including 41 patients with at least one measureable CNS lesion showed a CNS ORR of 91% in the osimertinib arm, compared to 68% in the EGFR-TKI arm, but this difference did not reach statistical significance (OR, 4.6; 95% CI, 0.9–34.9; *P* = .066).[467] Twenty-three percent of patients in the osimertinib arm had a complete CNS response, compared to none of the patients in the EGFR-TKI arm. CNS disease control rate did not significantly differ

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between the study arms in patients with at least one measureable CNS lesion.

Osimertinib has also been evaluated in the randomized phase III AURA3 trial, in which it was compared to pemetrexed with platinum-based therapy in 419 patients with *T790M* mutation-positive advanced NSCLC that progressed after first-line EGFR-TKI therapy.[468] CNS metastases were reported in 34.4% of the sample. Median PFS was greater for these patients in the osimertinib arm than in the pemetrexed/platinum arm (8.5 months vs. 4.2 months, respectively; HR, 0.32; 95% CI, 0.21–0.49). Preplanned analyses including 46 patients with at least one measureable CNS lesion showed a significantly greater CNS ORR for the osimertinib arm than in the pemetrexed/platinum arm (70% vs. 31%, respectively; OR, 5.13; 95% CI, 1.44–20.64; *P* = .015).[469] CNS disease control rate was 93% in the osimertinib arm, compared to 63% in the pemetrexed/platinum arm. Median CNS duration of response was also longer in the patients who received osimertinib. Pooled analyses from two phase II studies[470,471] including patients with *T790M*-positive advanced NSCLC that progressed following treatment with EGFR-TKI therapy showed a CNS ORR of 54% and disease control rate of 92%.[472] Median CNS duration of response and median PFS were not reached.

Other Systemic Therapy Options

A phase I/II study of topotecan plus WBRT has shown a 72% response rate in 75 patients with brain metastases.[473] Unfortunately, a follow-up phase III trial including only patients with brain metastases from lung cancer was closed early due to slow accrual.[474]

Breast Cancer

Capecitabine combined with the TKI lapatinib for patients with brain metastases from HER2-positive breast cancer is supported by a systematic review and pooled analysis showing an ORR of 29.2%, a disease control rate of 65.1%, and a 2-year OS rate of 33.4%.[475] A phase II study supports use of capecitabine combined with the TKI neratinib in patients with CNS metastases from HER2-positive breast cancer.[476] CNS metastases in most of the patients were previously treated with surgery or RT. Capecitabine monotherapy treatment in patients with brain metastases from breast cancer is supported by a phase I trial[477] and case reports.[478-481] In a randomized phase II trial evaluating paclitaxel combined with neratinib, compared to trastuzumab combined with paclitaxel, in patients with untreated metastatic HER2-positive breast cancer, incidence of symptomatic or progressive CNS events were significantly lower in the neratinib arm (8.3% vs. 17.3%, respectively; HR, 0.48; 95% CI, 0.29–0.79; *P* = .002).[482] Though patients with asymptomatic CNS metastases at baseline were eligible to participate in this trial, they comprised only 3.8% of the study sample, limiting the conclusions that can be drawn about the efficacy of this regimen for these patients.

A study of high-dose methotrexate in patients mostly with breast cancer achieved disease control in 56% of patients.[483] The use of cisplatin and etoposide monotherapies and combination therapy in patients with brain metastases from breast cancer is supported by nonrandomized studies published in the 1990s.[484-486]

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.

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Treatment for Limited Metastatic Lesions

The panel defines "limited" brain metastases as patients for whom SRS is equally effective as WBRT, but with more cognitive protection.[400] Because brain metastases are often managed by physicians from multiple disciplines, the NCCN Panel encourages multidisciplinary consultation prior to treatment for optimal planning.

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.[397] 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 year and then every 4 to 6 months indefinitely. Closer follow-up every 2 months is particularly helpful for patients treated with SRS alone.[398] Recurrence on radiograph can be confounded by treatment effects of SRS. Consider tumor tissue sampling if there is a high index of suspicion of recurrence. 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, 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 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, or SRS. WBRT re-irradiation is generally discouraged due to toxicity to cognition and quality of life and should only be administered in highly selected circumstances.

Treatment for 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. Palliative neurosurgery should be considered if a lesion is causing a life-threatening mass effect, hemorrhage, or hydrocephalus.

After WBRT or SRS, patients should have a repeat contrast-enhanced MRI scan every 2 to 3 months for 1 year, then every 4 to 6 months indefinitely. Treatment for recurrences are individualized and may include

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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.

Leptomeningeal Metastases

Leptomeningeal metastasis or neoplastic meningitis refers to the multifocal seeding of the leptomeninges by malignant cells. It is known as leptomeningeal carcinomatosis or carcinomatous meningitis when these cells originate from a solid tumor. When it is related to a systemic lymphoma, it is called lymphomatous meningitis, and when associated with leukemia, it is termed leukemic meningitis. Leptomeningeal metastasis occurs in approximately 5% of patients with cancer.[487] This disorder is being diagnosed with increasing frequency as patients live longer and as neuroimaging studies improve. Most cases arise from breast and lung cancers, and melanoma has the highest rate of leptomeningeal spread.[488,489]

Tumor cells gain access to the leptomeninges by hematogenous dissemination, lymphatic spread, or direct extension. Once these cells reach the CSF, they are disseminated throughout the neuraxis by the constant flow of CSF. Infiltration of the leptomeninges by any malignancy is a serious complication that results in substantial morbidity and mortality. Cranial nerve palsies, headaches, focal deficits from cortical disturbances, mental changes, and motor weakness are among the most common presenting symptoms.[487] The median survival of patients diagnosed with this disorder is <3 months with death resulting from progressive neurologic dysfunction, but may be extended by early detection and intervention.[488,489]

Treatment Overview

The goals of treatment in patients with leptomeningeal metastases are to improve or stabilize the neurologic status of the patient and to prolong survival.[490] Unfortunately, there is a lack of standard treatments due to meager evidence in literature. Because treatment is largely palliative, aggressive chemotherapy should only be given to patients most likely to benefit (see *Patient Stratification*).

Radiation Therapy

RT is mainly given for symptom alleviation, CSF flow correction, or for debulking to facilitate chemotherapy.[489,491,492]

Surgery

The role of neurosurgery for leptomeningeal metastases is mainly limited to intraventricular catheter and subcutaneous reservoir placement for drug administration.[493] This is preferred over lumbar punctures because of improved drug delivery, safety, superior pharmacokinetics, lower inter-patient variability, and patient comfort.[494]

Systemic Therapy

Chemotherapy can reach the whole neuraxis and can improve outcome of patients. Intrathecal (intra-CSF) chemotherapy is widely used, although drugs with good CNS penetration, particularly organ-specific targeted therapies, may be administered systemically in high doses.[490] Intrathecal therapy can involve either administration via a lumbar puncture or intraventricular injections via an Ommaya reservoir. However, both intra-CSF therapy and high-dose systemic therapy are associated with significant toxicity or complications and are therefore restricted to patients with good PS.

Agents used for intra-CSF therapy are often histology-specific with good penetration capacity. The panel included options deemed appropriate based on moderate benefit: methotrexate for breast cancer, lymphoma,

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and leukemia[495-497]; cytarabine for lymphoma and leukemia[496,498,499]; thiotepa[497,500]; rituximab for lymphoma[501]; topotecan[502]; etoposide[503]; trastuzumab for breast cancer[504]; and interferon alfa.[505] Interferon alfa received a category 2B designation due to concerns of its toxicity and limited evidence of efficacy.

Breast cancers[483] and lymphomas[498,506] are also particularly responsive to high-dose methotrexate. In addition, osimertinib and weekly pulse erlotinib have been used for metastatic NSCLC with EGFR sensitizing mutations [exon 19 or exon 21 deletions only for erlotinib (category 2B)].[464,507]

NCCN Recommendations

Patient Evaluation

Patients present with signs and symptoms ranging from injury to nerves that traverse the subarachnoid space, direct tumor invasion of the brain or spinal cord, alteration of the local blood supply, obstruction of normal CSF flow pathways leading to increased intracranial pressure, or interference with normal brain function. Patients should have a physical examination with a careful neurologic evaluation. MRI of the brain and spine should also be performed for accurate staging, particularly if the patient is a candidate for active treatment. A definitive diagnosis is most commonly made by CSF analysis via lumbar puncture if it is safe for the patient. The CSF protein is typically increased, and there may be a pleocytosis or decreased glucose levels and ultimately positive CSF cytology for tumor cells. Assessment of circulating tumor cells increases the sensitivity of tumor cell detection in CSF.[508-510] This assessment is now CLIA-approved in some states and should be done when it is available. The CSF cytology is positive approximately 50% of the time with the first lumbar puncture, and 90% of the time after repeated CSF analyses in affected patients.[492] Clinicians should be aware that lumbar punctures may be contraindicated in patients with anticoagulation, thrombocytopenia, or bulky intracranial disease. In these cases, suspicious CSF biochemical results combined with suggestive clinical and/or radiologic features should be taken into consideration. Although a positive CSF cytology in patients with solid tumors is virtually always diagnostic, reactive lymphocytes from infections (for example, herpes zoster infection) can often be mistaken for malignant lymphocytes.

Patient Stratification

Once the diagnosis has been established, the patient's overall status should be carefully assessed to determine how aggressively the carcinomatous or lymphomatous meningitis should be treated. Unfortunately, this disease is most common in patients with advanced, treatment-refractory systemic malignancies for whom treatment options are limited. In general, fixed neurologic deficits (such as cranial nerve palsies or paraplegia) do not resolve with therapy, although encephalopathies may improve dramatically. As a result, patients should be stratified into "poor-risk" and "good-risk" groups. The poor-risk group includes patients with KPS below 60; multiple, serious, major neurologic deficits; extensive systemic disease with few treatment options; bulky CNS disease; and neoplastic meningitis related to encephalopathy. The good-risk group includes patients with KPS greater than or equal to 60, no major neurologic deficits, minimal systemic disease, and reasonable systemic treatment options. Many patients fall in between these two groups, and clinical judgment will dictate how aggressive their treatment should be.

Treatment

Patients in the poor-risk group are usually offered palliative/supportive care measures, though patients considered good-risk may also receive palliative/best supportive care if they do not desire further treatment. Fractionated EBRT to neurologically symptomatic sites (eg, to the whole brain for increased intracranial pressure or to the lumbosacral spine for a developing cauda equina syndrome) can be considered to temporarily improve function.

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Chemotherapy (systemic or intrathecal) is recommended for patients considered good-risk. These patients may also receive WBRT or involved-field RT to neurologically symptomatic or painful sites and to areas of bulky disease identified on neuroimaging studies. Craniospinal RT may also be considered, but only in highly select patients given the substantial toxicity and resultant bone marrow suppression.

CSF flow abnormalities are common in patients with neoplastic meningitis, and these often lead to increased intracranial pressure. Administering chemotherapy into the ventricle of a patient with a ventricular outlet obstruction increases the patient's risk for leukoencephalopathy. In addition, the agent administered will not reach the lumbar subarachnoid space where the original CSF cytology was positive. Therefore, a CSF flow scan should be carried out if there are concerns about a blockage (eg, a patient with hydrocephalus) prior to administration of intrathecal systemic therapy. If significant flow abnormalities are seen, fractionated EBRT can be administered to the sites of obstruction before repeating a CSF flow scan. High-dose systemically administered methotrexate remains an option for patients with breast cancer or lymphoma, as normal CSF flow is not required to reach cytotoxic concentrations.

The patient should be reassessed clinically and with a repeat CSF cytology. Cytology should be sampled from the lumbar spine. Neuraxis imaging with MRI is recommended if CSF cytology was initially negative and can also be considered for sites that were previously positive on a radiograph.

If negative cytology is achieved after induction, continue the induction chemotherapy for another month before switching to maintenance intrathecal chemotherapy. The CSF cytology status should be followed every 4 to 8 weeks. If the patient is clinically stable or improving after induction and there is no clinical or radiologic evidence of progressive leptomeningeal disease, the patient should receive another 4 weeks of "induction" intrathecal chemotherapy or should consider switching intrathecal drugs for 4 weeks. This regimen should be followed by maintenance therapy and monthly cytology if the cytology has converted to negative or is improving (still positive) while the patient is clinically stable.

Progressive Disease

If the patient's clinical status is deteriorating from progressive leptomeningeal disease or if the cytology is persistently positive, the clinician has several options: 1) RT to symptomatic sites, 2) systemic chemotherapy, or 3) palliative or best supportive care.

Metastatic Spinal Tumors

Bone metastases are a growing problem among patients with cancer due to increasing life expectancy, with the spine being the most frequently affected site. Spinal metastases primarily arise from breast, lung, prostate, and renal cancers.[511,512] Extradural lesions account for about 95% of spinal tumors, mostly in the thoracic region.

Some patients are found to have vertebral involvement as an asymptomatic, incidental finding. However, for most affected patients, pain is the primary presenting symptom preceding neurologic dysfunction. Three types of pain have been classically defined. Local pain due to tumor growth is often described as a constant, deep aching that improves with steroid medications. Mechanical back pain varies with movement and position and is attributed to structural spinal instability. While seldom responsive to steroids, mechanical pain can be alleviated by surgical stabilization. Radicular pain is a sharp or stabbing sensation that occurs when nerve roots are compressed by the tumor. Patients may experience any one or a combination of these types of pain.

Spinal cord compression is the most debilitating complication of spine metastases. It affects 5% to 10% of all patients with cancer, with more

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than 20,000 cases diagnosed each year in the United States.[513] The majority of patients initially complain of progressive radicular pain.[514] This is followed by neurologic symptoms such as motor weakness and sensory loss, and may even include autonomic bladder dysfunction. If left untreated, neurologic deficits rapidly progress to paralysis. Unfortunately, a study of 319 patients with cord compression revealed significant delay in the report of initial pain (3 months) as well as diagnosis (2 months) that can lead to irreversible spinal cord damage.[515] Therefore, it is paramount that the clinician watches for early suspicious signs and establishes prompt diagnosis by spine MRI. Once diagnosed, spinal cord compression is considered a medical emergency; intervention should be implemented immediately to prevent further neurologic decline.

Treatment Overview

Dissemination to the spinal column is largely incurable. Therefore, the goals of treatment are palliation and improvement of quality of life through preservation of neurologic function, pain relief, and stabilization of mechanical structure. One exception is slow-growing cancers (mainly renal cell carcinoma) with solitary spinal metastasis, for which surgery may achieve possible cure.[516] Patients with spine metastases require care from a multidisciplinary team, including neurosurgeons; orthopedic surgeons; radiologists and interventional radiologists; and specialists in pain management, care of the bowel, bladder, and back, and ambulatory support.

The type and aggressiveness of the primary tumor often dictates the choice of treatment, as different cancers have varying sensitivities to systemic therapy and RT. In addition, patient characteristics including PS and comorbidities will determine whether they can tolerate surgery and, if so, which surgical technique should be used.

Surgery

There is general consensus that a patient should have a life expectancy of at least 3 months to be a surgical candidate. Paraplegia for over 24 hours is a strong relative contraindication due to low chances of improvement when prolonged neurologic deficits exist before surgery.[517] Patients with hematologic malignancies should also be excluded, as they are best managed by RT or chemotherapy. Because estimation of life expectancy can be difficult, several groups have developed prognostic scoring systems to help predict surgical outcomes.[518-521]

Modern surgical techniques enable surgeons to achieve 360° decompression of the spinal cord, and stabilization can be performed concomitantly, if required. The development of a plethora of spinal implants composed of high-quality materials such as titanium greatly improves reconstruction outcome. The surgical approach—anterior, posterior, or combined/circumferential—is primarily determined by disease anatomy.[522,523]

Sundaresan and colleagues[516] reported favorable results using a variety of surgical approaches on 80 patients with solitary spine metastases. Both pain and mobility were improved in the majority of patients. OS reached 30 months, with 18% of patients surviving 5 years or more. The best outcome was observed in patients with kidney and breast cancers.

Surgery followed by adjuvant EBRT has emerged as a highly effective approach in relieving spinal cord compression and restoring function, especially for solid tumors. A meta-analysis including 24 surgery cohort studies and four RT studies found that patients are twice as likely to regain ambulatory function after surgery than RT alone.[524] However, data also revealed significant surgery-related mortality (6.3%) and morbidity (23%). In another review of literature from 1964 to 2005, anterior decompression with stabilization plus RT was associated with superior outcome over RT alone or laminectomy, achieving 75% mean improvement in neurologic

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function. However, high surgical mortality rate (mean 10%) was also reported.[525]

To date, only one relevant randomized trial has been reported.[526] Approximately 100 patients with metastatic spinal compression were randomized to surgery plus postoperative RT or RT alone. Compared to the RT group, significantly more patients in the surgery group regained walking ability (84% vs. 57%; *P* = .001) and for a longer period of time (median 122 days vs. 13 days; *P* = .003). The impressive results were obtained with strict eligibility criteria. The study excluded patients with radiosensitive tumors, neurologic deficits for 24 hours, multiple spinal tumors, lesions only compressing spinal roots, and prior RT to the vertebrae. Although studies demonstrated high efficacy of surgery, the formidable complications related to surgery cannot be overlooked. Using the Nationwide Inpatient Sample all-payer database, Patil et al[527] reviewed data of over 26,000 patients who had undergone surgery for spinal metastases. The in-hospital mortality and complication rates were 5.6% and 22%, respectively. The most common complications were pulmonary (6.7%) and hemorrhages or hematomas (5.9%). Clearly, careful individual patient selection based on life expectancy and overall health is warranted.

Radiation Therapy

Traditionally, EBRT has been the main form of treatment for spinal metastases. In the modern surgery era, RT alone is often not sufficient in achieving decompression or stabilization (see above), but it is routinely used as adjuvant therapy following surgery as it is difficult to obtain wide negative margins. Given the potential impact of RT on wound healing, most studies posed an interval of 1 to 3 weeks between resection and subsequent RT.[528]

An excellent response to RT alone for spinal compression was reported by Marazano and colleagues.[529] Three hundred patients were randomized to a short-course (8 Gy x 2 days) or split-course (5 Gy x 3 days; 3 Gy x 5 days) schedule. After RT, 35% of nonambulatory patients regained walking ability, and pain relief was recorded in 57% of patients with a median survival of 4 months. Efficacy of RT was highly dependent on the histology: 70% of patients with nonambulatory breast cancer recovered mobility compared to only 20% of hepatocellular carcinoma patients. In general, solid tumors are considered either moderately radiosensitive (eg, breast and prostate cancers) or radioresistant (eg, melanoma; osteosarcomas; cancers of the thyroid, colon, and kidney).[530] On the other hand, hematologic malignancies such as lymphomas and multiple myelomas are highly responsive to RT. Hence, RT alone is routinely utilized as therapy for these cancers, even in the presence of cord compression.

Where there is no compression, fracture, or instability, EBRT is effective in achieving local control as primary treatment. A mean 77% local control rate from seven retrospective studies including 885 patients was found in a systematic review by Gerszten and colleagues.[530] RT is also a mainstay of palliative treatment for patients with poor PS, significant comorbidities, and/or limited life expectancy (<3–4 months). Klimo's meta-analysis, including 543 patients treated by RT, revealed pain control rates of 54% to 83%.[524] Unlike surgery, RT has no immediate significant treatment-related complications and very few local recurrences. However, it increases surgical complications as it impairs wound healing.

Stereotactic radiation approaches (SRS or stereotactic body RT [SBRT]) allow precise high-dose targeting in one or two fractions while minimizing exposure of the surrounding cord.[531] This is especially important in pre-irradiated patients. The largest prospective study involved a cohort of nearly 400 patients with 500 spinal metastases, 70% of which had previous conventional irradiation.[532] At a median follow-up of 21 months, radiosurgery resulted in long-term pain improvement and tumor control in 85% and 90% of cases, respectively. Other single-institution reports also

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suggest that SRS is safe and offers more durable response than conventional therapy,[530] and results of the phase II RTOG 0631 trial demonstrated the feasibility of SRS for these patients.[533] The phase III component of this trial is ongoing and is comparing single-dose stereotactic RT of 16 Gy to single-dose EBRT of 8 Gy in patients with one to three spinal metastases (NCT00922974). Consensus guidelines should be followed for stereotactic radiation planning and delivery.[531,534,535] Reasonable dosing schedules for the postoperative setting have been published by Redmond et al.[535]

Vertebral Augmentation

Percutaneous vertebroplasty and kyphoplasty involve injection of cement (polymethyl methacrylate) into the vertebral body. Vertebroplasty is a direct injection, while kyphoplasty involves inserting a balloon that provides a cavity for the injection. These vertebral augmentation procedures immediately reinforce and stabilize the column, thereby relieving pain and preventing further fractures.[536] They are suitable in poor surgical candidates with painful fractures, but are relatively contraindicated in the case of spinal cord compression because they do not achieve decompression. Symptomatic complications occur in up to 8% of patients (mostly with vertebroplasty), including embolization of the cement and local metastasis along the needle tract.

Systemic Therapy

Corticosteroids remain a routine initial prescription for patients presenting with cord compression, with a number of theoretical benefits including anti-inflammation, reduction in edema, short-term neurologic function improvement, and enhanced blood flow. However, the preference between high-dose (96 mg daily) and low-dose (10–16 mg daily) is still unclear.[537-539]

Chemotherapy has a limited role in metastatic spinal tumors except for chemosensitive tumors such as lymphoma, myeloma, and germ cell tumors. Agents efficacious for the primary tumor are used.

NCCN Recommendations

Workup

Initial workup depends on the presence or absence of symptoms. Patients with an incidental, asymptomatic, metastatic lesion confirmed by systemic imaging can be observed with MRI. However, biopsy and further treatment of an incidental lesion are indicated if treatment of the patient is altered as a result of treatment of the incidental lesion. In the absence of symptoms, it is not mandatory to obtain a spinal MRI for every incidental metastatic lesion seen on surveillance bone scans. The alternate category involves severe or new back pain. Increasing intensity, duration, and changes in the character of pain should trigger an evaluation with an MRI study, even in patients with pre-existing degenerative spine conditions. Immediate spinal MRI is warranted in the occurrence of neurologic symptoms including weakness, paresthesias, and bladder or bowel incontinence. Contrast can be used to highlight and further evaluate any focal abnormality. The MRI can be used to image the entire spine or a focal area of interest. If the patient is unable to have an MRI, then a CT myelogram is recommended.

A normal neurologic examination implies that there is no spinal radiculopathy or myelopathy correlating with the patient's symptoms. In this case, other causes should be considered (eg, leptomeningeal disease). An abnormal neurologic examination includes motor abnormalities, sphincter abnormalities, and/or sensory deficits attributable to a dysfunction of nerve root(s) and/or the spinal cord. Therefore, detection of radiculopathy, myelopathy, or cauda equina syndrome is indicative of an abnormal examination. However, reflex asymmetry and/or

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presence of pathologic reflexes, as well as sensory deficits of a stocking/glove distribution are excluded.

Treatment

Once metastatic vertebral involvement is diagnosed, treatment is based on whether the patient is suffering from spinal cord compression, fracture, or spinal instability. In the presence of multiple metastatic spinal tumors, the one causing the patient's main symptoms is addressed first. Additional tumors can be treated at a later point according to the algorithm.

Radiographic spinal cord compression implies deformation of the spinal cord because of epidural tumor, retropulsed bone fragment, or both. It should be noted that epidural tumor may occupy part of the spinal canal with or without partial obliteration of CSF around the spinal cord. Those cases are excluded because there is no cord deformation. For tumors occurring below L1, any canal compression of 50% or more should be considered of equal importance as spinal cord compression. Patients with radiographic cord compression should start on dexamethasone (10–100 mg) to alleviate symptoms. Decompressive surgery (concomitant stabilization if indicated) and adjuvant RT is the preferred treatment (category 1) where there is spinal instability and no surgical contraindication. Primary EBRT alone is appropriate for patients with radiosensitive cancers (hematologic malignancies) and without evidence of spinal instability. Many fractionation schemes are available (8 Gy in 1 fraction, 20 Gy in 5 fractions, or 30 Gy in 10 fractions); the most common is a total of 30 Gy in 3-Gy daily fractions for 10 days.[540,541] Tolerance at the spine and/or nerve route must be considered in determining dose. Primary chemotherapy is also an option for chemo-responsive tumors in the absence of clinical myelopathy. In general, a treatment interval of at least 6 months is recommended.

Metastases to the spine without cord compression include the presence of tumor in the vertebral body, pedicle(s), lamina, transverse, or spinous process. It can also include epidural disease without cord deformation. Patients in this category should be assessed for fractures and spinal instability. Because the criteria for spinal destabilization secondary to tumor remain unclear, consultation by a surgeon is recommended. *Spinal instability* is grossly defined as the presence of significant kyphosis or subluxation (deformity) or of significantly retropulsed bone fragment. Not every pathologic fracture implies unstable structure. The degree of kyphosis or subluxation compatible with instability depends on the location of the tumor in the spine. The cross-sectional area of the vertebral body unaffected by the tumor and the patient's bone mineral density are additional factors affecting stability. In addition, vertebral body involvement is more important than dorsal element involvement with regard to stability. Circumferential disease as well as junctional and contiguous tumor location should be taken into account when assessing spinal stability. If fracture or instability is detected, the patient should undergo surgical stabilization or minimally invasive vertebral augmentation to relieve pain. These procedures should be followed by adjuvant RT to obtain local control.

If no fracture or instability is found, EBRT is the treatment of choice. Stereotactic RT may be appropriate in select cases of limited disease. Other alternatives are chemotherapy for responsive tumors, or surgery plus adjuvant RT in select cases. Patients experiencing intractable pain or rapid neurologic decline during RT should consider surgery, or stereotactic RT is an option if oligometastases are present or if the disease is radioresistant. Neurologic deterioration is apparent when the patient's neurologic examination is becoming worse on a daily basis and the patient's ambulatory status is threatened. Intractable pain means either that pain is not controlled with oral analgesics or that the patient cannot tolerate the medication due to side effects.

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Progression and Recurrence

Follow-up involves MRI or CT imaging within 1 to 3 months post-treatment, then every 3 to 4 months for 1 year, then as clinically indicated. Upon detection of progression or recurrence on imaging scans, management strategy is based on previous treatment. Patients who underwent prior RT or surgery plus adjuvant RT may consider surgery or re-irradiation to the recurred area. Stereotactic RT may be appropriate for select patients. Clinicians should plan 6 months or more between treatments in consideration of tolerance of the spine and its nerve roots. Retreatment dose should be limited to no more than 10 Gy to the surface of the spinal cord. In patients who were previously treated with chemotherapy, surgery may be indicated depending upon the degree of spinal stability/cord compression. RT may also be considered.

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