National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Central Nervous System Cancers

Version 2.2012

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Central Nervous System Cancers

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Principles of Brain Tumor Therapy:

Clinical Trials: The NCCN believes that the best management for any cancer patient 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/physician.html

NCCN Categories of Evidence and Consensus: All recommendations are Category 2A unless otherwise specified.

See NCCN Categories of Evidence and Consensus

NCCN Guidelines Version 2.2012 Updates Central Nervous System Cancers

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The 2.2012 version of the NCCN Central Nervous System Cancer Guidelines represents the addition of the Discussion text (MS-1).

Updates in Version 1.2012 of the NCCN Central Nervous System Cancers Guidelines from Version 2.2011 include:

Global Changes:

- "Best Supportive Care" change to "Palliative/Best supportive care" throughout the algorithms.

Adult Low-Grade Infiltrative Supratentorial Astrocytoma/Oligodendroglioma (excluding pilocytic astrocytoma):

ASTR-1

- "Maximal safe resection" pathway: The decision point is now based on "Low risk" versus "High risk" patients. Previously the pathway decision point was based on "Age > 40 y" versus "Age ≤ 40 y".
- Footnotes g and h regarding definitions for Low-risk and High-risk features are new to the algorithm.

ASTR-2

- No prior fractionated external beam RT pathway: "Progression" was added for clarity.

Anaplastic Gliomas/Glioblastoma

GLIO-2

- Good performance status; Adjuvant treatment:
  - After "Chemotherapy" the recommendation "(may be considered for patients with 1p19q co-deletion)" was added.
  - "Combined chemoradiation (category 3 off clinical trial, category 2A on trial)" changed to "Combined chemoradiation (category 3)".
- Poor performance status: The recommendation "Chemotherapy" changed from category 2A to category 2B.

GLIO-3

- The recommendations on this page were extensively revised. The decision points after "Glioblastoma ± carmustine (BCNU) wafer" are now based on "Performance status". Previously, after "Glioblastoma" the decision points were based on whether the patient was treated with or without a carmustine (BCNU) wafer.

Adult Medulloblastoma Supratentorial PNET

AMED-1

- Footnote "a" previously read "Excluding pineoblastomas and esthesioneuroblastoma.". "Pineoblastomas" was removed.

Primary CNS Lymphoma

PCNS-1

- The recommendation "Biopsy with least invasive approach. Hold initiation of steroids, if possible prior to diagnostic procedure" was moved to the third column. Previously it was in the second column.

PCNS-2

- Workup; Fifth bullet: "Platelets, liver function tests" changed to "CBC, Comprehensive chemistry profile".

Meningiomas

MENI-2

- After "Recurrent disease": A new pathway "Treatment not clinically indicated" was added that includes the recommendation "Observation".

Limited (1-3) Metastatic Lesions

LTD-3

- Footnote "i" was revised to read "After stereotactic radiosurgery, recurrence on radiograph can be confounded by treatment effects, consider tumor tissue sampling if there is a high index of suspicion of recurrence." "...strongly consider tumor tissue sampling..." changed to "consider tumor tissue..."

LTD-4

- First column changed to "Systemic disease progression, with limited systemic treatment options and poor PS."

Continue

Leptomeningeal Metastases

LEPT-1

- **Footnotes regarding CSF exams were combined and now footnote "d" reads, "With all malignancies, send for a cell count, differential (including hematopathology review), glucose, and protein. For solid malignancies, CSF analysis utilizes cytopathology. For hematologic malignancies, use flow cytometry."**

LEPT-3

- **Normal flow; Primary Treatment: The recommendation "Consider placing ventricular catheter and subcutaneous reservoir" was added. Previously this recommendation was on page LEPT-2 as an option for Good risk patients.**

BRAIN-A---Principles of Brain Tumor Imaging

- **First bullet:**
  - **"Enhanced MRI of the brain and spine" changed to "MRI of the brain and spine (± contrast)".**
  - **Third arrow; Benefits: Statement was revised to read "Provides a reasonably good delineation of tumors. Higher grade tumors and brain leptomeningeal metastasis usually enhance. Lower grade tumors usually do not enhance".**
- **Second bullet: "Enhanced CT of the brain and spine" changed to "CT of the brain and spine (± contrast)".**
- **Third bullet (MR Spectroscopy) and Fifth bullet (Brain FDG-PET scanning): The statement "Optimal use in differentiating tumor from radiation necrosis..." changed to "May be useful in differentiating tumor from radiation necrosis..."**

BRAIN-B---Principles of Brain Tumor Surgery

- **Options: The following recommendation was added "Chemotherapy implants, when indicated (See footnote g on GLIO-1)**
- **Tissue: The first bullet, "Maximum to pathologist" changed to "Sufficient tissue to pathologist for neuropathlogy evaluation and molecular correlates.**

BRAIN-C---Principles of Brain Tumor Radiation Therapy

Page 1 of 3:

- **High Grade Gliomas (Grades III/IV): First bullet was revised to read, "The gross tumor volume (GTV) is best defined using pre- and postoperative MRI imaging using enhanced T1 and FLAIR/T2. The GTV is expanded by 2-3 cm (Clinical target volume, CTV) to account for sub-diagnostic tumor infiltration. Fields are usually reduced for the last phase of the treatment (boost)".**
- **Adult Medulloblastoma and Supratentorial PNET: Standard risk for recurrence: This section was revised to include "Conventional dose" and "Reduced dose".**

Page 2 of 3:

- **Meningiomas; Third bullet: Changed "WHO grade 1 meningiomas may also be treated with stereotactic radiosurgery doses of 12-14 Gy in a single fraction when appropriate." Previously this recommendation only applied to "Small WHO grade 1" and the stereotactic radiosurgery dose was 12-15 Gy.**

Continue

BRAIN-D---Principles of Brain Tumor Systemic Therapy
Page 1 of 6

- **Anaplastic Gliomas; Recurrence/Salvage therapy; fifth bullet: BCNU changed to BCNU/CCNU. A similar change was made for treatment options for recurrence/salvage therapy for Glioblastoma.**
- **Glioblastoma; Recurrence/Salvage therapy: Nitrosurea wafer was added.**

Page 2 of 6:

- **Adult Medulloblastoma and Supratentorial PNET; Recurrence/Salvage Therapy**
  - **Prior chemotherapy: "Temozolomide ± 13 cis retinoic acid" changed to "Temozolomide".**
- **Primary CNS Lymphoma**
  - **Primary Treatment**
    - **First arrow: High dose methotrexate 3.5 g/m^2 or higher as single agent or in combination with: ..." changed to "High dose methotrexate 3.5 g/m^2 combined with the following plus RT:"**
    - **First arrow: The following systemic therapies were added for High dose methotrexate 3.5 g/m^2 combined with the following plus RT:**
      -Vincristine, procarbazine, cytarabine ± rituximab
      -Ifosfamide ± RT
    - **Vincristine and Procarbazine were removed as single agents used in combination with high dose methotrexate.**
    - **Second arrow: This is a new section that contains the following primary treatment options:**
      -High dose methotrexate 8.0 g/m^2 combined with the following plus deferred RT:
      ***Rituximab**
      ***Rituximab and temozolomide**

Page 3 of 6:

- **Limited (1-3) Metastatic or Multiple (> 3) Metastatic Lesions:**
  - **Recurrent Disease: Carmustine wafer was added as an option**
  - **Organ specific therapy;**
    - **First arrow: cyclophosphamide was removed as option for breast and lymphoma.**
    - **Second arrow: "Capecitabine" changed to "Capecitabine ± lapatinib".**
    - **Third arrow: "Topotecan (lung)" was clarified as "Topotecan (small cell lung)"**
- **Leptomeningeal Metastases**
  - **Treatment; Second arrow: topotecan, etoposide, and interferon alfa were added as options for intra-CSF chemotherapy.**

BRAIN-E---Principles of Brain Tumor Management
Page 1 of 3:

- **Multidisciplinary care: The following statement was added, "Patients should be informed of the possibility of pseudoprogression, its approximate incidence and potential investigations that may be needed in the event pseudoprogression is suspected. Close follow-up imaging, MR Spectroscopy, PET/CT imaging, and repeat surgery may be necessary if clinically indicated."**

Page 2 of 3:

- **Medical management;Antiepileptic drugs; First bullet: The last sentence was revised to read,"Seizure prophylaxis is not recommended as routine in asymptomatic patients; but reasonable to consider perioperatively".**

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Adult Low-Grade Infiltrative Supratentorial Astrocytoma/Oligodendroglioma (Excluding Pilocytic Astrocytoma)

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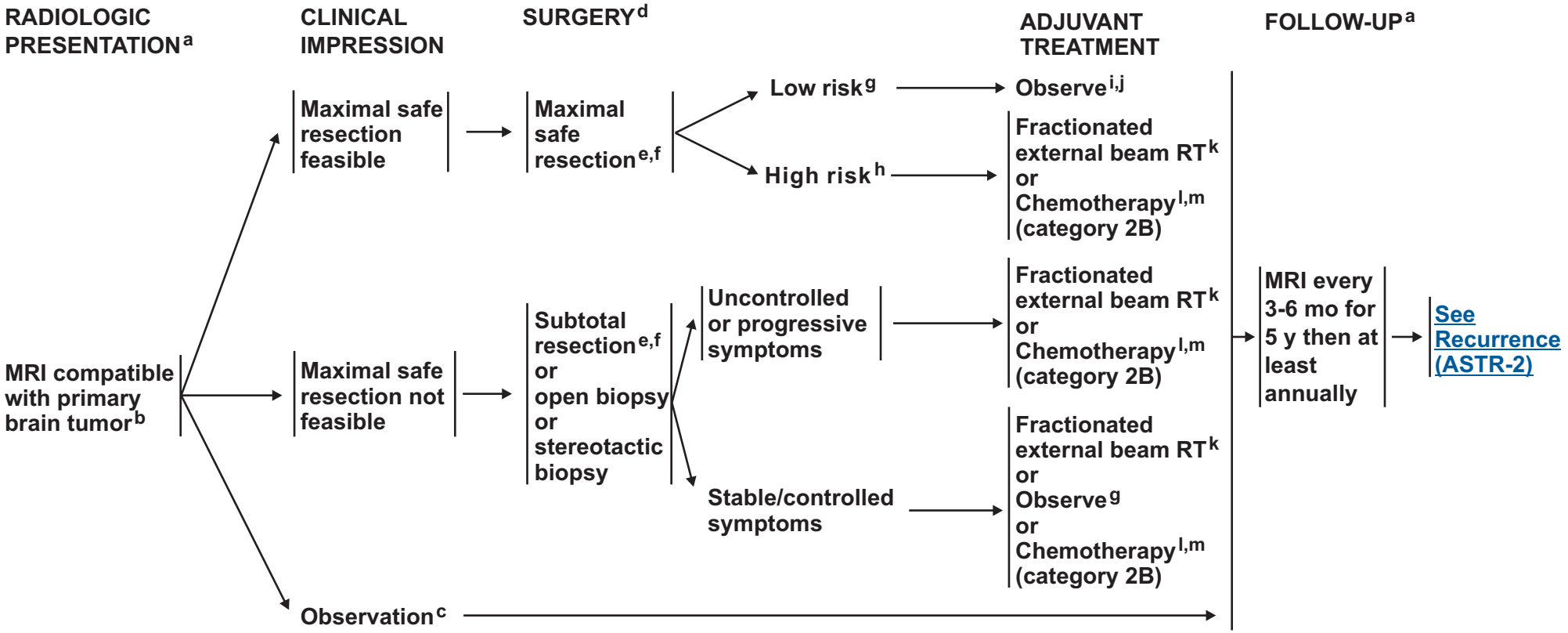

[a] See Principles of Brain Tumor Imaging (BRAIN-A).

[b] Consider a multidisciplinary review in treatment planning, especially once pathology is available (See Principles of Brain Tumor Management [BRAIN-E]).

[c] Surgery is generally recommended, but serial observations are appropriate for selected patients.

[d] See Principles of Brain Tumor Surgery (BRAIN-B).

[e] Consider testing for deletions in 1p19q if tumor has components of oligodendroglioma for prognostic purposes.

[f] Post-operative MRI should be done within 72 hours after surgery.

[g] Low-risk features: Oligodendroglioma or mixed oligoastrocytoma, ≤ 40 y, KPS ≥ 70, tumor dimension < 6 cm, minor or no neurological deficit, 1p and 19q codeleted, IDH1 or 2 mutated.

[h] High-risk features: 3 or more of: Astrocytoma, Age > 40 y, KPS < 70, tumor dimension > 6 cm, tumor crossing midline, preoperative neurological deficit of more than minor degree, one or no deletions on 1p and 19q, IDH1 or 2 not mutated.

[i] Regular follow-up is essential for patients receiving observation alone after resection.

[j] If gross total resection (GTR) is achieved, consider further observation.

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

[l] Oligodendrogliomas, particularly those that have chromosomal loss of combined 1p19q, have been reported to be sensitive to alkylator chemotherapy. Consider chemotherapy for these patients.

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

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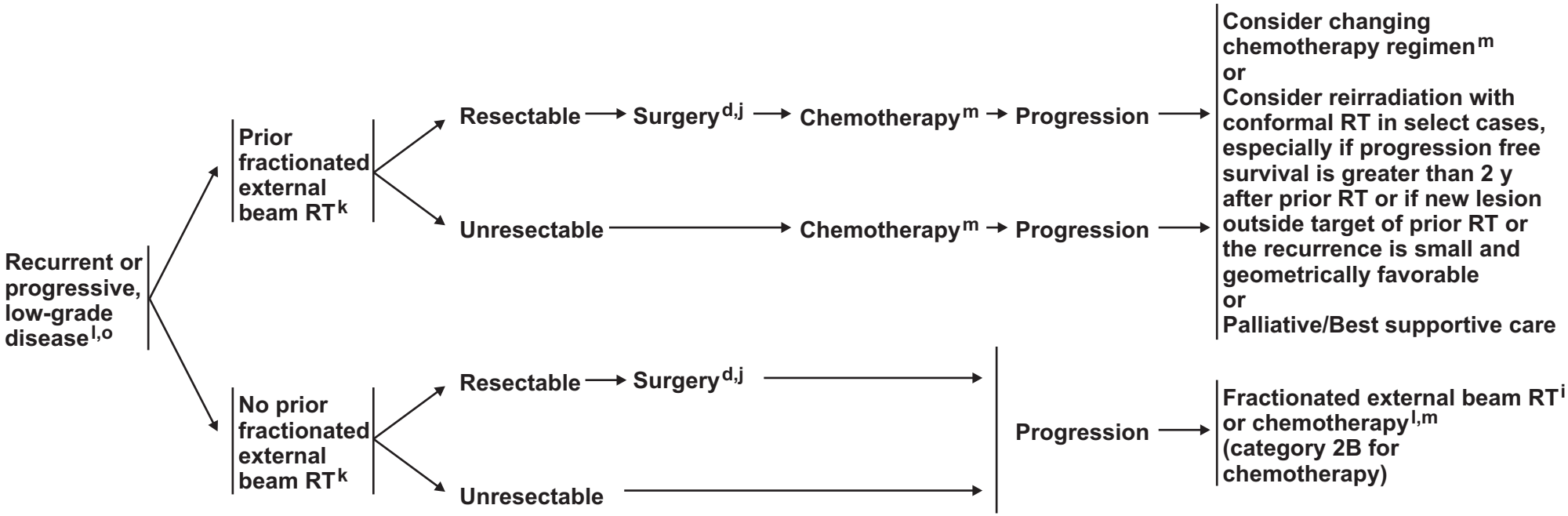
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

RECURRENCE[n]



[d] See Principles of Brain Tumor Surgery (BRAIN-B).

[j] If gross total resection (GTR) is achieved, consider further observation.

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

[l] Oligodendrogliomas, particularly those that have chromosomal loss of combined 1p19q, have been reported to be sensitive to alkylator chemotherapy. Consider chemotherapy for these patients.

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

[n] Recurrence on neuroimaging can be confounded by treatment effects. Strongly consider tumor tissue sampling if there is a high index of suspicion of recurrence.

[o] At recurrence, there is a high propensity for these tumors to undergo malignant transformation. Sixty percent or more of astrocytomas and 40%-50% of oligodendrogliomas will eventually undergo transformation to a higher grade. (Chaichana KL, McGirt MJ, Laterra J, et al. Recurrence and malignant degeneration after resection of adult hemispheric low-grade gliomas. J Neurosurg. 2010;112:10-17.)

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Anaplastic Gliomas/Glioblastoma[a]

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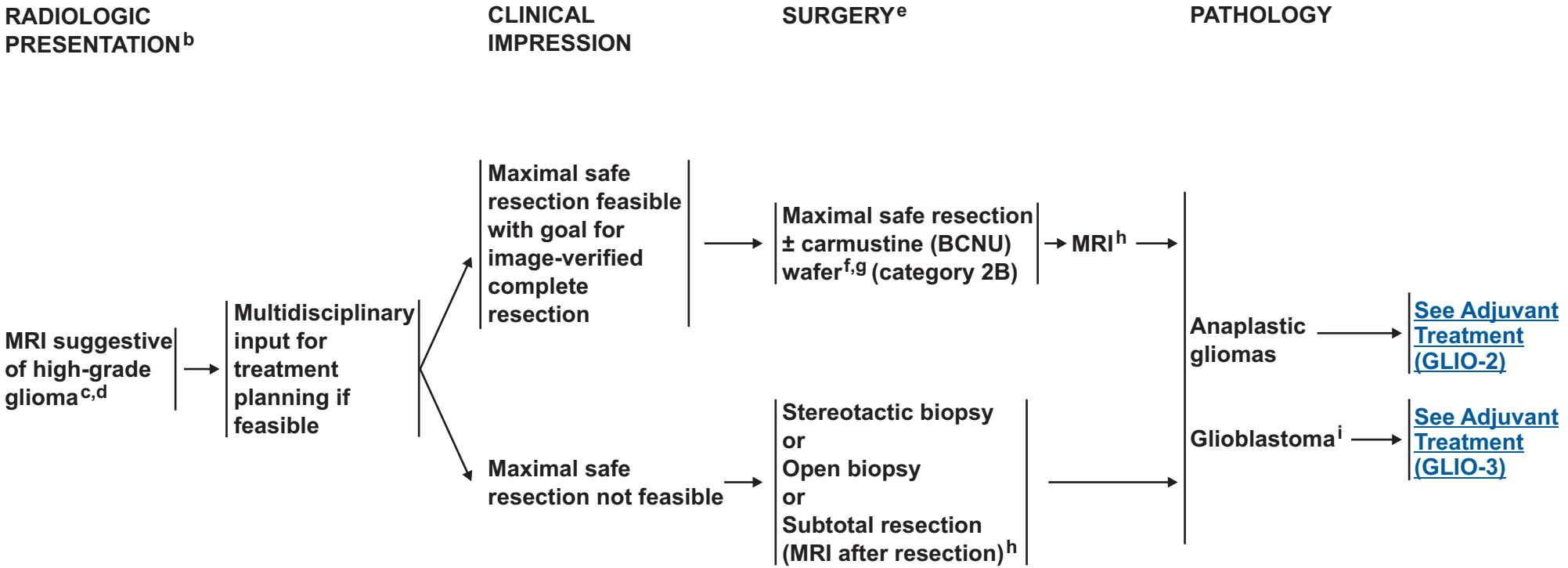

[a] This pathway includes the classification of mixed anaplastic oligoastrocytoma (AOA), anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), and other rare anaplastic gliomas.

[b] See Principles of Brain Tumor Imaging (BRAIN-A).

[c] Biopsy first if MRI compatible with CNS lymphoma.

[d] Consider a multidisciplinary review in treatment planning, especially once pathology is available (See Principles of Brain Tumor Management [BRAIN-E]).

[e] See Principles of Brain Tumor Surgery (BRAIN-B).

[f] If frozen section diagnosis supports high-grade glioma.

[g] Treatment with carmustine wafer may impact enrollment in some adjuvant clinical trials.

[h] Post-operative MRI should be done within 72 hours after surgery.

[i] This pathway also includes gliosarcoma.

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Anaplastic Gliomas/Glioblastoma[a]

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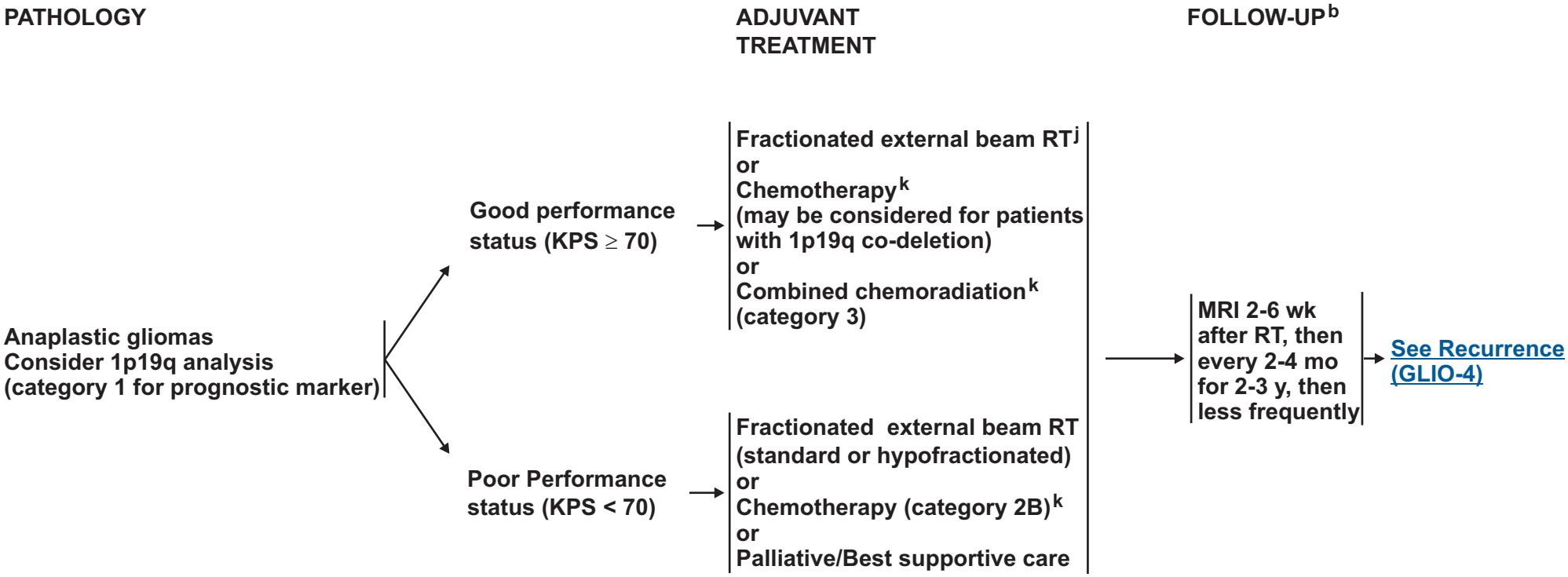

[a] This pathway includes the classification of mixed anaplastic oligoastrocytoma (AOA), anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), and other rare anaplastic gliomas.

[b] See Principles of Brain Tumor Imaging (BRAIN-A).

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

[k] See Principles of Brain Tumor Systemic Therapy (BRAIN-D).

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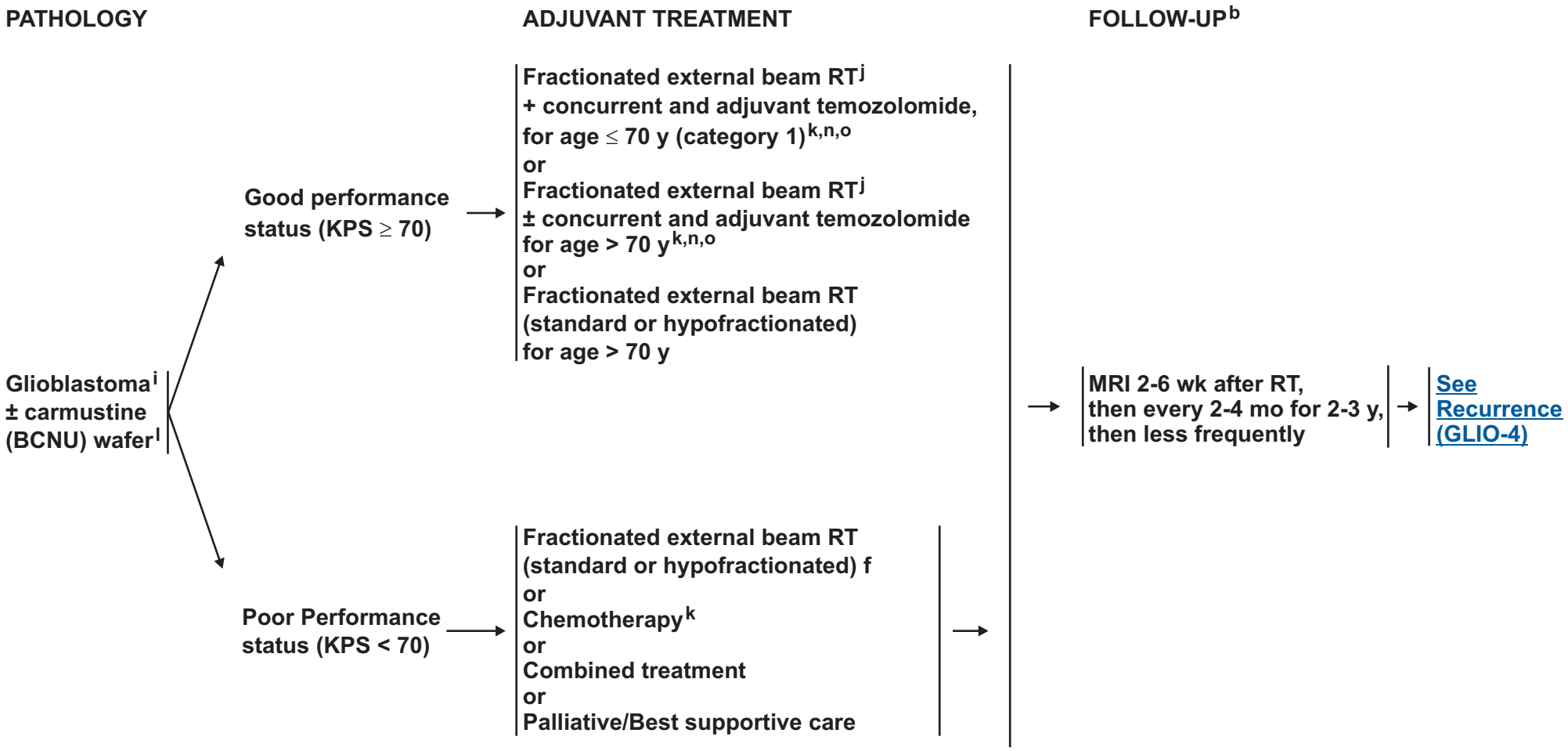

[a] This pathway includes the classification of mixed anaplastic oligoastrocytoma (AOA), anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), and other rare anaplastic gliomas.

[b] See Principles of Brain Tumor Imaging (BRAIN-A).

[i] This pathway also includes gliosarcoma.

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

[k] See Principles of Brain Tumor Systemic Therapy (BRAIN-D).

[l] Treatment with carmustine wafer, reirradiation, or multiple prior systemic therapies, may impact enrollment in some adjuvant clinical trials.

[m] Combination of agents may lead to increased toxicity or radiographic changes.

[n] Stupp R, Mason WP, van den Bent MJ et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352:987-996.

[o] Duration of treatment for glioblastomas beyond 6 months is unknown. Duration of therapy for anaplastic astrocytoma is unknown.

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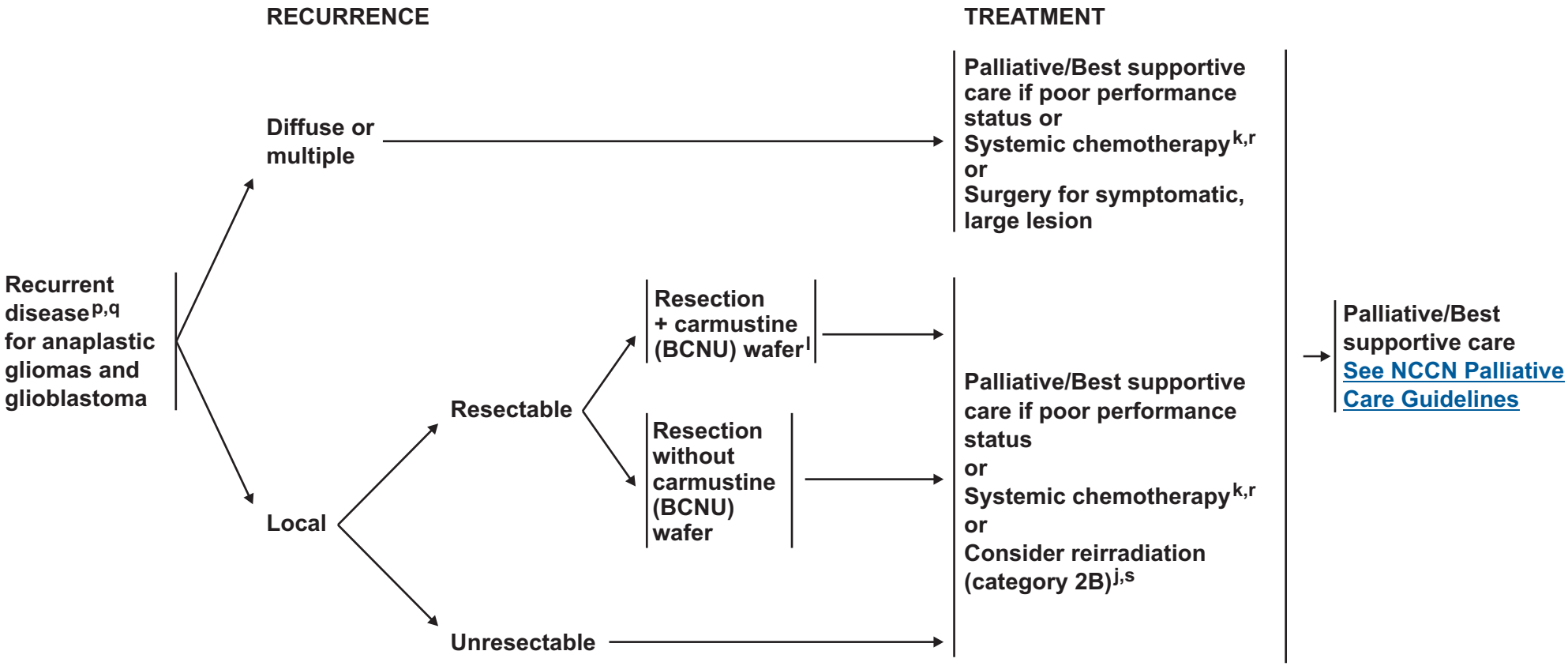

[a] This pathway includes the classification of mixed anaplastic oligoastrocytoma (AOA), anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), and other rare anaplastic gliomas.

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

[k] See Principles of Brain Tumor Systemic Therapy (BRAIN-D).

[l] Treatment with carmustine wafer, reirradiation, or multiple prior systemic therapies, may impact enrollment in some adjuvant clinical trials.

[p] Consider MR spectroscopy, MR perfusion, or brain PET to rule out radiation necrosis.

[q] Within the first 3 months after completion of RT and concomitant temozolomide, diagnosis of recurrence can be indistinguishable from pseudoprogression on neuroimaging. With pseudoprogression, stabilization or improvement should be expected within 3 mo of the end of radiotherapy.

[r] Anaplastic oligodendrogliomas have been reported to be especially sensitive to chemotherapy. Chemotherapy using temozolomide or nitrosourea-based regimens may be appropriate.

[s] Especially if long interval since prior RT and/or if there was a good response to prior RT.

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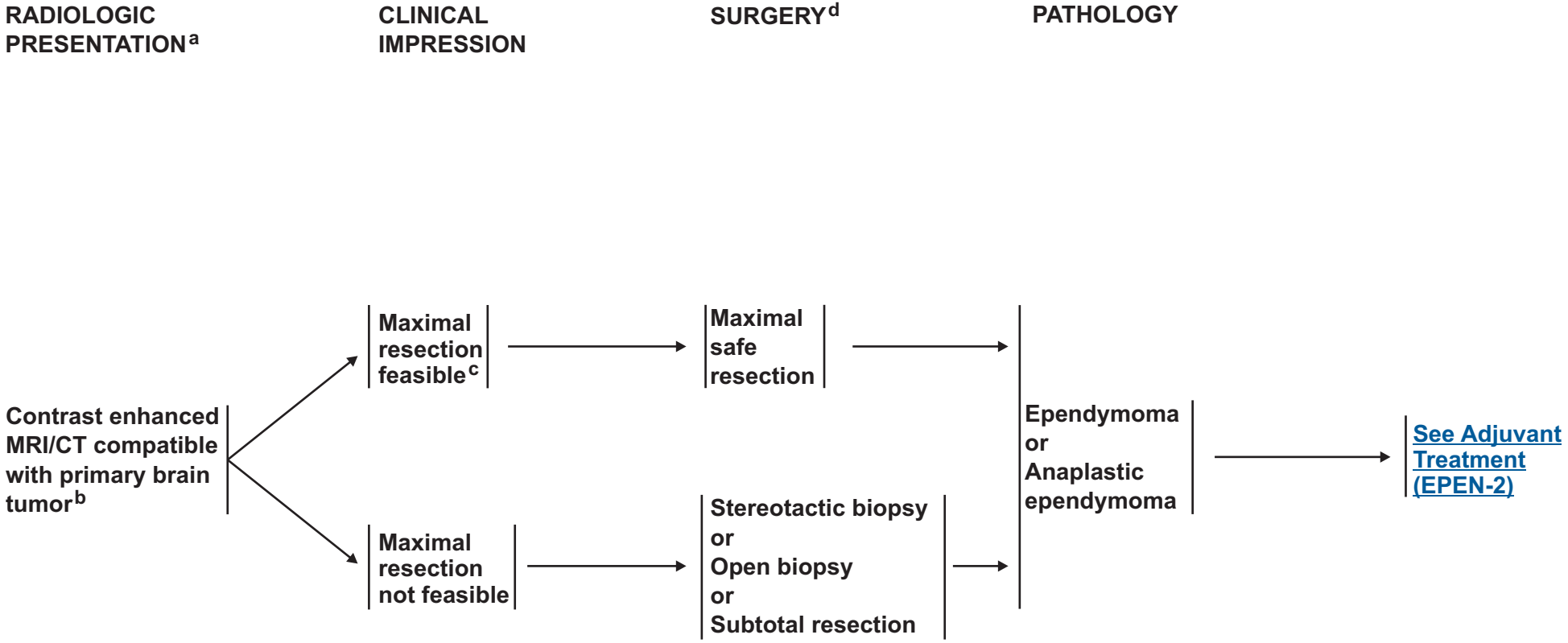

[a] See Principles of Brain Tumor Imaging (BRAIN-A).
[b] Consider a multidisciplinary review in treatment planning, especially once pathology is available (See Principles of Brain Tumor Management [BRAIN-E]).
[c] If image-confirmed GTR not achieved, consider multidisciplinary review and reresection.
[d] See Principles of Brain Tumor Surgery (BRAIN-B).

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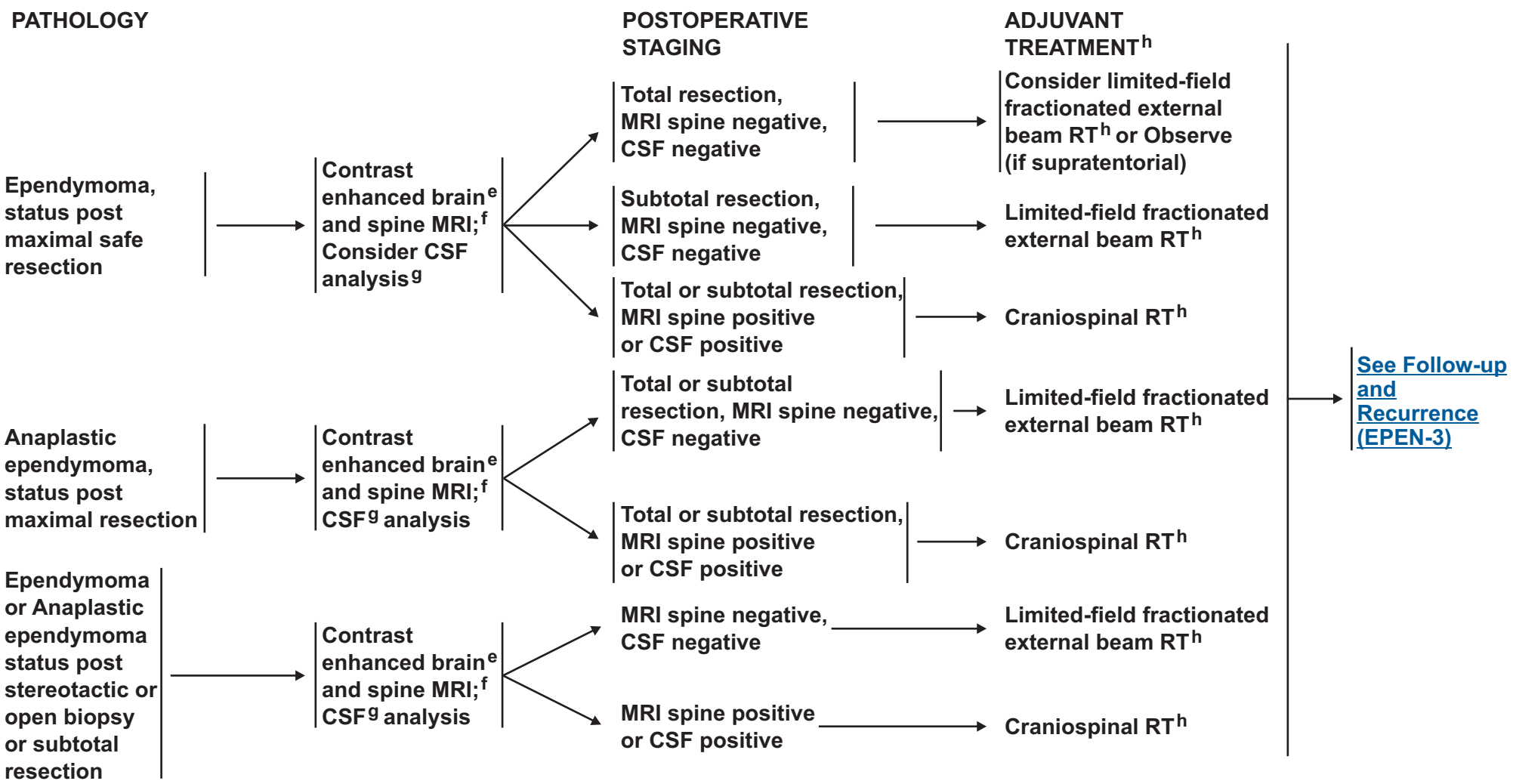

[e]Within 24-72 hours.

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

[g]If MRI spine negative, then lumbar puncture should be done after MRI. 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).

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

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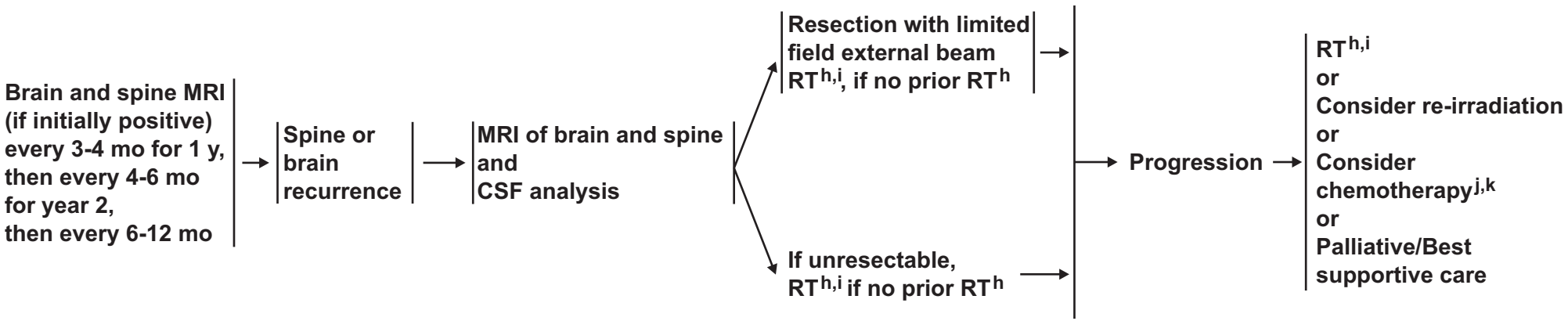

[a] See Principles of Brain Tumor Imaging (BRAIN-A).
[h] See Principles of Brain Tumor Radiation Therapy (BRAIN-C).
[i] Consider stereotactic radiosurgery (SRS) if geometrically favorable.
[j] Chemotherapy should be reserved for patients who are refractory to surgery or radiation.
[k] See Principles of Brain Tumor Systemic Therapy (BRAIN-D).

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NCCN Guidelines Version 2.2012
Adult Medulloblastoma and Supratentorial PNET[a]

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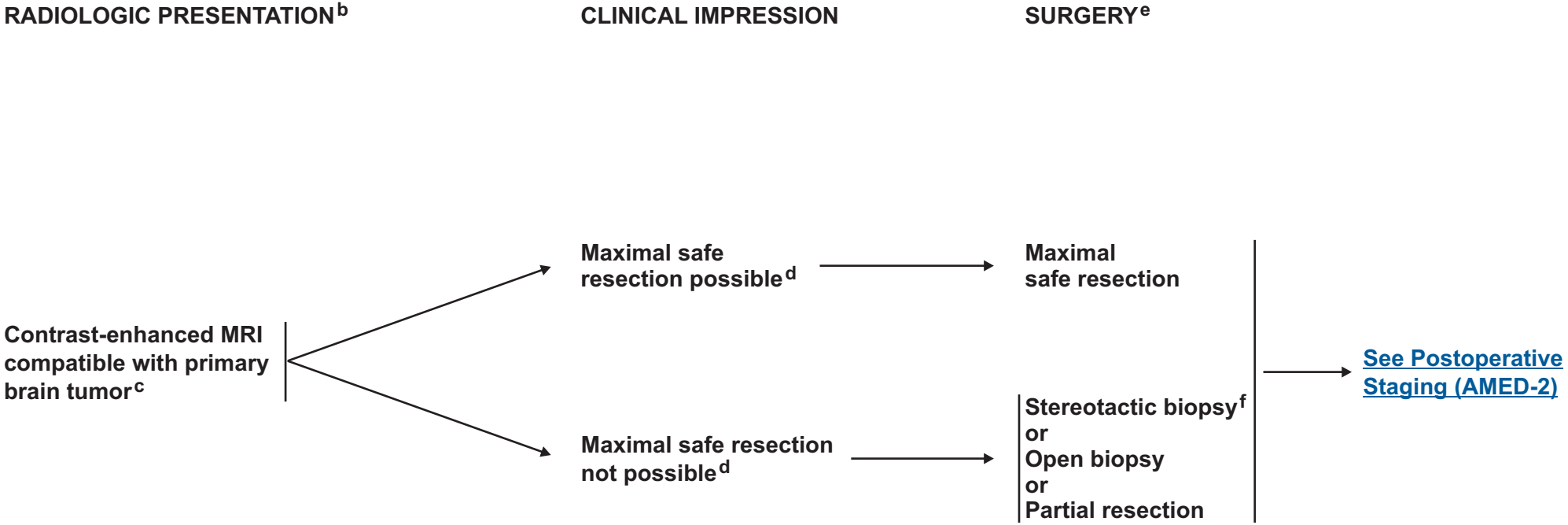

[a] Excluding esthesioneuroblastoma.
[b] See Principles of Brain Tumor Imaging (BRAIN-A).
[c] Consider a multidisciplinary review in treatment planning, before surgery and once pathology is available (See Principles of Brain Tumor Management [BRAIN-E]).
[d] Placement of ventriculoperitoneal (VP) shunt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

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

NCCN Guidelines Version 2.2012
Adult Medulloblastoma and Supratentorial PNET[a]

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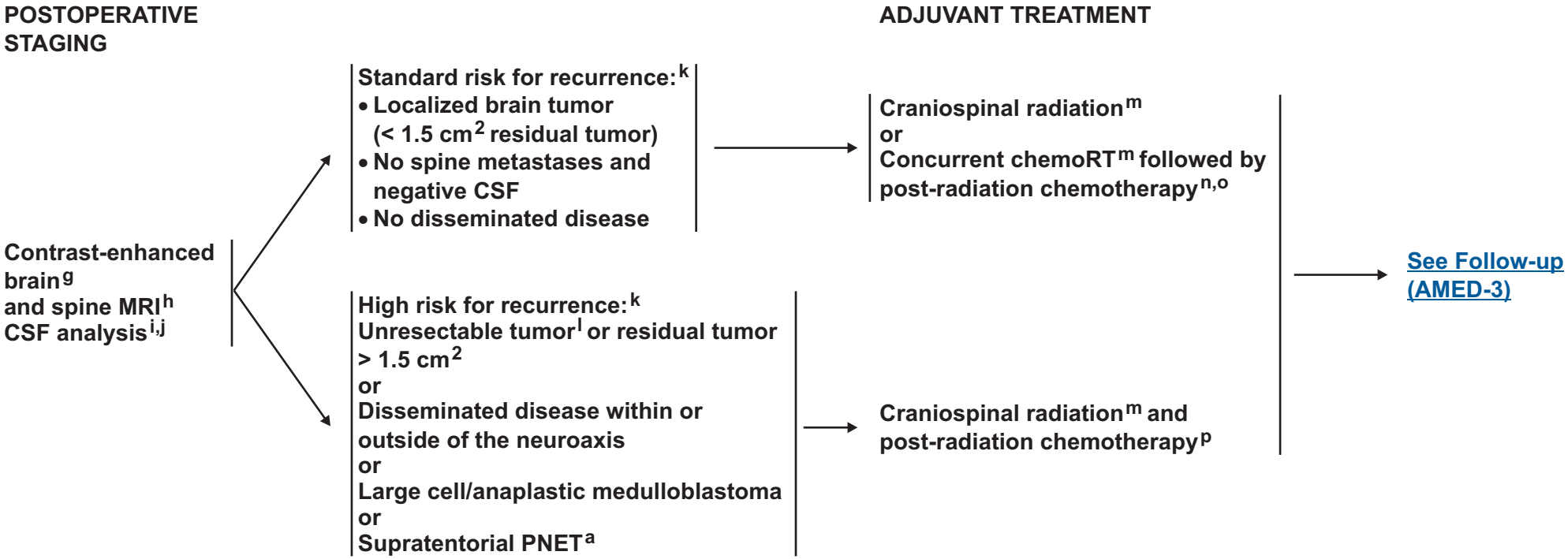

[a] Excluding esthesioneuroblastoma.

[g] Within 24-72 hours.

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

[i] 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.

[j] Bone scan, CT scans of chest, abdomen and pelvis and bone marrow biopsy only if clinically indicated.

[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 pre-irradiation chemotherapy followed by an attempt at resection.

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

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

[o] 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. 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.

[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 o.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

NCCN Guidelines Version 2.2012
Adult Medulloblastoma and Supratentorial PNET[a]

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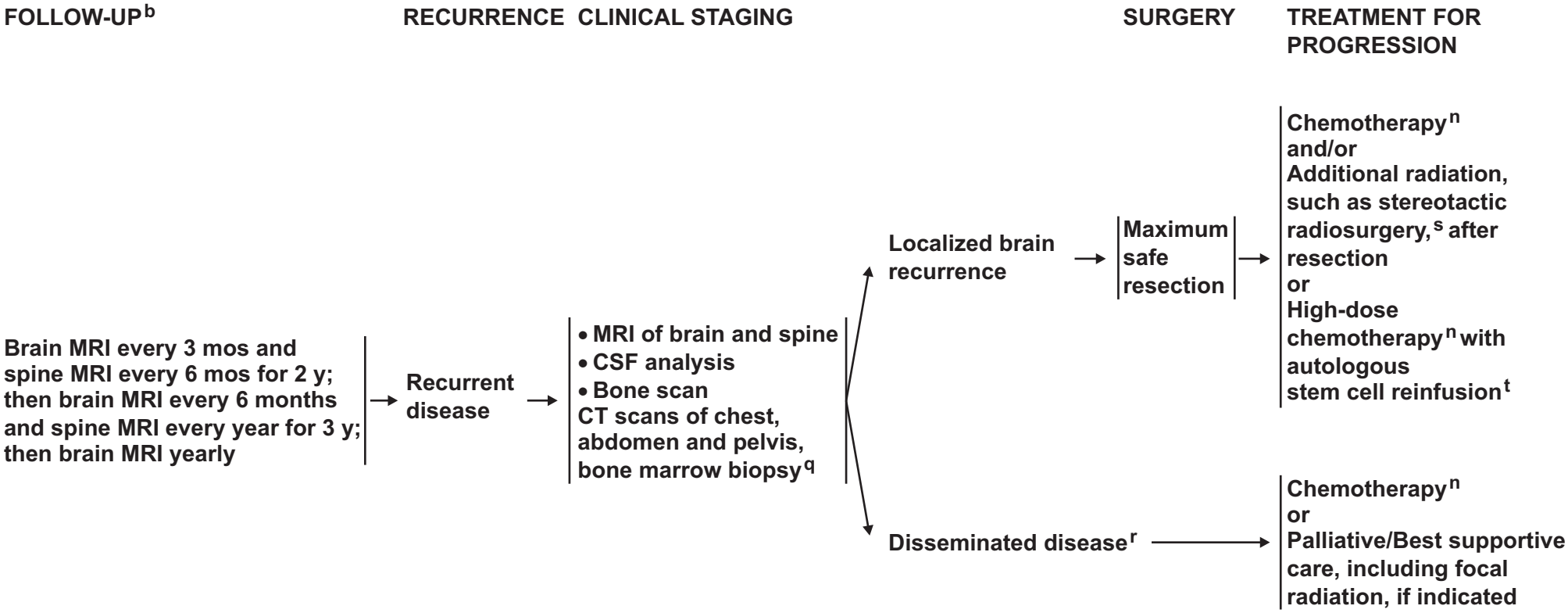

[a] Excluding esthesioneuroblastoma.

[b] See Principles of Brain Tumor Imaging (BRAIN-A).

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

[q] If clinically indicated. If patient was treated with radiation only at diagnosis, then a bone scan should be part of restaging imaging at time of recurrence, even if patient is asymptomatic.

[r] Consider resection for palliation of symptoms where indicated.

[s] Germanwala AV, Mai JC, Tomycz ND, et al. Boost gamma knife during multimodality management of adult medulloblastoma J of Neurosurgery 2008;108:204-209 (Pittsburgh group) and Hodgson DC, Goumnerova LC, Loeffler JS, et al. Radiosurgery in the management of pediatric brain tumors. Int J Radiat Oncol Biol Phys 2001;50:929-935.

[t] Only if the patient is without evidence of disease after surgery or conventional dose re-induction chemotherapy.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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Primary CNS Lymphoma[a]

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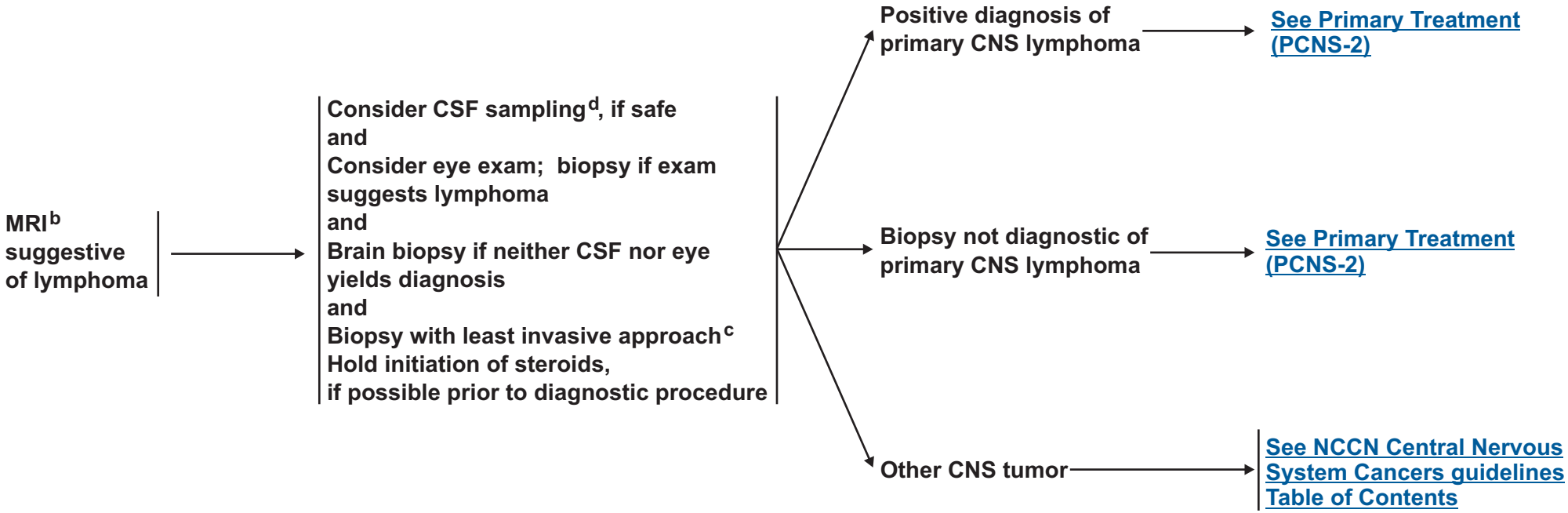
DIAGNOSIS BY TISSUE EVALUATION



[a] If patient is HIV positive, consider highly active antiretroviral therapy.
[b] Contrast CT, if patient cannot have MRI.
[c] If stereotatic biopsy is not available refer to a specialized center.
[d] Tissue sampling and CSF should include flow cytometry, CSF cytology, and may consider gene rearrangements.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

NCCN Guidelines Version 2.2012
Primary CNS Lymphoma[a]

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STAGING EVALUATION/WORKUP

Positive diagnosis of primary CNS lymphoma[e] →

Initiate steroids
- **Slit lamp eye exam**
- **Lumbar puncture (LP)[f] if safe**
- **Spine MRI, if symptomatic or positive CSF**
- **HIV[a]**
- **CBC, Comprehensive chemistry profile**
- **CT chest/abdomen/pelvis**
- **Bone marrow biopsy[g] (category 2B)**
- **Consider testicular ultrasound for men > 60 y (category 2B)**
- **Consider body FDG-PET scan[h,i] (category 2B)**

PRIMARY TREATMENT

KPS ≥ 40[j] →

High-dose methotrexate-based regimen[k,l] ± WBRT[m,n] after completion of chemotherapy
- **If CSF positive or spinal MRI positive, consider intra-CSF chemotherapy (category 2B)**
- **If eye exam positive, RT[o] to globe or intraocular chemotherapy (category 2B)**

KPS < 40[j] despite treatment with corticosteroids →

WBRT[o]
- **If eye exam positive, RT to globe**
- **If LP positive or spinal MRI positive, consider intrathecal chemotherapy[l] + focal spinal RT**

or

Chemotherapy[l,p]

Biopsy not diagnostic of primary CNS lymphoma

Prior steroids → **Discontinue steroids and rebiopsy when disease progresses**

No prior steroids → **Work-up for other CNS diagnosis or rebiopsy**

[a] If patient is HIV positive, consider highly active antiretroviral therapy.
[e] May institute primary therapy and workup simultaneously.
[f] Caution is indicated in patients who are anticoagulated, thrombocytopenic, or who have a bulky intra-cranial mass.
[g] Some institutions do bone marrow biopsy, however, evidence is lacking.
[h] Body PET scan may replace CT, bone marrow, and testicular ultrasound, but data for its use in Primary CNS lymphoma (PCNSL) is lacking.
[i] For full primary CNS lymphoma staging guidelines, 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.
[j] KPS may improve dramatically with steroids. Reassess KPS after initial course of steroids for potential change in therapy.
[k] Dose adjusted for GFR.
[l] See Principles of Brain Tumor Systemic Therapy (BRAIN-D).
[m] WBRT may increase toxicity, especially in patients > 60 y and may be withheld in the primary setting.
[n] If eye exam positive, monitor carefully for response to treatment. Consider RT to orbits or intraocular chemotherapy.
[o] See Principles of Brain Tumor Radiation Therapy (BRAIN-C).
[p] Consider alternate chemotherapy regimens for patients who cannot tolerate methotrexate.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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Primary CNS Lymphoma[a]

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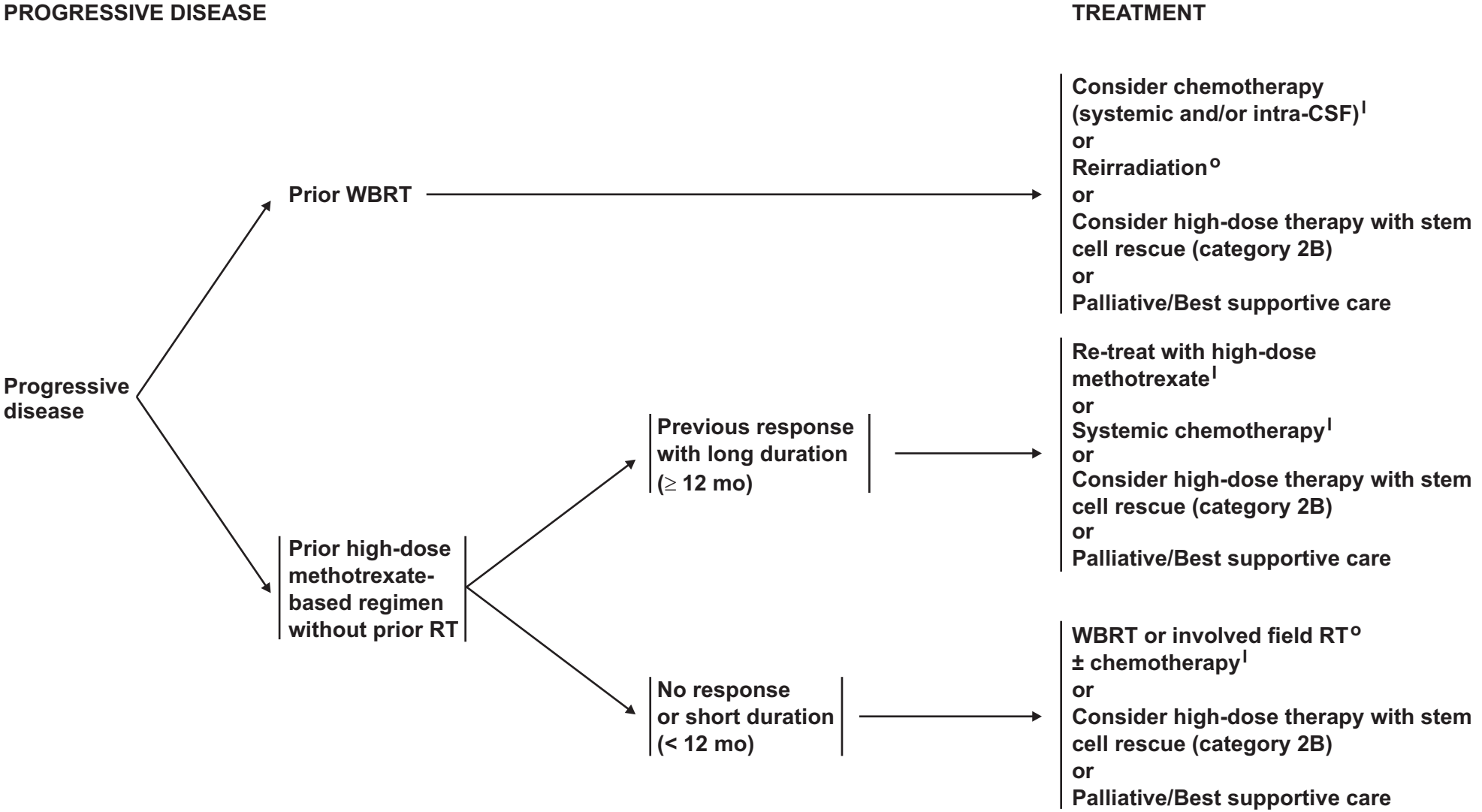

[a] If patient is HIV positive, consider highly active antiretroviral therapy.
[l] See Principles of Brain Tumor Systemic Therapy (BRAIN-D).
[o] See Principles of Brain Tumor Radiation Therapy (BRAIN-C).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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Primary Spinal Cord Tumors

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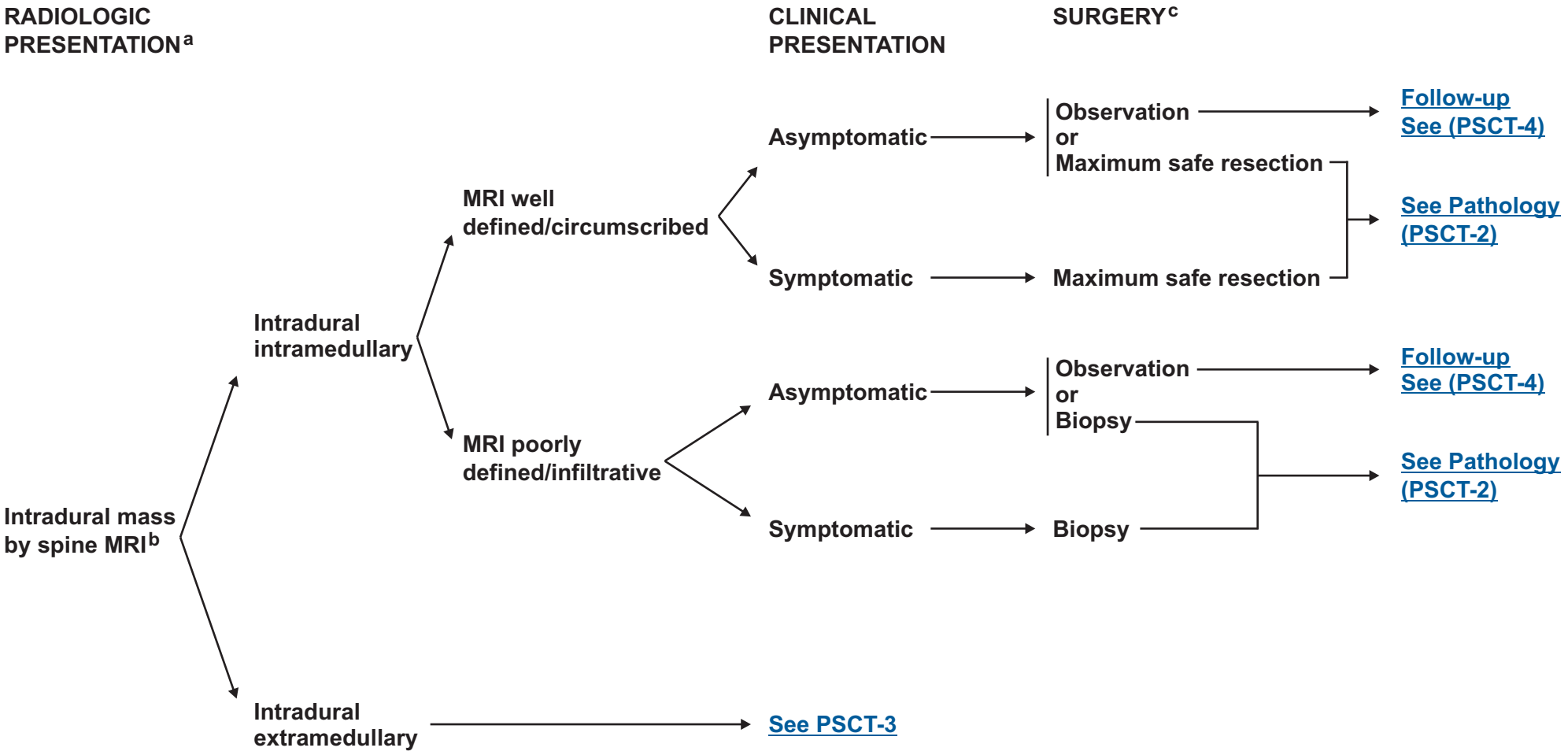

[a] See Principles of Brain Tumor Imaging (BRAIN-A).
[b] Consider a multidisciplinary review in treatment planning, before surgery and once pathology is available (See Principles of Brain Tumor Management [BRAIN-E]).
[c] See Principles of Brain Tumor Surgery (BRAIN-B).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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Primary Spinal Cord Tumors

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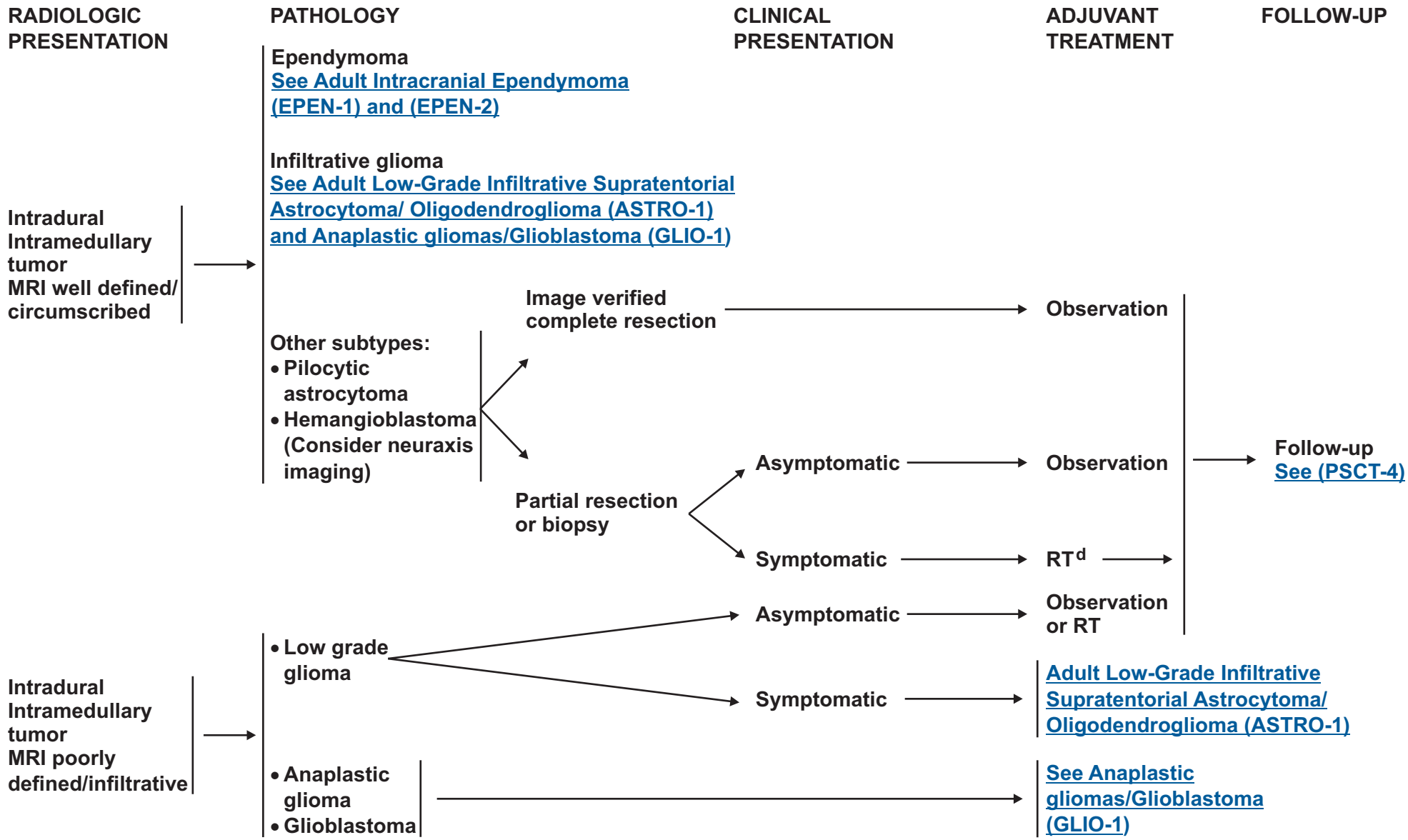
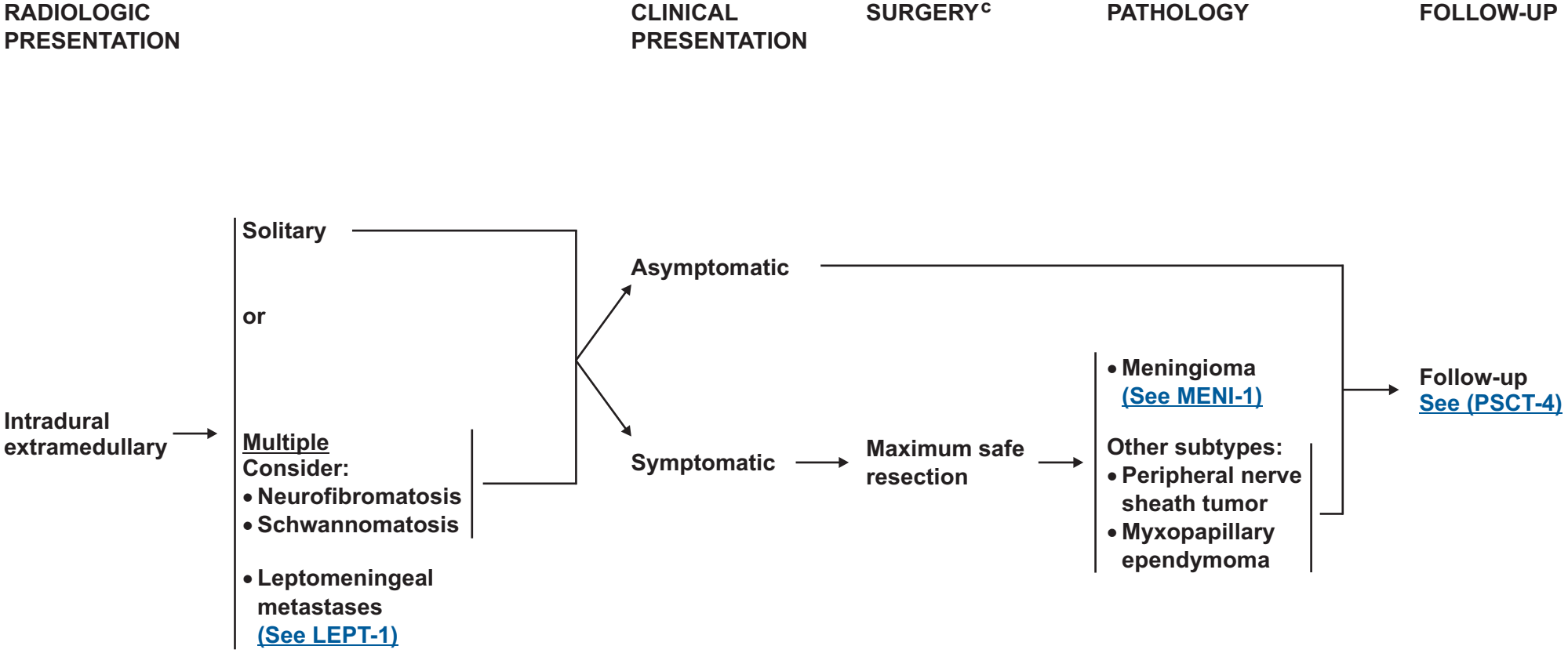


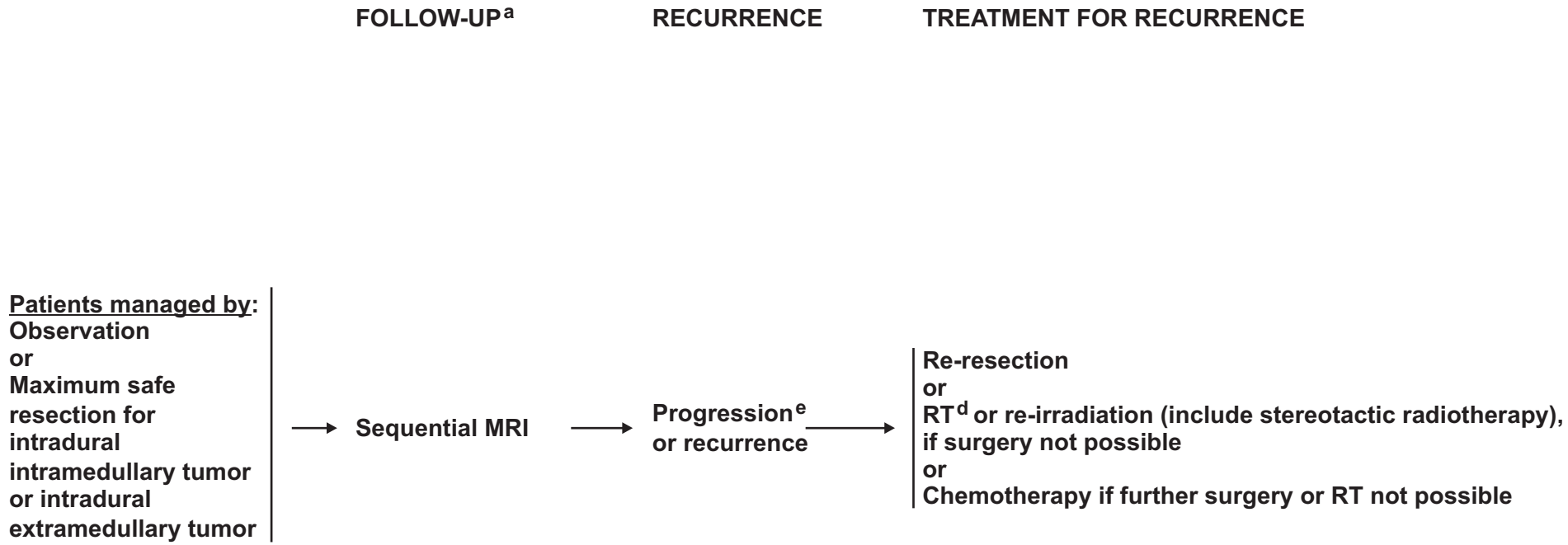
[d] See Principles of Brain Tumor Radiation Therapy (BRAIN-C).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



[c] See Principles of Brain Tumor Surgery (BRAIN-B).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



[a] See Principles of Brain Tumor Imaging (BRAIN-A).
[d] See Principles of Brain Tumor Radiation Therapy (BRAIN-C).
[e] New or worsening symptoms or radiographic progression.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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NCCN Guidelines Version 2.2012
Meningiomas

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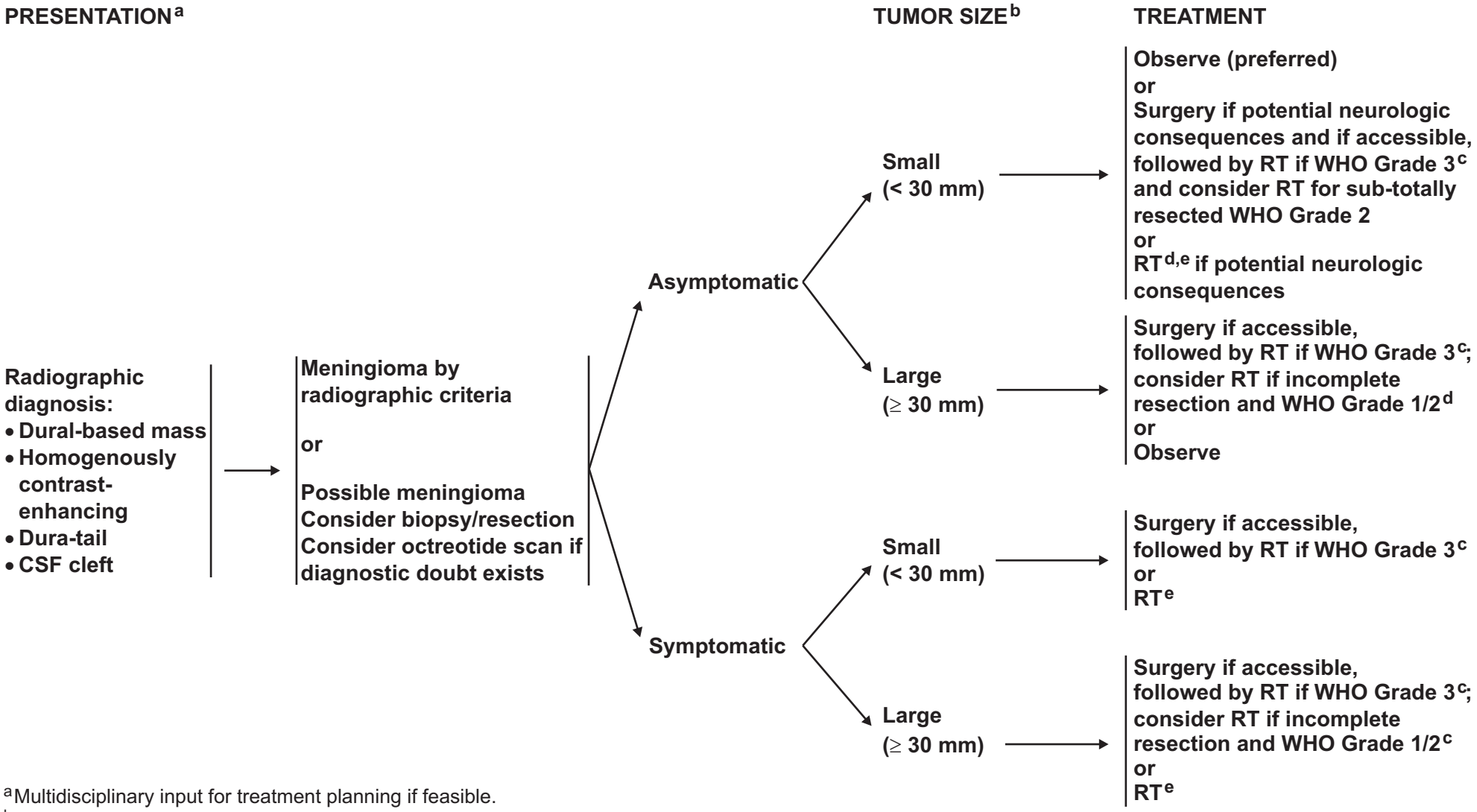
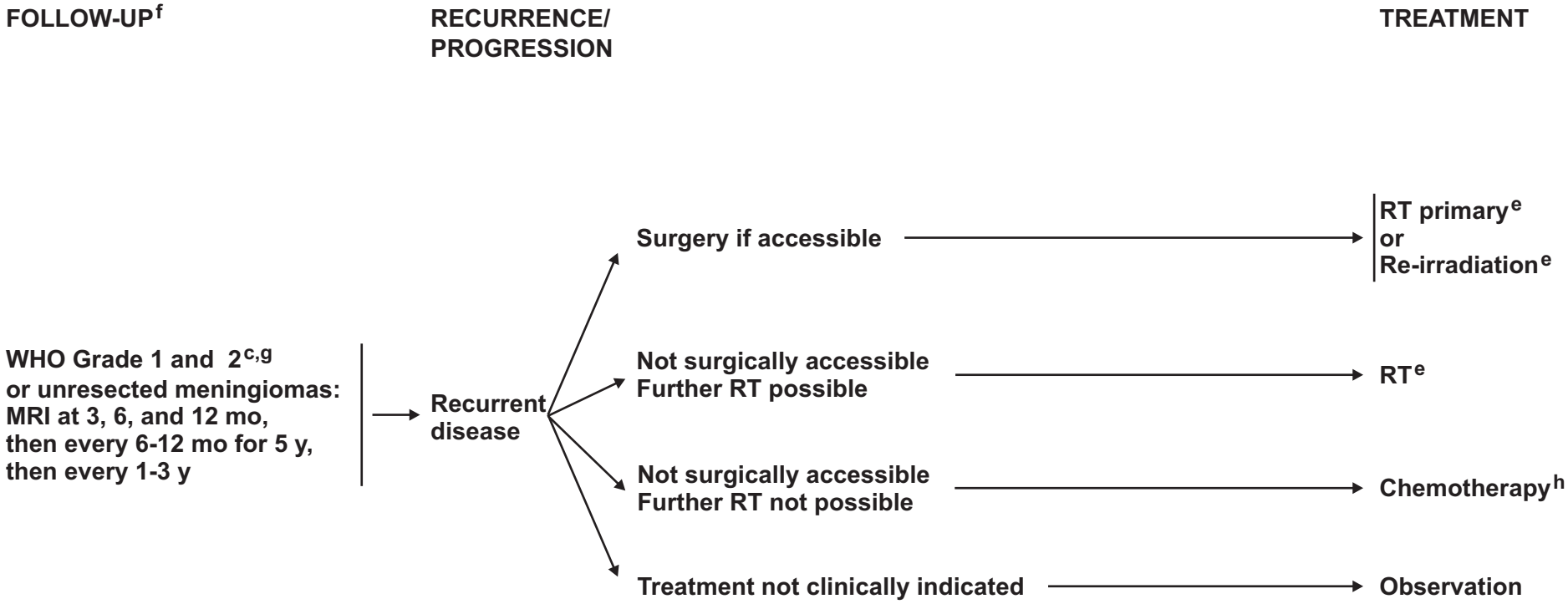


[a] Multidisciplinary input for treatment planning if feasible.
[b] The median growth rate for meningiomas is 4mm per annum.
[c] WHO Grade 1 = Benign meningioma, WHO Grade 2 = Atypical meningioma, WHO Grade 3 = Malignant (anaplastic) meningioma
[d] RT can be either external-beam or stereotactic radiosurgery (SRS).
[e] See Principles of Brain Tumor Radiation Therapy (BRAIN-C).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



[c]WHO Grade 1 = Benign meningioma, WHO Grade 2 = Atypical meningioma, WHO Grade 3 = Malignant (anaplastic) meningioma

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

[f]Less frequent follow-up after 5-10 y.

[g]More frequent imaging may be required for WHO Grade 3 meningiomas, and for meningioma of any grade that are treated for recurrence or with chemotherapy.

[h]See Principles of Brain Tumor Systemic Therapy (BRAIN-D).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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NCCN Guidelines Version 2.2012
Limited (1-3) Metastatic Lesions

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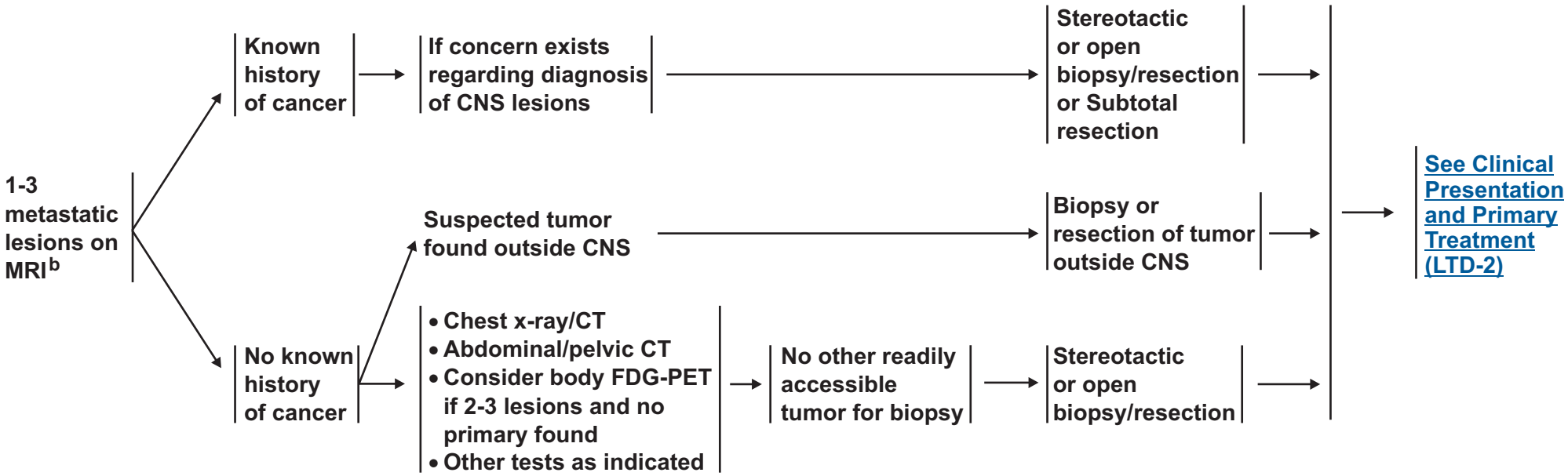
CLINICAL PRESENTATION[a]

WORKUP



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

[b] Consider a multidisciplinary review in treatment planning, especially once pathology is available (See Principles of Brain Tumor Management [BRAIN-E]).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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Limited (1-3) Metastatic Lesions

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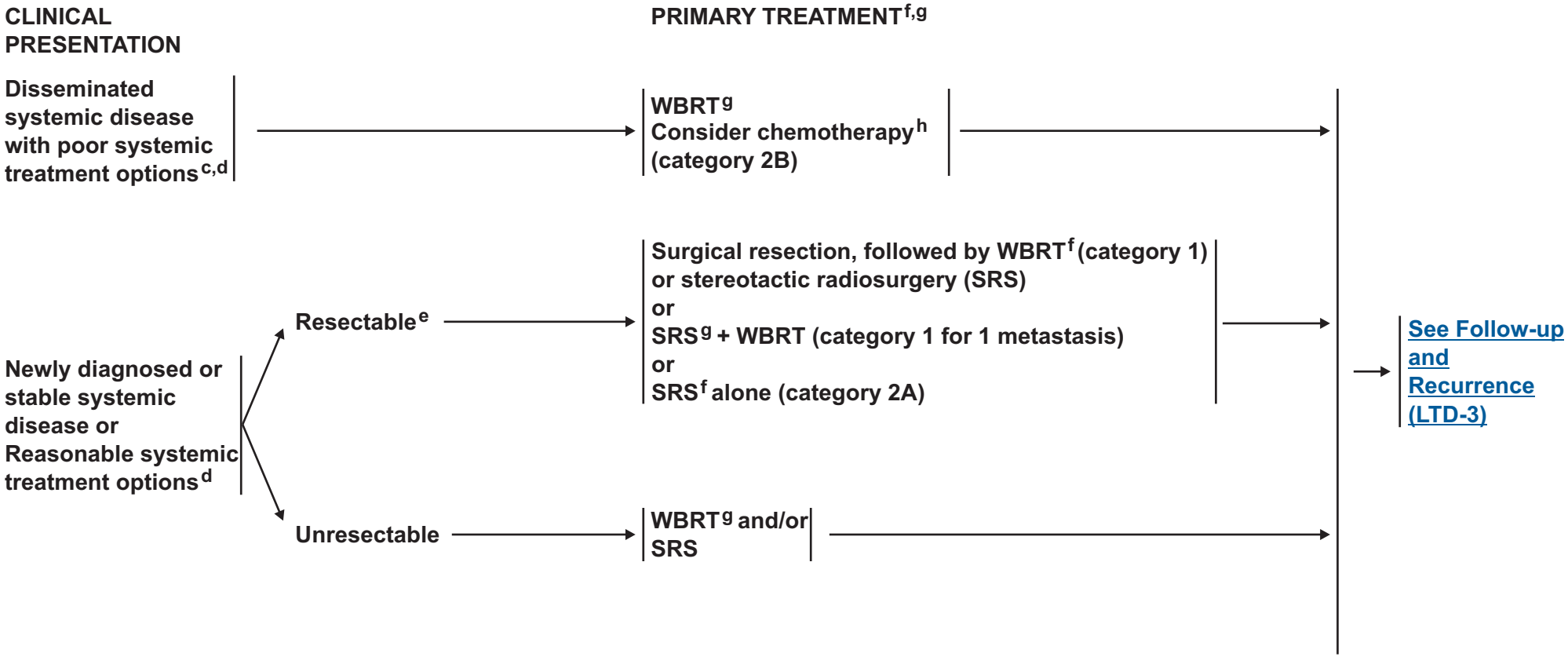

[c] Consider surgery to relieve mass effect.

[d] Solid brain metastases with systemic non-primary CNS lymphoma are not well defined, but treatment may include systemic treatment, whole-brain radiotherapy, or focal RT.

[e] The decision to resect a tumor may depend upon the need to establish histologic diagnosis, the size of the lesion, its location, and institutional expertise. For example, smaller (< 2cm), 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.)

[f] See Principles of Brain Tumor Surgery (BRAIN-B).

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

[h] Chemotherapy may be considered in select patients (eg, patients who have asymptomatic brain metastases that are otherwise small and who have not had prior chemotherapy). Treatment as per the regimens of the primary tumor.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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Limited (1-3) Metastatic Lesions

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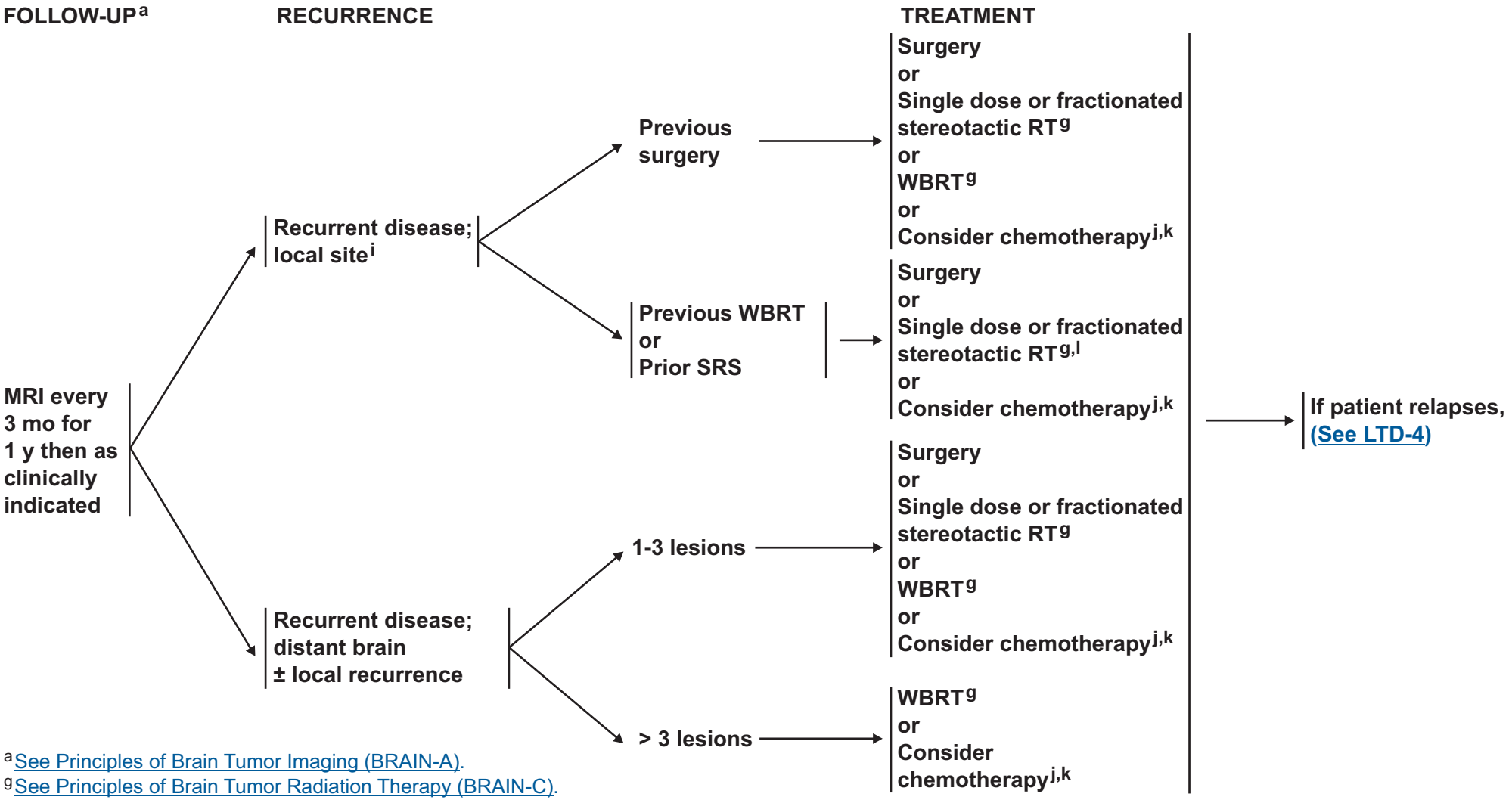
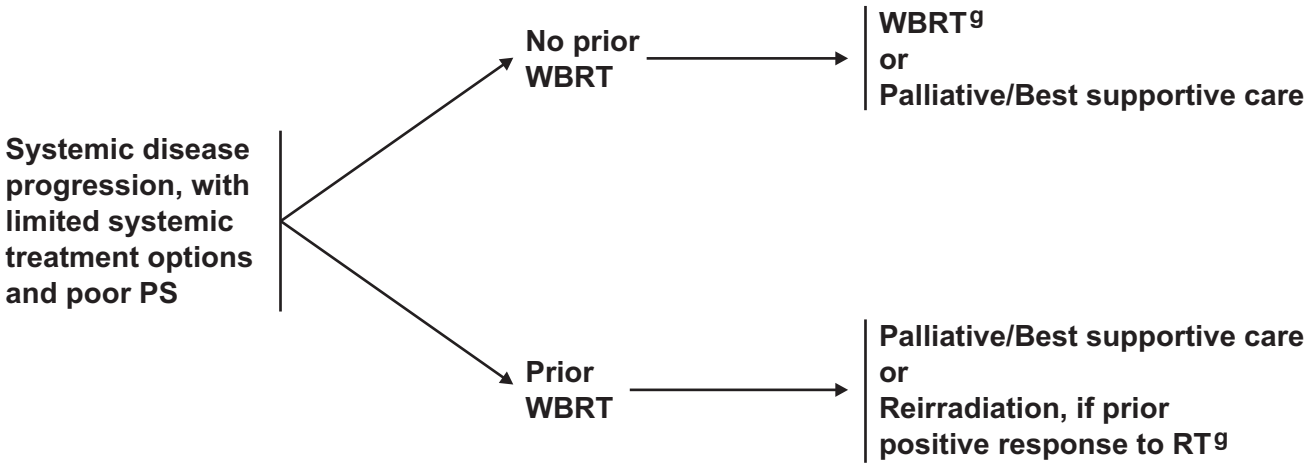


[a] See Principles of Brain Tumor Imaging (BRAIN-A).
[g] See Principles of Brain Tumor Radiation Therapy (BRAIN-C).
[i] After stereotactic radiosurgery, recurrence on radiograph can be confounded by treatment effects, consider tumor tissue sampling if there is a high index of suspicion of recurrence.
[j] See Principles of Brain Tumor Systemic Therapy (BRAIN-D).
[k] Local or systemic chemotherapy.
[l] If patient had previous SRS with a good response > 6 mo, then reconsider SRS if imaging supports active tumor and not necrosis.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

RECURRENCE | **TREATMENT**



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

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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Multiple (>3) Metastatic Lesions

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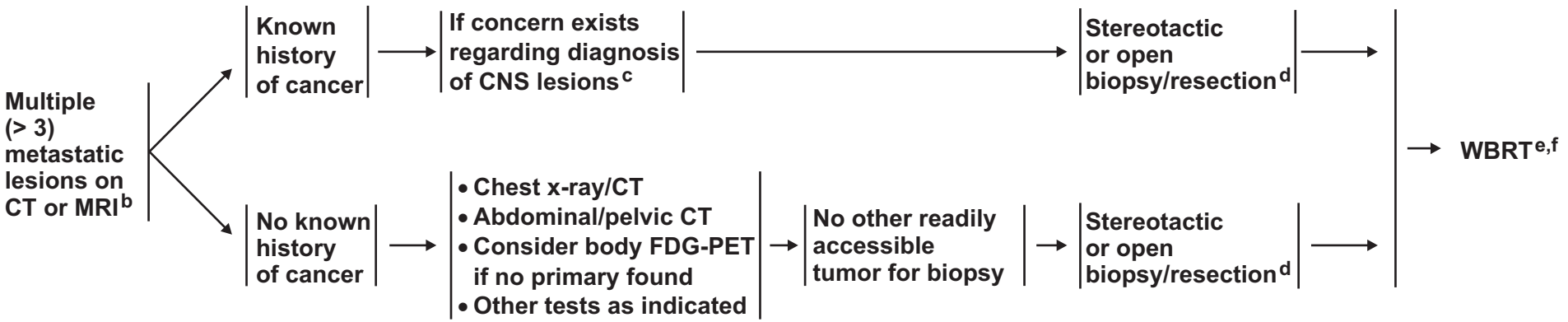

[a] See Principles of Brain Tumor Imaging (BRAIN-A).
[b] Consider a multidisciplinary review in treatment planning, especially once pathology is available (See Principles of Brain Tumor Management [BRAIN-E]).
[c] As part of diagnostic evaluation, neuroimaging modalities such as MRI, DW-MRI, MRI-SPECT, or PET scan may be considered.
[d] Consider surgery to relieve mass effect.
[e] See Principles of Brain Tumor Radiation Therapy (BRAIN-C).
[f] SRS should only be considered in selected cases (eg, limited number of lesions).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

See Follow-up and Recurrence (MU-2)

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Multiple (>3) Metastatic Lesions

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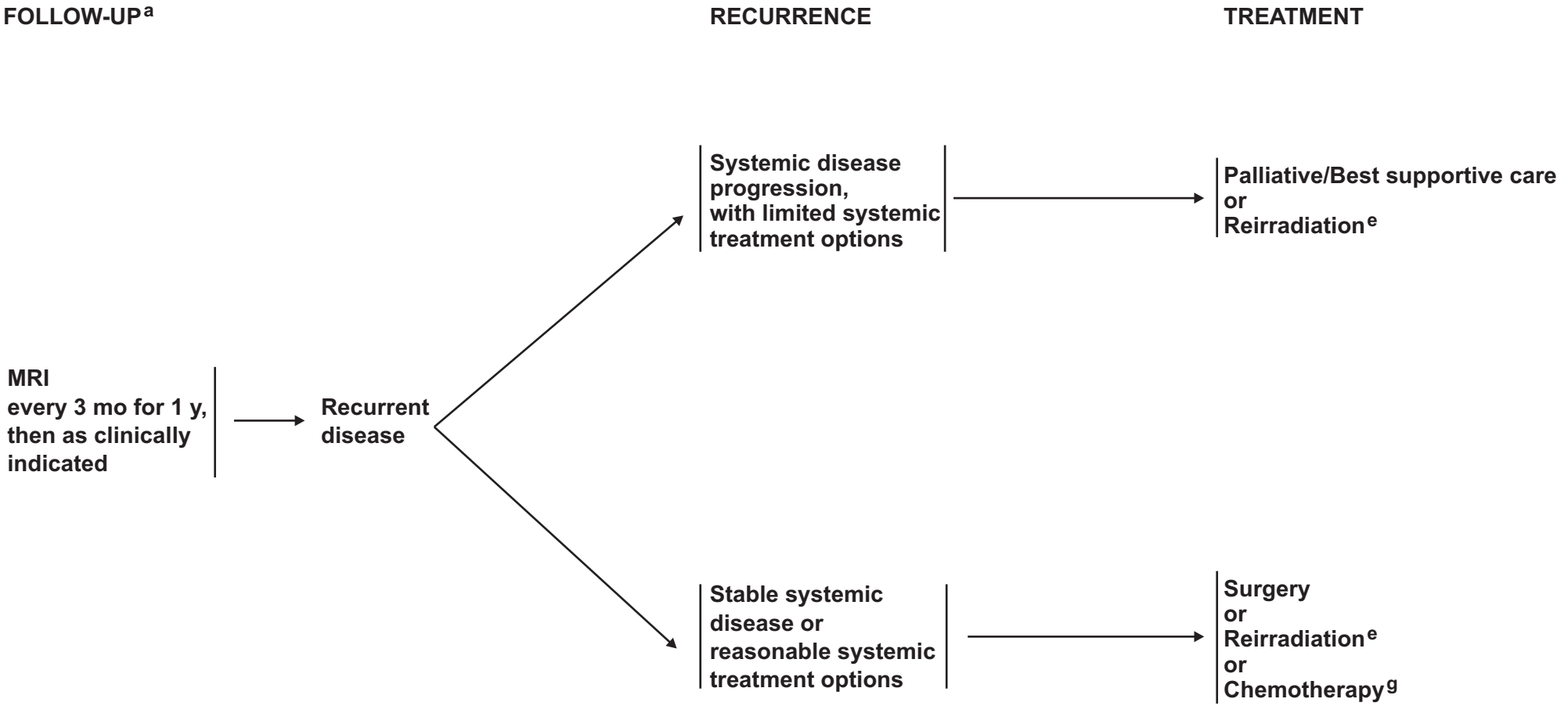

[a] See Principles of Brain Tumor Imaging (BRAIN-A).
[e] See Principles of Brain Tumor Radiation Therapy (BRAIN-C).
[g] See Principles of Brain Tumor Systemic Therapy (BRAIN-D).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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Leptomeningeal Metastases

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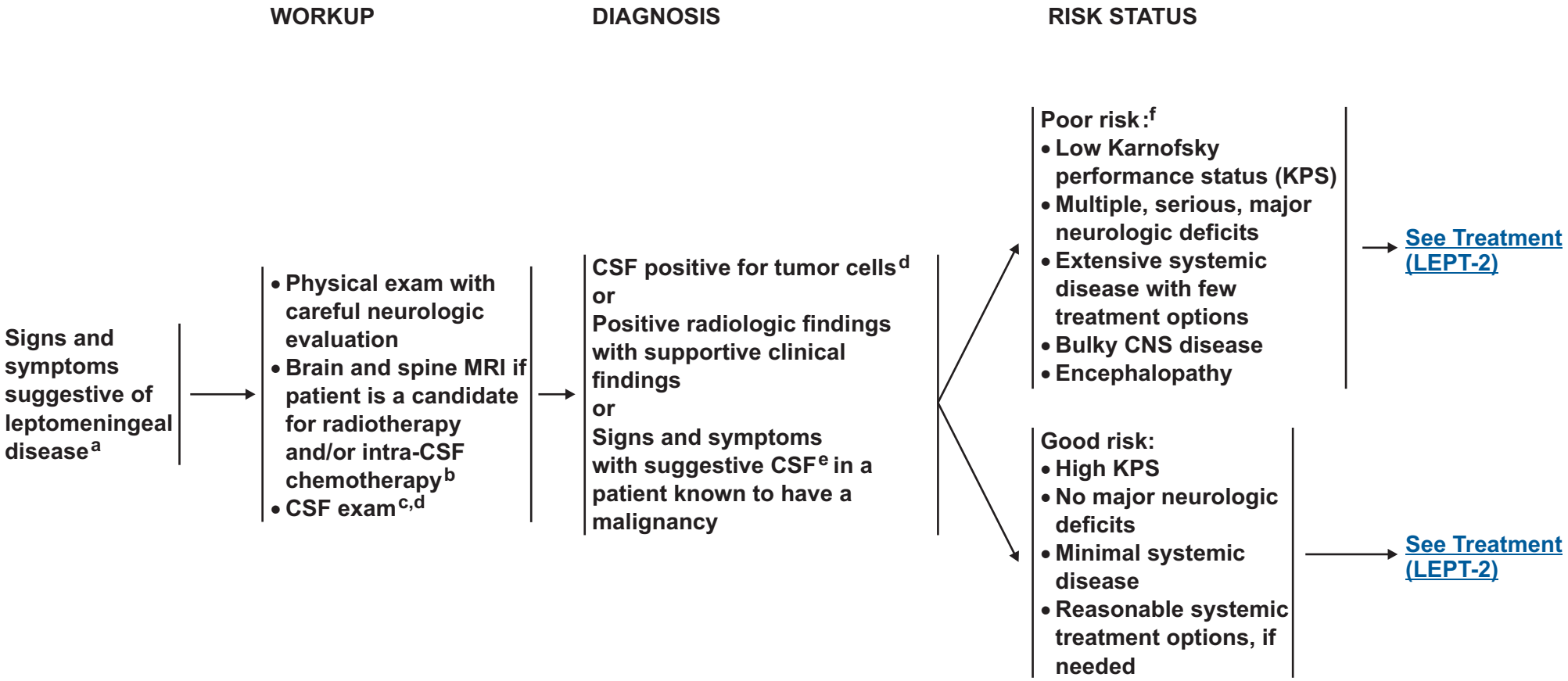


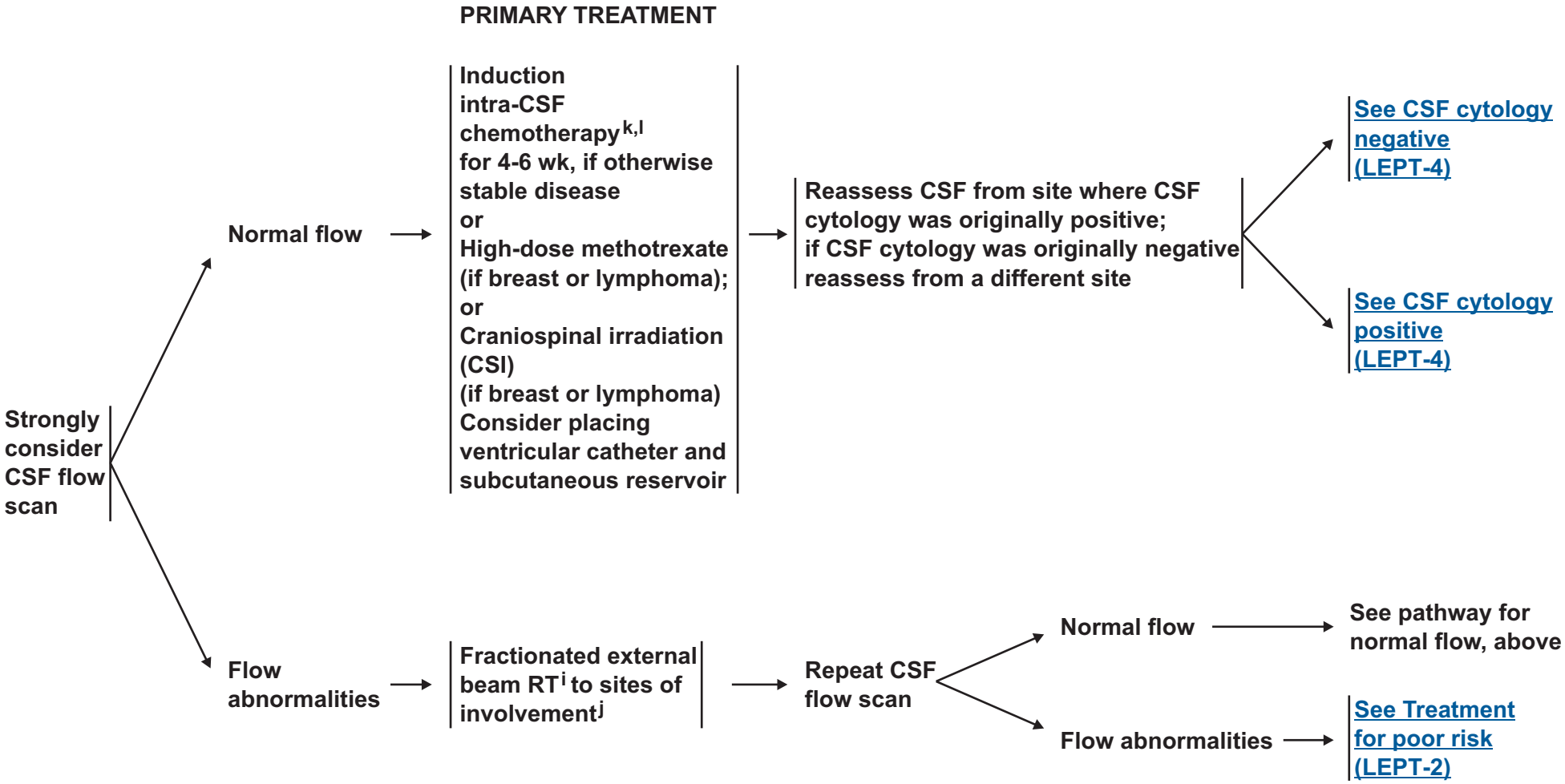
[a] Consider a multidisciplinary review in treatment planning, especially once pathology is available (See Principles of Brain Tumor Management [BRAIN-E]).
[b] Intra-CSF chemotherapy includes intrathecal (intralumbar) and intraventricular (intra-Ommaya).
[c] Caution is indicated in patients who are anticoagulated, thrombocytopenic, or who have a bulky intra-cranial mass.
[d] With all malignancies, send for a cell count, differential (including hematopathology review), glucose, and protein. For solid malignancies, CSF analysis utilizes cytopathology. 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.
[f] Patients with exceptionally chemosensitive tumors (eg, small cell lung cancer, lymphoma) may be treated.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

RISK STATUS	TREATMENT
Poor risk:[f] • Low KPS • Multiple, serious, major neurologic deficits • Extensive systemic disease with few treatment options • Bulky CNS disease • Encephalopathy	→ Consider fractionated external beam RT[g] to symptomatic sites[h] and Palliative/Best supportive care
Good risk: • High KPS • No major neurologic deficits • Minimal systemic disease • Reasonable systemic treatment options, if needed	→ Involved field RT[g] to bulky disease, symptomatic sites → See CSF flow scan (LEPT-3)

[f]Patients with exceptionally chemosensitive tumors (eg, SCLC, lymphoma) may be treated.
[g]See Principles of Brain Tumor Radiation Therapy (BRAIN-C).
[h]Usually WBRT and/or partial spine field recommended.

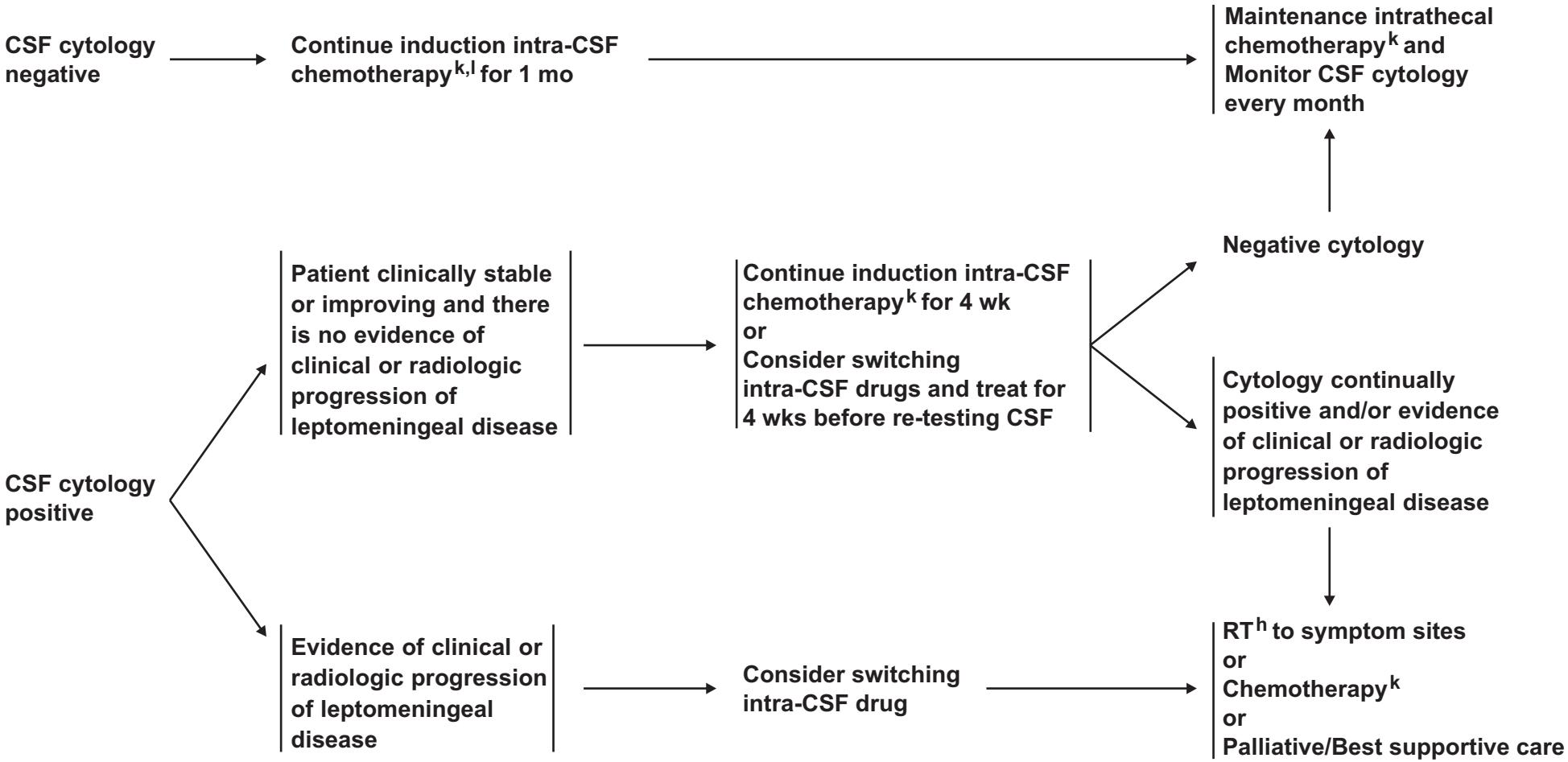
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



[i] See Principles of Brain Tumor Radiation Therapy (BRAIN-C).
[j] Usually WBRT and/or partial spine field recommended.
[k] See Principles of Brain Tumor Systemic Therapy (BRAIN-D).
[l] Induction intra-CSF chemotherapy can start with radiation (concomitant) or high-dose methotrexate for lymphoma or CSI.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

POSTINDUCTION THERAPY



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

[k] See Principles of Brain Tumor Systemic Therapy (BRAIN-D).

[l] Induction intra-CSF chemotherapy can start with radiation (concomitant) or high-dose methotrexate for lymphoma or CSI.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

NCCN Guidelines Version 2.2012
Metastatic Spine Tumors

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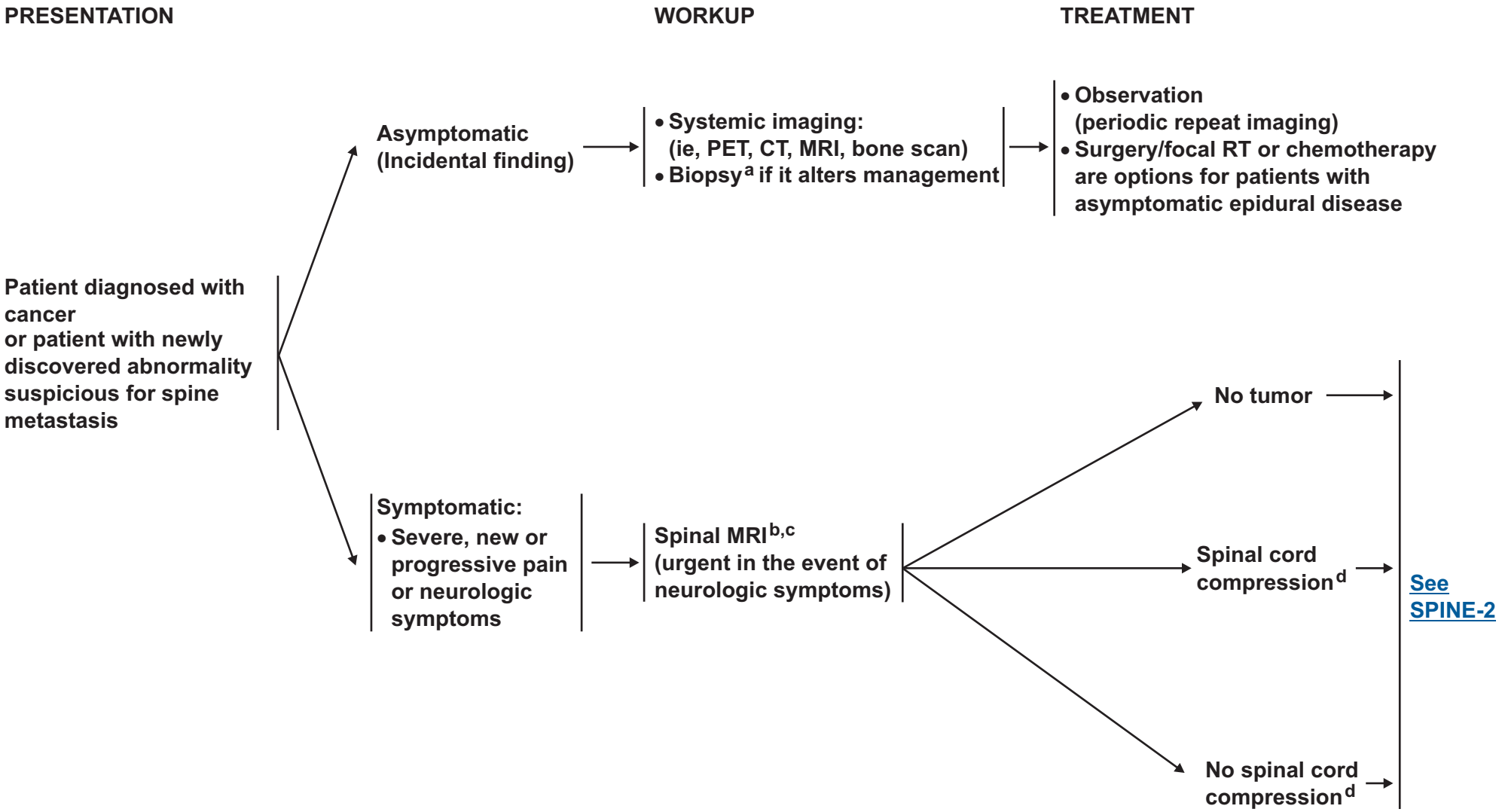

[a] Biopsy if remote history of cancer.
[b] If the patient is unable to have an MRI, then a CT myelogram is recommended.
[c] 15-20% of patients have additional lesions. Highly recommend complete spine imaging.
[d] Includes cauda equina syndrome.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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Metastatic Spine Tumors

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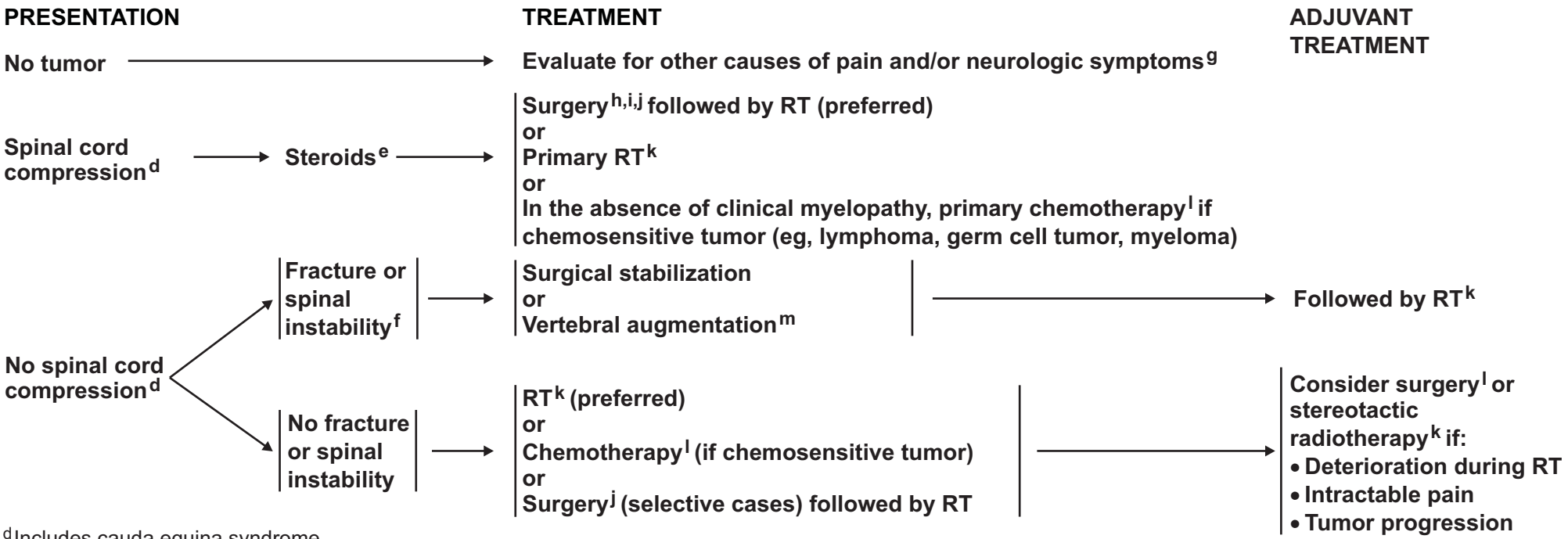

[d] Includes cauda equina syndrome.

[e] 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).

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

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

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

[i] Regarding surgery, note the following:

- Category 1 evidence supports the role of surgery in patients with epidural spinal cord compression willing to undergo surgery. (Patchell RA, et al. Lancet 2005;366(9486):643-648)
- For surgery, patients with hematologic tumors (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.

[j] See Principles of Brain Tumor Surgery (BRAIN-B).

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

[l] See Principles of Brain Tumor Systemic Therapy (BRAIN-D).

[m] Vertebral augmentation: vertebroplasty, kyphoplasty.

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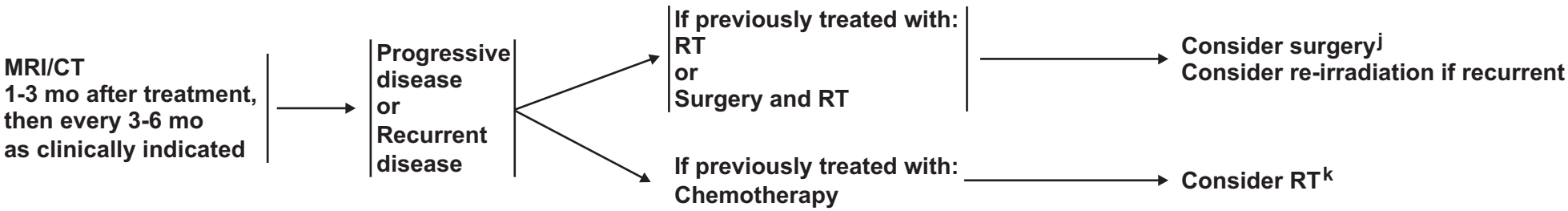

[j] See Principles of Brain Turmor Surgery (BRAIN-B).
[k] See Principles of Brain Tumor Radiation Therapy (BRAIN-C).

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PRINCIPLES OF BRAIN TUMOR IMAGING[1]

- **MRI[2] of the brain and spine (± 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**

- **CT of the brain and spine (± 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**

- **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 FDG-PET scanning: Assess metabolism within tumor and normal tissue by using radio-labeled 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**

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 body PET is to differentiate radiation necrosis from active tumor, as this might obviate the need for surgery or the discontinuation of an effective therapy.

[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
- Maximal tumor removal 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

OPTIONS
- Gross total resection where feasible
- Stereotactic biopsy
- Open biopsy/debulking followed by planned observation or adjuvant therapy
- Chemotherapy implants, when indicated (See footnote g on GLIO-1)

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 MRI should be performed within 24-72 hours for gliomas and parenchymal brain tumors to determine the extent of resection.
- The extent of resection should be judged on the postoperative study and used as a baseline to assess further therapeutic efficacy or tumor progression.

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PRINCIPLES OF BRAIN TUMOR RADIATION THERAPY

Low Grade Gliomas (Grades I/II)

- Tumor volumes are best defined using pre- and postoperative imaging, usually FLAIR and or T2 signal abnormality on MRI for GTV. CTV (GTV plus 1-2 cm margin) should receive 45-54 Gy in 1.8-2.0 Gy fractions.
- SRS has not been established to have a role in the management of low grade gliomas. Phase I trials using SRS do not support its role as initial treatment.

High Grade Gliomas (Grades III/IV)

- The gross tumor volume (GTV) is best defined using pre- and postoperative MRI imaging using enhanced T1 and FLAIR/T2. The GTV is expanded by 2-3 cm (Clinical target volume, CTV) to account for sub-diagnostic tumor infiltration. Fields are usually reduced for the last phase of the treatment (boost).
- The recommended dose is 60 Gy in 1.8 to 2.0 Gy fractions. A slightly lower dose, 55-57 Gy, can be applied when the tumor volume is very large (gliomatosis) or for Grade III astrocytoma.
- In poorly performing patients or the elderly a hypofractionated accelerated course was found to be effective with the goal of completing the treatment in 3-4 weeks. Total doses vary between 40-50 Gy.

Ependymoma

- Limited Fields: Tumor volumes are best defined using pre- and postoperative imaging, usually enhanced T1 and or FLAIR/T2. Anatomic areas touched by preoperative tumor volume plus postoperative signal abnormality on MRI for GTV. CTV (GTV plus 1-2 cm margin) should receive 54-59.4 Gy in 1.8 to 2.0 Gy fractions.
- Craniospinal: 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. Primary brain site should receive total dose of 54-59.4 Gy in 1.8 to 2.0 Gy fractions.

Adult Medulloblastoma and Supratentorial PNET:

- Standard risk for recurrence:
  - Conventional dose: 30-36 Gy CSI and boosting the primary brain site to 55.8 Gy without adjuvant chemotherapy
  - Reduced dose: 23.4 Gy CSI and boosting the primary brain site to 55.8 Gy with adjuvant chemotherapy †
- High risk for recurrence: 36 Gy with boosting primary brain site to 55.8 Gy†

Primary CNS Lymphoma

- WBRT may be withheld in the primary setting in patients treated with chemotherapy. When used, WBRT doses should be limited to 24-36 Gy in 1.8-2.0 Gy fractions following a CR to chemotherapy. For less than CR, consider the same WBRT dose followed by a limited field to gross disease to 45 Gy.
- Lower doses of radiation are less toxic and may be as effective.

CR: Complete response
CTV: Clinical target volume
FLAIR: Fluid-attenuated inversion recovery
GTV: Gross tumor volume

†Regimen supported by data from pediatric trials only.

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Continued

PRINCIPLES OF BRAIN TUMOR RADIATION THERAPY
(References)

[1]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.

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[4]Aoyama H, Shirato H, Tago M, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: A randomized controlled trial. JAMA 2006;295:2483-2491.

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PRINCIPLES OF BRAIN TUMOR RADIATION THERAPY

Primary Spinal Cord Tumors:

- Doses of 45-50.4 Gy are recommended using fractions of 1.8 Gy. In tumors below the conus medularis (ie, myxopapillary ependymoma) higher doses up to 60 Gy can be delivered.

Meningiomas

- WHO grade 1 and 2 meningiomas may be treated by fractionated conformal radiotherapy with doses of 45-54 Gy.
- WHO grade 3 meningiomas should be treated as malignant tumors with tumor bed and gross tumor + a margin (2-3 cm) receiving 54-60 Gy in 1.8-2 Gy fractions.
- WHO grade 1 meningiomas may also be treated with stereotactic radiosurgery doses of 12-14 Gy in a single fraction when appropriate.

Brain Metastases

- Whole brain radiotherapy (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 in poor performers.[2]
- Stereotactic radiosurgery: Recommend maximum marginal doses of 24, 18, or 15 Gy according to tumor volume is recommended (RTOG 90-05).[3,4]

Leptomeningeal Metastases

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

Metastatic Spine

- Doses to vertebral body metastases will depend on patient's performance status and primary histology. Generally doses of 20-37.5 Gy are delivered in 5-15 fractions over 1-3 weeks. In selected cases, or recurrences after previous radiation, stereotactic radiotherapy is appropriate.

CR: Complete response
CTV: Clinical target volume
FLAIR: Fluid-attenuated inversion recovery
GTV: Gross tumor volume

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PRINCIPLES OF BRAIN AND SPINAL CORD TUMOR SYSTEMIC THERAPY

Adult Low-Grade Infiltrative Supratentorial Astrocytoma/ Oligodendroglioma (excluding pilocytic astrocytoma)

- Adjuvant Treatment:
  - Temozolomide[1-4]
- Recurrence or Progressive, Low grade disease:
  - Temozolomide*,[3-5]
  - Nitrosourea
  - Combination PCV (CCNU + procarbazine + vincristine)[6]
  - Platinum based regimens[7-9]

Anaplastic Gliomas

- Adjuvant Treatment:
  - Temozolomide or PCV with deferred RT[10-12]
- Recurrence/Salvage therapy
  - Temozolomide[4,5,13,14]
  - Nitrosourea[15]
  - Combination PCV
  - Bevacizumab[16-18]
  - Bevacizumab + chemotherapy (irinotecan,[19,20] BCNU/CCNU,[21] temozolomide)
  - Irinotecan[22,23]
  - Cyclophosphamide
  - Platinum-based regimens$^{\alpha}$
  - Etoposide[24]

Glioblastoma

- Adjuvant Treatment:
  - Concurrent (with RT) temozolomide[1] 75 mg/m^2 daily
  - Post RT temozolomide[1] 150-200 mg/m^2 5/28 schedule
- Recurrence/Salvage therapy
  - Bevacizumab††,[16,26,27]
  - Bevacizumab + chemotherapy (irinotecan,[26-28] BCNU/CCNU,[21] temozolomide)
  - Temozolomide[1,5,29]
  - Nitrosourea[15]
  - Nitrosourea wafer[30]
  - Combination PCV
  - Cyclophosphamide[31]
  - Platinum-based regimens$^{\alpha}$

Adult Intracranial Ependymoma (excluding subependymoma and myxopapillary)

- Recurrence
  - Platinum-based regimens:$^{\alpha}$ Single agent or combination[32]
  - Etoposide
  - Nitrosourea[32]
  - Bevacizumab

*For patients not previously treated.
$^{\alpha}$Platinum-based regimens include cisplatin or carboplatin.
††Discontinuation of bevacizumab after progression may be associated with rapid neurological deterioration and bevacizumab may be continued in these circumstances.

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Continued

PRINCIPLES OF BRAIN AND SPINAL CORD TUMOR SYSTEMIC THERAPY

Adult Medulloblastoma and Supratentorial PNET

- **Adjuvant Treatment**
  - **Weekly vincristine[φ] during craniospinal radiation therapy followed by either of the following regimens:**
    - **Cisplatin, cyclophosphamide, and vincristine[33,φ]**
    - **Cisplatin, lomustine, and vincristine[33,φ]**
- **Recurrence/Salvage therapy**
  - **No prior chemotherapy**
    - **High-dose cyclophosphamide ± etoposide**
    - **Carboplatin, etoposide, and cyclophosphamide**
    - **Cisplatin, etoposide, and cyclophosphamide**
    - **High-dose chemotherapy with autologous stem cell reinfusion[34] in patients who achieve a complete response with conventional doses of salvage chemotherapy or have no residual disease after re-resection**
  - **Prior chemotherapy**
    - **High dose cyclophosphamide ± etoposide**
    - **Oral etoposide[35,36]**
    - **Temozolomide[4]**
    - **High-dose chemotherapy with autologous stem cell reinfusion[34] in patients who achieve a complete response with conventional doses of salvage chemotherapy or have no residual disease after re-resection**

Primary CNS Lymphoma

- **Primary Treatment**
  - **High dose methotrexate 3.5 g/m^2 combined with the following plus RT[λ]:**
    - **Vincristine, procarbazine, cytarabine ± rituximab[37-39]**
    - **Cytarabine[40]**
    - **Ifosfamide ± RT[41]**
  - **High dose methotrexate 8 g/m^2 combined with the following plus deferred RT[42]**
    - **Rituximab[43]**
    - **Rituximab and temozolomide[44]**
- **Recurrence or Progressive Disease**
  - **Retreat with high-dose methotrexate[42]**
  - **Temozolomide**
  - **Rituximab ± temozolomide[45]**
  - **Topotecan**
  - **Consider high-dose chemotherapy with autologous stem cell reinfusion in patients who achieve a complete response with conventional doses of salvage chemotherapy or have no residual disease after re-resection**
  - **High-dose ARA-C[46]**

Meningiomas

- **Hydroxyurea[47]**
- **Alpha-interferon[48]**
- **Somatostatin analogue[49]**

φ 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.

λ Other combinations with methotrexate may be used.

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PRINCIPLES OF BRAIN AND SPINAL CORD TUMOR SYSTEMIC THERAPY

Limited (1-3) Metastatic or Multiple (> 3) Metastatic Lesions

- Recurrent Disease‡
  - Treatment as per the regimens of the primary tumor
  - Carmustine wafer[50]
- Temozolomide 5/28 schedule
- Organ specific therapy
  - High dose methotrexate[51,52] (breast[51] and lymphoma)
  - Capecitabine ± lapatinib,[53,54] cisplatin,[55,56] etoposide[55,56] (breast)[57-61]
  - Topotecan (small cell lung)

Leptomeningeal Metastases

- Treatment
  - Organ specific systemic chemotherapy; emphasizing drugs with good CNS penetration
  - Intra-CSF chemotherapy[62] (liposomal cytarabine,[63,64] methotrexate,[9] cytarabine, thiotepa, rituximab,[64] topotecan,[65] etoposide,[66] interferon alfa[67])
  - High-dose methotrexate for lymphomatous meningitis[52]

Metastatic Spine Tumors

- Use regimen for disease specific site

‡Use agents active against primary tumor.

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PRINCIPLES OF BRAIN AND SPINAL CORD TUMOR SYSTEMIC THERAPY (References)

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PRINCIPLES OF BRAIN AND SPINAL CORD TUMOR SYSTEMIC THERAPY (References)

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PRINCIPLES OF BRAIN AND SPINAL CORD TUMOR SYSTEMIC THERAPY (References)

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Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

PRINCIPLES OF BRAIN 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, as well as culturally and educationally sensitive.

Multidisciplinary Care

- **During the course of their treatment, most patients will be seen by physicians from more than one specialty. Where possible, use of a local brain tumor board, or multidisciplinary clinic facilitates these interactions and allows for input from each of the major neuro-oncology disciplines, as well as allied services (Physical/Occupational Therapy, Social Work, Psychology) when available, in formulating a plan of care for the patient. When not possible in a single clinic or institution, close and regular communication between the various disciplines involved becomes essential.**
- **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.**
- **As the patient's treatment unfolds, their quality of life is the highest priority and should guide clinical decisions. While responses on imaging are benchmarks of successive 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 Spectroscopy, PET/CT imaging, and repeat surgery may be necessary if clinically indicated.**

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

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

Continued

PRINCIPLES OF BRAIN TUMOR MANAGEMENT

Medical Management

1. Corticosteroids

- **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 24h before radiation therapy. Patients with high risk of GI side effects (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]**

2. Antiepileptic Drugs (AED's)

- **Seizures are frequent in patients with primary or metastatic brain tumors . Despite this, studies have shown that the use of older, "traditional" antiepileptic drugs (AED's) 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 (levetiracetam, topiramate, lamotrigine, pregabalin) have not yet been systematically studied. Seizure prophylaxis is not recommended as routine in asymptomatic patients; but reasonable to consider perioperatively.**
- **Many AED's have significant effects on the cytochrome P450 system, and may have effects on the metabolism of numerous chemotherapeutic agents such as irinotecan, gefitinib, erlotinib, temsirolimus among others). Where possible, such enzyme inducing AED's (EIAED's) should be avoided (phenytoin, phenobarbital, carbamazepine), and nonEIAED's should be used instead (levetiracetam, topiramate, valproic acid). Patients should be closely monitored for any adverse effects of the AED's or chemotherapeutic agents.**

3. Endocrine disorders

- **Endocrinopathies are common with brain tumor patients. This may be affected by concomitant steroid use as well as 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.**

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

- **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 is 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.

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

Continued

PRINCIPLES OF BRAIN TUMOR MANAGEMENT

Medical Management---continued

5. Psychiatric disorders (Also see the NCCN Distress Management Guidelines)

- **Depression is common in brain tumor 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 healthcare 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.**
- **Antiepileptic drugs, 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 reversible causes, including endocrine disorders, infection, side effects of medication or tumor progression.**

6. Venous thromboembolism (VTE)

- **See the NCCN Venous Thromboembolic Disease Guidelines.**

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 pre-requisite 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 for referrals to social service, tumor support, and educational agencies for their patients. 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.**
- **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, of no further treatment or abandonment.**

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

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 noted.

Overview

In the year 2012, an estimated 22,910 new cases of primary brain and other nervous system neoplasms will be diagnosed in the United States.[1] These tumors will be responsible for approximately 13,700 deaths. The incidence of primary malignant brain tumors has been increasing over the last 30 years, especially in elderly persons.[2] Metastatic disease to the central nervous system (CNS) occurs much more frequently, with an estimated incidence about 10 times that of primary brain tumors. It is estimated between 20% and 40% of patients with systemic cancer will develop brain metastases.[3]

Principles of Management

Primary and metastatic brain tumors are a heterogeneous group of neoplasms with varied outcomes and management strategies. Primary brain tumors range from pilocytic astrocytomas which are very uncommon, noninvasive, and surgically curable to glioblastoma multiforme, the most common intraparenchymal 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 or chemotherapy. Because of this marked heterogeneity, the prognostic features and treatment options for brain tumors must be carefully reviewed on an individual basis and sensitively communicated to each patient. In addition, CNS tumors are associated with a range of symptoms and complications such as edema, seizures, endocrinopathy, fatigue, psychiatric disorders, venous thromboembolism that can seriously impact quality of life of patients. The involvement of an interdisciplinary team, including neurosurgeons, radiation therapists, oncologists, neurologists, or neuroradiologists, is a key factor in the appropriate management of these patients. For any subtype of malignant brain lesions, the NCCN panel encourages thorough multidisciplinary review of each patient 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 algorithm section “Principles of Brain Tumor Management”.

Treatment Principles

Several important principles guide surgical and radiation therapy (RT) 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 possible, keep surgical morbidity to a minimum, and ensure an accurate diagnosis. Decisions regarding aggressiveness of surgery for primary brain lesions 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) in patients with recurrent disease, the time since the last surgery.[4]

The surgical options include stereotactic biopsy, open biopsy or debulking procedure, subtotal resection, or maximal safe resection. The pathologic diagnosis is critical and often difficult to determine accurately; therefore, as much tissue as possible should be delivered to the pathologist. Review by an experienced neuropathologist is highly recommended. In addition, a postoperative magnetic resonance imaging (MRI) scan, with and without contrast, should be obtained 24 to 72 hours after surgery to document the extent of disease after surgical intervention.

Radiation oncologists use several different treatment approaches in patients with primary brain tumors, including brachytherapy, stereotactic fractionated RT, and stereotactic radiosurgery (SRS). Standard fractionated external beam radiation therapy (EBRT) is the most common approach, while hypofractionation is emerging as an option for select patients. RT for patients with primary brain tumors usually involves only the tumor volume and margins, while whole brain radiotherapy (WBRT) and SRS are used for brain metastases.

Clinicians are advised to consult the algorithm sections "Principles of Brain Tumor Imaging", "Principles of Brain Tumor Surgery" and for further discussion of these diagnostic and treatment modalities. The dose of radiation administered varies depending on the pathology as seen in "Principles of Brain Tumor Radiation Therapy". Appropriate chemotherapeutic and biologic regimens for each tumor subtype are listed under "Principles of Brain Tumor Systemic Therapy".

Tumor Types

These NCCN CNS Cancers guidelines focus on management of adult CNS cancers: anaplastic gliomas and glioblastoma multiforme, low-grade infiltrative astrocytomas, oligodendrogliomas, ependymomas, brain metastases, leptomeningeal metastases, primary CNS lymphomas (non-AIDS), and metastatic spinal tumors. In version 2010 and 2011, specific guidelines on managing meningiomas, primary spinal cord tumors, and primitive neuroectodermal tumors (PNETs) excluding esthesioneuroblastomas are also added. These guidelines are updated annually to include new information or treatment philosophies as they become available. However, because this field evolves continually, practitioners should use all of the available information to determine the best clinical options for their patients.

Low-Grade Infiltrative Astrocytomas and Oligodendrogliomas

Diffusely infiltrative low-grade gliomas (astrocytomas, oligodendrogliomas, mixed gliomas) are a diverse group of relatively uncommon malignancies classified as grade II under the World Health Organization (WHO) grading system.[5] Multivariate analysis on two phase III trials conducted by the European Organisation for Research and Treatment of Cancer (EORTC) revealed age ≥ 40 years, astrocytoma histology, largest dimension of tumor ≥ 6 cm, tumor crossing midline, and presence of neurologic deficit before resection to be unfavorable prognostic factors.[6] In a separate validation study on 203 patients treated in a North American Intergroup trial, high-risk patients as defined by EORTC criteria (more than two risk factors) had a median overall survival of 3.9 years compared to 10.8 years in the low-risk group.[7]

Seizure is a common symptom (81%) of low-grade gliomas, and is more frequently associated with oligodendrogliomas.[8] The median duration from onset of symptoms to diagnosis ranges from 6 to 17 months. These tumors typically are non-enhancing, low-attenuation lesions on CT scans and MRI scans.

Diffuse astrocytomas are poorly circumscribed, invasive, and 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.[9,10] The most common non-infiltrative astrocytomas are pilocytic astrocytomas, which are circumscribed, often surgically resectable, and rarely transform; however, the NCCN algorithm does not encompass pilocytic astrocytomas because these tumors are curable by surgery alone.

Oligodendrogliomas are thought to arise from oligodendrocytes, whereas mixed oligoastrocytomas probably develop from a common glial stem cell. 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. Over half of oligodendrogliomas have specific molecular genetic alterations (allelic losses of chromosomes 1p and 19q) that can help distinguish them from other types of gliomas.[11] Grade II oligodendrogliomas have a much better 5-year survival rate (70%) than mixed gliomas (56%) and astrocytomas (37%).[12]

Treatment Overview

Surgery

The best management strategy for infiltrative low-grade gliomas has yet to be defined.[13] Surgery remains an important diagnostic and therapeutic modality. The primary surgical goal is 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.

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, most patients also received RT, and thus the net effect of the surgical procedure on outcome is difficult to evaluate. Most of the available retrospective biomedical literature suggests a survival benefit from aggressive surgical resection,[14-17] although there are data that reported no difference.[18] Maximal safe resection may also delay or prevent malignant progression[19-21] and recurrence.[22]

Biological considerations also favor an attempt at a complete excision of an astrocytoma. 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 astrocytoma.[19] 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 an astrocytoma 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.

Radiation therapy

No consensus exists regarding the proper timing of postoperative EBRT in low-grade gliomas. Some oncologists advocate immediate fractionated EBRT whereas others delay radiation until tumor progression is evident. A randomized trial of early versus delayed radiotherapy in adult patients was conducted by the European Organization for Research and Treatment of Cancer (EORTC).[23] In this EORTC 22845 trial, patients with low-grade gliomas were randomly assigned to either 54-Gy postoperative radiation or no immediate therapy. In an interim analysis, the 5-year disease-free survival was better with immediate postoperative radiation (44% vs. 37%; $P = 0.02$). However, overall survival was similar indicating that deferring postoperative therapy can be an option for a selected group of patients. Long-term follow-up of these patients showed that overall survival was not increased in patients who had received early radiotherapy (7.4 vs. 7.2 years); however, seizures were better controlled in these patients.[24] Although delaying radiation in young healthy patients without progressive neurological decline can be controversial, there is a consensus to proceed with immediate postoperative radiation in older patients after a less-than-total resection, because their survival is as poor as patients with anaplastic astrocytoma. When radiation is deferred, regular follow-up is essential for patients receiving observation alone after resection.

When radiation is given to patients with low-grade gliomas, it is administered with restricted margins. A T2-weighted and/or fluid attenuated inversion recovery (FLAIR) MRI scan is the best means for evaluating tumor extent, because these tumors enhance weakly or not at all. The clinical target volume is defined by the FLAIR or T2-weighted tumor with a 1-2 cm margin. Every attempt should be made to decrease the radiation dose outside the target volume. This can be achieved with 3-dimensional planning or IMRT (Intensity Modulated Radiation Therapy). The standard radiation dose for low-grade astrocytomas is 45 to 54 Gy, delivered in 1.8 to 2.0 Gy fractions. The selection of 45 to 54 Gy as the standard dose range is based on its relative safety when applied to a limited volume of the brain and on the lack of evidence for increased efficacy with higher doses.[25,26] In a randomized trial conducted by the EORTC in patients with low-grade astrocytomas, no survival difference was observed when 45 Gy was compared with 59.4 Gy.[27] With a median follow-up of 6 years, the 5-year disease-free survival and overall survival were the same. Patients were randomly assigned to receive either (1) 50.4 Gy in 28 fractions, or (2) 64.8 Gy in 36 fractions in another combined NCCTG (North Central Cancer Treatment Group), Radiation Therapy Oncology Group (RTOG), and ECOG (Eastern Cooperative Oncology Group) study.[28] With a median follow-up of 6.3 years, the 5-year disease-free survival and overall survival were again the same indicating that lower doses of RT are probably as effective as higher doses of radiation for low-grade gliomas. Enthusiasm for SRS in low-grade gliomas has waned due to insufficient evidence for therapeutic advantage.[29]

Systemic therapy

Chemotherapy is not a traditional mainstay of upfront treatment for low-grade gliomas. There is some data that support temozolomide as adjuvant therapy and it is included as a category 2B recommendation based on non-uniform panel consensus. A phase II trial of temozolomide achieved a 61% objective response rate in 46 patients.[30] Alternate protracted dosing schedules have produced response rates of 20% to 52%.[31,32] RTOG conducted a clinical trial (RTOG 9802) that allowed observation alone for favorable patients (age < 40 with gross total resection) and randomly assigned unfavorable patients (age ≥ 40

following any resection or younger patients who were subtotally resected) to postoperative radiation with or without combination PCV (lomustine [CCNU], procarbazine, and vincristine). Results have been presented in abstract form. In the favorable arm, the 5-year progression-free survival and overall survival were 50% and 94%, respectively.[33] In the unfavorable arm, the addition of chemotherapy to radiation conferred a survival advantage beyond two years.[34]

In the absence of randomized trial data, a number of regimens are currently considered acceptable for recurrence or progressive disease, including temozolomide,[31,35] nitrosourea, PCV, and platinum-based therapy.[36-38]

Patients with low-grade oligodendrogliomas, especially those with 1p/19q deletions, are candidates for chemotherapy in light of good response rates reported in literature.[39-44]

NCCN Recommendations

Primary and adjuvant treatment

When possible, maximal safe resection is recommended for low-grade infiltrative astrocytomas and oligodendrogliomas, and the actual extent of resection should be documented with a T2-weighted or FLAIR MRI scan within 72 hours after surgery. If the tumor is found to have components of oligodendroglioma, 1p19q deletion testing should be considered, as it is a favorable prognostic factor. Managing the disease by serial observation alone is appropriate for selected patients. The NCCN panel also discussed the role of the isocitrate dehydrogenase 1 or 2 (IDH1, IDH2) genes in low-grade gliomas. Mutations in the IDH genes are common in patients and reported to be a significant marker of positive prognosis.[45] However, routine IDH testing as a recommendation is not included in the algorithm at this point because its impact on treatment is still unclear.

The following are considered low-risk features for low-grade gliomas: age ≤ 40 years, Karnofsky Performance Status (KPS) ≥ 70, minor to no neurological deficit, oligodendroglioma or mixed oligoastrocytoma, tumor dimension < 6 cm, 1p and 19q co-deleted, IDH1 or 2 mutated. Patients are categorized as having high risk if they have three or more of the following: age > 40 years, KPS < 70, tumor > 6 cm, tumor crossing midline, preoperative neurological deficit of more than minor degree, one or no deletion on 1p and 19q, wild type IDH1 or 2. If gross total resection (GTR) is achieved, low-risk patients may be observed without adjuvant therapy. However, close follow-up is essential as over half of these patients eventually progress.[46] Low-grade gliomas can behave aggressively in high-risk patients and adjuvant radiation or chemotherapy (category 2B for chemotherapy) is recommended for this group.

Patients who only had a stereotactic biopsy, open biopsy, or subtotal excision should be treated with immediate fractionated EBRT or chemotherapy (category 2B), especially if their symptoms are uncontrolled or progressive. Because of concerns about the neurotoxicity of RT,[47] patients with asymptomatic residual tumors or stable symptoms may also be followed until their disease progresses. Patients should be followed using MRI every 3 to 6 months for 5 years and then at least annually.

Recurrence

At the time of recurrence, surgery is recommended (if resectable) followed by chemotherapy if patients have previously had fractionated EBRT. At progression following chemotherapy, the options are: 1) consider another regimen, 2) consider reirradiation, and 3) palliative/best supportive care. Reirradiation is a good choice if the patient has been progression-free for over 2 years after prior RT, the new lesion is outside the target of previous RT, or the recurrence is

small and geometrically favorable. If the patient has not previously received radiation, they should first undergo surgery if the lesion is resectable. On progression, patients may receive RT or chemotherapy (category 2B for chemotherapy).

Anaplastic Gliomas and Glioblastomas

Anaplastic astrocytomas (grade III) and glioblastomas (grade IV astrocytomas) are the most common primary brain tumors in adults, accounting for 7% and 54% of all gliomas, respectively.[48] Glioblastoma is the deadliest brain tumor with only a third of patients surviving for one year and less than 5% living beyond 5 years. The 5-year survival rate for anaplastic astrocytoma is 27%. The most important prognostic factors identified in an analysis of 1,578 patients are histologic diagnosis, age, and performance status.[49]

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 to associated peritumoral edema. These tumors usually do not have associated hemorrhage or calcification but produce considerable edema and mass effect in image study as well as 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 radiation treatment portals.

It is difficult to assess the results of therapy using CT scans or MRI scans, because the extent and distribution of contrast enhancement, edema, and mass effect are more a function of blood-brain barrier integrity than of changes in the size of the tumor. Thus, other factors that exacerbate blood-brain barrier dysfunction (such as surgery, radiation, and tapering of corticosteroids) can mimic tumor progression by increasing contrast enhancement, T2-weighted abnormalities, and mass effect.

Anaplastic oligodendrogliomas are relatively rare; they are characterized by high cellularity, nuclear pleomorphism, frequent mitosis, endothelial proliferation, and necrosis. On histopathologic assessment, these tumors can be confused with glioblastoma multiforme; however, characteristic allelic losses of chromosomes 1p and 19q are present in anaplastic oligodendrogliomas.[11] This distinct histologic subtype has a much better prognosis compared to anaplastic astrocytomas and glioblastomas due to its marked sensitivity to chemotherapy;[50] half of the patients are alive at 5 years.[48]

Treatment Overview

Surgery

The goals of surgery are to obtain a diagnosis, alleviate symptoms related to increased intracranial pressure or compression, increase survival, and decrease the need for corticosteroids. A prospective study in 565 patients with malignant glioma showed that aggressive surgery is a strong prognostic factor when compared with biopsy alone ($P<0.0001$).[51] Retrospective analyses also suggest that gross total resection lengthens survival and is especially effective in patients with good performance status.[52-54] Unfortunately, the infiltrative nature of high-grade astrocytomas frequently renders gross total removal difficult. On the other hand, total resection is often possible for oligodendrogliomas, because most occur in the frontal lobes and because the tumors are frequently well demarcated.

Unfortunately, nearly all glioblastomas recur. At this point, reoperation may improve the outcome for selected patients.[55] According to an analysis by Park et al,[56] tumor involvement in specific critical brain

areas, poor Karnofsky score, and large tumor volume were associated with unfavorable re-resection outcomes.

Radiation therapy

Fractionated EBRT after surgery is standard adjuvant therapy for patients with high-grade astrocytomas. Use of radiation is based on two randomized trials conducted in the 1970s which showed extension in survival. Walker et al[57] compared postoperative supportive care, carmustine (BCNU), radiation, and radiation plus BCNU in 303 patients; median survival was 14 weeks, 18.5 weeks, 35 weeks, and 34.5 weeks, respectively. Another trial of 118 patients also found a benefit in median survival with radiation following surgery compared to no radiotherapy (10.8 vs. 5.2 months).[58] The typical dose is 60 Gy in 1.8 to 2.0 Gy fractions. Use of abbreviated courses of radiation (total 40 to 50 Gy) in older patients has been shown to be efficacious.[59,60]

RTOG conducted a randomized trial of conventional radiotherapy to 60 Gy plus BCNU or preceded by a radiosurgery boost (to 15-24 Gy) in patients with glioblastoma of 4 cm or less.[61] However, the results were disappointing with no improvement in local control or survival with the SRS boost. Another trial that randomly assigned patients to 50 Gy EBRT with or without temporary I-125 seed implant to 60 Gy also failed to show any survival benefit with a brachytherapy boost.[62]

Chemotherapy/systemic therapy

Traditionally, chemotherapy was felt to be of marginal value in the treatment of newly diagnosed patients with high-grade gliomas, but this perception is beginning to change in recent years. Most of the earlier trials studied nitrosourea-based chemotherapy regimens. The Medical Research Council reported results from the largest randomized trial of adjuvant chemotherapy in high-grade gliomas.[63] In this study, 674 patients were randomly assigned either to radiation alone or to radiation plus PCV. No survival benefit was seen with the addition of PCV, even in patients with anaplastic astrocytomas. In contrast, 2 meta-analyses reviewed data from randomized trials of high-grade glioma patients, and both found a modest survival benefit when chemotherapy was added to postoperative radiation.[64,65] Specifically, the Glioma Meta-Analysis Trialists Group reviewed 12 studies involving approximately 3000 patients and reported an absolute increase in 1-year survival from 40% to 46% and a 2-month increase in median survival when chemotherapy was added to postoperative radiation (HR, 0.85; 95% CI, 0.78-0.91; P<0.0001).[64] An earlier analysis by Fine and colleagues on 16 randomized trials also found a 10% and 9% increase in survival at 1 and 2 years, respectively.[65]

Wick et al[66] performed a phase III trial of sequential radiochemotherapy in 318 patients with anaplastic gliomas. The three randomized arms are: 1) RT; 2) PCV; 3) temozolomide. At progression, patients in arm 1 received PCV or temozolomide, while patients in arms 2 and 3 are irradiated. The three strategies resulted in comparable time-to-progression and survival. Some panel members expressed strong objection to recommending combined chemoradiation to patients with anaplastic glioma (category 3). There are no published data directly comparing the benefit of temozolomide to nitrosourea for postoperative chemoradiation in patients with newly diagnosed anaplastic astrocytomas. This study is currently underway through the RTOG (RTOG 9813). Another trial, RTOG 9402, is comparing radiation alone to PCV chemotherapy followed by RT in patients with 1p19q co-deleted anaplastic oligodendroglioma.

Other routes of drug 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=0.006).[67] As a result, the FDA approved the carmustine wafer for this indication. A phase III placebo-controlled study in 32 patients with malignant glioma showed a statistically significant prolongation of survival when BCNU polymer was used as initial therapy in combination with RT.[68] A larger phase III trial in 240 newly diagnosed patients with malignant glioma also found a statistically significant improvement in median survival from 11.6 months in the placebo group to 13.9 months in the BCNU-wafer treated group.[69] This benefit was maintained 2 and 3 years after implantation.[70] On the basis of these studies, the FDA extended the approval of BCNU polymer wafers for use in malignant gliomas as initial therapy. Clinicians and patients should be aware that carmustine can potentially interact with other agents resulting in increased toxicity (see below). Implantation of the wafer may preclude future participation of clinical trials of other adjuvant therapy.

Temozolomide, an alkylating agent, is becoming a standard addition to postoperative RT for younger, good performance patients with glioblastoma (without carmustine wafer). Stupp et al[71] conducted a phase III, randomized study that assessed the drug in 573 glioblastoma patients of age 70 or less with WHO performance status of 2 or less. They received either 1) daily temozolomide administered concomitantly with postoperative RT followed by 6 cycles of adjuvant temozolomide; or 2) radiotherapy alone. Side effects for temozolomide include hair loss, nausea, vomiting, headaches, fatigue, and anorexia. Due to the risk of lymphocytopenia and subsequent opportunistic infection, prophylaxis against *Pneumocystis carinii* pneumonia (PCP) is required when the agent is administered with radiotherapy. The chemoradiation arm resulted in a statistically better median survival (14.6 versus 12.1 months) and 2-year survival (26.5% versus 10.4%) when compared with RT. Final analysis confirmed the survival advantage at 5 years (10% vs 2%).[72] However, the study design does not shed light on which is responsible for the improvement: temozolomide administered with radiation, following radiation, or both. The dose used in this trial is 75 mg/m^2 daily concurrent temozolomide during the course of radiotherapy, then 150-200 mg/m^2 post-RT 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.[73] A comparison of the dose-dense 21/28 and standard 5/28 schedules have been completed with RTOG 0525. The results of that trial have not been reported.

There have been safety concerns regarding adjuvant use of temozolomide in patients with implanted carmustine wafer. However, temozolomide combined with radiotherapy after carmustine wafer placement appeared to be safe in recent studies.[74-76] For patients over 70 years but with good performance, there is some evidence from small studies suggesting the usefulness of temozolomide in addition to adjuvant radiation despite old age.[77,78] For frail patients, temozolomide may be administered alone. A retrospective review of patients of age 70 or above with mean Karnofsky score of 70 found no survival difference between those receiving radiation alone and those taking monthly temozolomide only.[79] Given the susceptibility of elderly patients to radiation-induced neurotoxicity, especially when the performance status is poor, chemotherapy alone appears to be a reasonable option.

Research suggests that MGMT (O-6-methylguanine-DNA methyltransferase) status may determine which patients obtain benefit from adjuvant temozolomide therapy.[80] MGMT is a DNA repair enzyme that may cause resistance to DNA-alkylating drugs. Oligodendrogliomas frequently exhibit MGMT hypermethylation and low expression levels, which may explain its high chemosensitivity.[81]

Unfortunately, currently available chemotherapy does not provide cures. Patients with malignant gliomas eventually recur or progress. In addition to temozolomide[35,82,83] and nitrosoureas,[67,84] regimens that are commonly used as second-line or salvage chemotherapy include combination PCV,[85] cyclophosphamide,[86] and platinum-based regimens.[38] Anaplastic gliomas may also be treated by irinotecan[87] or etoposide.[88]

Bevacizumab, an anti-angiogenic agent, received accelerated approval in 2009 for recurrent glioblastoma based on two phase II studies. AVF 3708g randomized 167 patients to bevacizumab with or without irinotecan; MRI-defined objective response was achieved in 28% and 38% of patients, respectively.[89] Median survival was around 9 months, similar to that of a previous phase II trial.[90] Published report of the other pivotal study (NCI 06-C-0064E) recorded a median survival of 31 weeks in 48 heavily-pretreated patients.[91] Bevacizumab alone or in combination with chemotherapy have also shown activity in anaplastic gliomas.[92-97] While efficacious, bevacizumab is associated with potentially serious adverse events including hypertension, impaired wound healing, colonic perforation, and thromboembolism.

NCCN Recommendations

Primary treatment

When a patient presents with a clinical and radiologic picture suggestive of high-grade glioma, neurosurgical input is needed regarding the feasibility of maximal safe tumor resection. Whenever possible, major tumor removal should be performed. 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. If high-grade glioma is supported by intraoperative frozen section diagnosis, BCNU wafer placement is an option (category 2B). The extent of tumor debulking should be documented with a postoperative MRI scan within 72 hours after surgery, with and without contrast. If major tumor removal is deemed too risky, a stereotactic or open biopsy or subtotal resection should be performed to establish the diagnosis. Multidisciplinary consultation is encouraged once the pathology is available.

Adjuvant therapy

After surgical intervention, the choice of adjuvant therapy depends on the tumor pathology and performance status of the patient. In the case of anaplastic gliomas, fractionated EBRT is the historical standard for patients with a good Karnofsky score (70 or above), but those with the 1p19q co-deletion may consider chemotherapy. Chemoradiation outside of a trial is controversial (category 3). Patients with a poor performance score (below 70) can be managed by radiation, chemotherapy (category 2B), or palliative/best supportive care.

If glioblastoma is diagnosed, the adjuvant options mainly depend on the patient performance status. For those with KPS below 70, options include: 1) EBRT; 2) chemotherapy; 3) combined treatment; 4) palliative/best supportive care. Patients aged 70 years or under with KPS 70 or above should undergo radiation plus concurrent and adjuvant temozolomide (category 1 recommendation). Elderly patients (over 70 years) but with a KPS of 70 or above can receive standard or hypofractionated EBRT with or without temozolomide.

Follow-up and recurrence

Patients should be followed closely with serial MRI scans (at 2-6 weeks, then every 2-4 months for 2-3 years, then less frequently) after the completion of RT. Because RT can produce additional blood-brain barrier dysfunction, corticosteroid requirements may actually increase; therefore, scans may appear worse during the first 3 months after completion of RT, even though there is no actual tumor progression.

Early MRI scans allow for appropriate titration of corticosteroid doses, depending on the extent of mass effect and brain edema. Later scans are used to identify tumor recurrence. Early detection of recurrence is warranted, because local and systemic treatment options are available for patients with recurrent disease. However, MR spectroscopy, MR perfusion, or PET can be considered to rule out radiation-induced necrosis or "pseudoprogression".[98,99]

Management of recurrent tumors depends on the extent of disease and patient condition. For local recurrence, repeat resection, with or without wafer placement in the surgical bed, can be performed if possible. Following re-resection, or if the local recurrence is unresectable, poor performance patients should undergo palliative/best supportive care without further active treatment. If performance status is favorable, systemic chemotherapy may be administered (especially for anaplastic oligodendrogliomas); re-irradiation is a category 2B option if prior radiation achieved a good/durable response. In the case of diffuse or multiple recurring lesions, the options are: 1) palliative/best supportive care for poor performance patients; 2) systemic chemotherapy; or 3) surgery to relieve mass effect. All patients should receive best supportive care.

Intracranial Ependymomas

Ependymomas constitute up to 4% of adult CNS tumors and 10% of pediatric CNS tumors.[100] In adults, ependymomas occur more often in the spinal canal than in the intracranial compartment (two-thirds infratentorial). 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.[101,102] This section focuses on adult intracranial grade II differentiated (termed ependymomas) and grade III (termed anaplastic ependymomas) ependymomas. Grade I ependymomas (subependymomas and myxopapillary) are non-infiltrative and can be cured by resection alone.

Treatment Overview

Surgery

There is a paucity of robust studies regarding 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.[103-107] Supratentorial ependymomas generally have a poorer prognosis than their infratentorial counterparts, because a greater proportion of supratentorial lesions are of high grade and because larger volumes of residual disease tend to be present after surgical resection at this location.

Radiation therapy

The survival benefits of RT following surgical recovery have been established for anaplastic ependymomas and suboptimally resected tumors, although much of the data are derived from pediatric patients. Rodriguez et al[108] reviewed over 2,400 cases of ependymomas in the Surveillance, Epidemiology, and End Results (SEER) database and reported the lack of radiation to be a poor prognostic factor in partially resected patients (HR = 1.75, P = 0.024). The short-term and 10-year survival rate after RT reached over 70% and 50%, respectively.[109-111] The value of RT is more controversial for differentiated ependymomas,[104,112] with data demonstrating improved survival mainly for subtotally resected tumors.[105,108]

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.[113-115] Prophylactic craniospinal or WBRT does not lead to improvement in survival compared to conformal regional radiation with higher doses in modern studies of non-disseminated disease.[106,112,116] SRS have been used as a boost after EBRT or to treat recurrence with some success, although long-term results are still lacking.[117-119]

Systemic therapy

Research on chemotherapeutic regimens has also centered on pediatric ependymomas, while the role of chemotherapy in the treatment of adult patients remains poorly defined. No study has demonstrated a survival advantage with the addition of chemotherapy to irradiation 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),[120,121] etoposide,[122] nitrosourea,[121] and bevacizumab.[123]

NCCN Recommendations

Primary and adjuvant treatment

Whenever possible, maximal safe resection should be attempted with contrast enhanced brain image verification within 24-72 hours. Spine MRI should be delayed by at least 2 to 3 weeks after surgery to avoid post-surgical artifacts. Due 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. If maximal resection is not feasible at diagnosis due to anatomical or other factors, biopsy (stereotactic or open) or subtotal resection should be performed.

The adjuvant treatment algorithm revolves around the extent of surgical resection, histology, and staging by cranial spinal MRI and cerebrospinal fluid (CSF) cytology. CSF dissemination develops in up to 15% of intracranial ependymomas. Lumbar puncture for CSF cytology, delayed at least 2 weeks after surgery, should be performed for anaplastic ependymoma and/or if resection is suboptimal. CSF analysis is also indicated for grade II ependymomas following GTR if spine MRI is negative. However, lumbar puncture may be contraindicated in some cases (for example, posterior fossa mass). Patients who have undergone GTR and have negative findings for both spine MRI and CSF may consider adjuvant regional fractionated EBRT or observation if the tumor is supratentorial. Limited-field fractionated radiation is the appropriate post-operative management for patients with anaplastic ependymoma and/or subtotal resection, provided spine and CSF findings are both negative. Craniospinal radiation is mandatory when MRI spine or CSF results reveal disease, regardless of histology and extent of resection. Dosage and specifics can be found in the “Principles of Brain Tumor Radiation Therapy” section of the algorithm.

Follow-up and recurrence

Follow-up of ependymoma depends on the extent and location 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 4-6 months in the second year and then every 6 to 12 months, 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. Resection is recommended if possible. Radiation should be administered (after

surgery if performed) if not given originally; SRS may be considered in geometrically favorable cases.

Upon disease progression, several options are available depending on the histologic type, extent of disease, age of the patient, and performance status: 1) radiation (including SRS or reirradiation of previously irradiated sites); 2) chemotherapy for patients who are refractory to surgery or RT, or 3) palliative/best supportive care.

Medulloblastoma and Supratentorial PNET

Cranial PNETs are embryonal neoplasms showing varying degrees of differentiation. They are described by their location as infratentorial (medulloblastomas) and supratentorial. The WHO classification system further divided these tumors into histological variants.[5] CNS PNETs are infrequent in children and very rare in adults, with an overall incidence of 0.26 per 100,000 person-years reported by the Central Brain Tumor Registry of the United States (CBTRUS).[124] Overall, it represents only 1.8% of all brain tumors, although it is the most common type among pediatric brain malignancies.

About half of the affected patients will present with elevated intracranial pressure. Headache, ataxia, and nausea are commonly observed symptoms.[125] All PNETs of the brain are WHO grade IV as they are invasive and rapidly growing. They also have the tendency to disseminate through the CSF. Larger retrospective case series of adult patients reported a 10-year survival of 48% to 55% with frequent recurrence beyond 5 years, commonly in the posterior fossa.[126,127]

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[125,128,129] and is associated with improved survival.[128,130] In addition, surgical placement of a ventriculoperitoneal shunt can be used to treat hydrocephalus.

Radiation therapy

Adjuvant radiation following surgery is the current standard of care, although most studies are based on the pediatric population. The conventional dose is 30-36 Gy craniospinal irradiation and a boost to a total of 55.8 Gy to the primary brain site.[128,130] A lower craniospinal dose of 23.4 Gy, combined with chemotherapy, has gained popularity for average-risk patients to lessen side effects while maintaining 55.8 Gy to the posterior fossa,[126,131,132] although one randomized trial found an increased relapse risk with dose reduction.[133] Recently, SRS demonstrated safety and efficacy in a small series of 12 adult patients with residual or recurrent disease.[134]

Systemic therapy

The use of post-irradiation chemotherapy to allow radiation dose reduction is becoming increasingly common especially for children,[131,132] but optimal use of adjuvant chemotherapy is still unclear for adult patients.[125-127,135,136] A phase III study that enrolled over 400 patients between ages 3 and 21 to receive post-irradiation cisplatin-based chemotherapy regimens recorded an encouraging 86% 5-year survival.[137]

Several regimens are in use in the recurrence setting, most of which include etoposide.[138-140] Temozolomide has also been used in this setting.[141] High-dose chemotherapy in combination with autologous stem cell transplantation is a feasible strategy for patients who have had good response with lower doses.[140,142]

NCCN Recommendations

Primary treatment

MRI scan is the gold standard in the assessment and diagnosis of PNET. The typical tumor shows enhancement and heterogeneity. Fourth ventricular floor infiltration is a common finding related to worse prognosis.[126,127,136] Multidisciplinary consultation before treatment initiation is advised. Maximal safe resection is recommended wherever possible. Contrast-enhanced brain MRI should be performed within 24-72 hours following surgery, but spinal MRI should be delayed by 2-3 weeks. Because of the propensity of PNET to CSF seeding, CSF sampling after spine imaging via lumbar puncture is also necessary for staging. Medulloblastoma should be staged according to the modified Chang system using information from both imaging and surgery.[143,144]

Adjuvant therapy

Patients should be stratified according to recurrence risk for planning of adjuvant therapy (reviewed by Brandes et al[145]). The NCCN panel agrees that patients with large cell or anaplastic medulloblastoma, supratentorial PNET, disease dissemination, unresectable tumors, or residual tumors over 1.5 cm^2 postsurgery are at heightened risk. These patients should undergo irradiation of the neuraxis followed by chemotherapy. For patients at average risk, craniospinal radiation alone or concurrent chemoradiation followed by chemotherapy are both viable options.

Recurrence and progression

There are no robust data supporting an optimal followup schedule for PNETs. General guidelines include brain MRI every 3 months and biannual spinal MRI for the first 2 years, biannual brain MRI and annual spinal MRI for the next 3 years, then yearly brain scans. If recurrent disease is detected on these scans, CSF sampling is also required. Bone scans, CT scans, and bone marrow biopsies should be conducted as indicated.

Maximal safe resection should be attempted on recurrent brain tumors. High-dose chemotherapy with autologous stem cell rescue is also feasible for patients showing no evidence of disease following resection or conventional reinduction chemotherapy. On disease progression, options include chemotherapy alone, radiation alone (including SRS), and chemoradiation. Patients with metastases should be managed by chemotherapy or best supportive care such as palliative radiation.

Primary CNS Lymphomas

Primary CNS lymphoma (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 human immunodeficiency virus (HIV) infections.[146] Non-immunosuppressed patients have a better prognosis than AIDS-related cases,[147] and survival of this group has improved over the years with treatment advances.[148]

Pathologically, PCNSL is an angiogecentric neoplasm composed of a dense monoclonal proliferation of lymphocytes, usually diffuse large B-cells.[149] 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 blood-brain barrier. 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.[150]

Treatment Overview

Steroid administration

Steroids can rapidly alleviate signs and symptoms of PCNSL and improve performance status. 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 stereotactic biopsy as the surgical method of choice.[151] This approach stems from the fact that data do not demonstrate a survival advantage for patients who have had a complete resection or extensive subtotal resection when compared with those who have had only a stereotactic biopsy. In addition, subtotal resection is associated with risk for postoperative neurologic deficits.[150]

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 ifosfamide, but it may also be administered as monotherapy if toxicity tolerance is a concern.[152-159] High doses of intravenous methotrexate are necessary (3.5 g/m^2 or higher) to overcome the blood-brain barrier (BBB). Intrathecal methotrexate, when given as prophylaxis in addition to intravenous methotrexate in primary treatment, confers no clinical advantage and is not recommended,[160] but it can be useful where CSF cytology yields positive findings.

Chemotherapy is usually followed by consolidation RT as initial treatment to maximize response and improve outcome (see section below). Pre-irradiation chemotherapy, as opposed to post-irradiation chemotherapy, has been emphasized for several theoretical reasons. Chemotherapy given before RT may be less neurotoxic than if given after. Also, drug delivery to a PCNSL may be increased before radiation, when the BBB is maximally disrupted by the tumor. Radiation results in tumor regression as well as partial repair and closure of the BBB behind the regressing tumor. Finally, pre-irradiation chemotherapy allows one to assess the efficacy of chemotherapy without the confounding variable of radiation.

Because patients over 60 years often suffer from significant and sometimes lethal neurotoxic effects from consolidation radiation,[156,161,162] a number of phase II trials have adopted the approach of chemotherapy with deferred radiation.[152,156,163-167] Complete response to chemotherapy ranged from 42% to 61%, with overall survival between 14 and 55 months. However, a high fraction of patients who have forgone initial radiation - typically older or with significant comorbidities – will fail to achieve complete response to chemotherapy and later require salvage WBRT.

Unfortunately, even for patients who initially achieved complete response, half of them will eventually relapse. Re-treatment with high-dose methotrexate may be useful in patients who achieved complete response with prior exposure.[168] Several other regimens, including temozolomide,[169,170] rituximab,[171] rituximab plus temozolomide,[172] topotecan,[173] and high-dose cytarabine,[174] have also shown activity in the recurrence or progressive disease setting, but none has been established as standard of care. Several groups have tested high-dose chemotherapy with autologous stem cell transplantation with some success,[175-177] although evidence of its advantage over conventional treatment is lacking. The panel included this as an option to consider for progressive or recurrent disease (category 2B).

There has been discussion among panel members regarding the role of intra-arterial therapy with mannitol disruption of the BBB.[178,179] A series of 149 patients reported a response rate of 82% and overall survival reaching 3.1 years.[178] However, given the complexity of the procedure and the high level of expertise required for safety, the panel opted not to recommend this technique at the present time.

Radiation therapy

Historically, WBRT has been the treatment standard to cover the multifocal nature of the disease. The majority of studies demonstrated the limitation of high-dose radiation and led to the currently recommended dose of 24 to 36 Gy in 1.8 to 2.0 Gy fractions to the whole brain, without a boost.[154,157,180-183] Although RT alone is useful in initial tumor control, frequent and rapid relapse of the disease lead to a short overall survival of 12 to 17 months.[147,182] This dismal outcome has prompted the addition of pre-irradiation methotrexate-based combination chemotherapy in later studies. This approach yields impressive response rates of up to 94% and improved overall survival ranging from 33 to 60 months.[154-157,161,162,180,184,185] However, excessive grade 3 and 4 hematologic toxicity (up to 78%) as well as radiation-induced delayed neurotoxicity (up to 32%) sometimes leading to deaths is a primary concern, although most of these studies utilized a high radiation dose of 40 Gy or above. Of note, younger patients (< age 60) consistently fare better, and there is a higher incidence of late neurotoxic effects in older patients.

Thiel and colleagues[158] 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 overall survival (HR = 1.06; 95% CI, 0.80-1.40; P = 0.71), 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%).

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 salvage therapy following chemotherapy failure, with response rates reaching nearly 75%.[186]

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.[187] In addition, restricted diffusion can be seen in the area of the enhancing abnormality on diffusion weighted imaging (DWI) 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 enhanced-contrasted MRI (or contrast 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.

A lumbar puncture with evaluation of CSF should be considered, if it can be done safely and without concern for herniation from increased intracranial pressure. The yield for a positive diagnostic test can be increased by the use of molecular markers of monoclonality, such as an immunoglobulin gene rearrangement. If the CSF is negative, consider an ophthalmologic evaluation including a slit-lamp examination, to exclude an obvious malignant uveitis. Ocular biopsy should follow suspicious findings. Despite CSF or uveal evaluation, the intracranial lesion often requires a brain biopsy for a definitive diagnosis.[151] Because the role of maximal surgical resection is limited to alleviating symptoms of raised intracranial pressure or prevent herniation,[150] stereotactic biopsy is generally preferred to minimize invasiveness. 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 recommended that the steroids be tapered and the patient followed closely, both clinically and radiographically. If and when the lesion recurs, the lesion should be promptly rebiopsied before the initiation of steroids. If, on the other hand, no definitive diagnosis of lymphoma is made from biopsy and the patient has not received steroid therapy, work-up for other diagnoses (for example, inflammatory processes) or rebiopsy is recommended.

Staging workup

Once the diagnosis of PCNSL is established, the patient should undergo a thorough staging workup detailed by The International PCNSL Collaborative Group.[151] This workup involves a complete CNS evaluation including imaging of the entire neuraxis (MRI of the spine with contrast). 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 slit-lamp eye examination, if not previously performed, should also be done, as well as a lumbar puncture for CSF flow cytometry. In addition, blood work (complete blood count and chemistry panel) and a CT of the chest, abdomen and pelvis are required to rule out systemic involvement.

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.

More elaborate tests such as bone marrow biopsy, testicular ultrasound for older men, and body PET scan[188] may be considered (category 2B), although their value in routine workup is still under debate.

Primary treatment

Treatment should be initiated as soon as possible following confirmation of diagnosis. Given the dramatic effect of steroids on symptom relief, they are commonly administered concurrently with workup. Selection of primary therapy depends on the general health condition and age of the patient. For healthier patients with KPS $\geq$ 40, a high-dose methotrexate-containing regimen is recommended. Whether one performs WBRT after systemic chemotherapy depends on the responsiveness of the disease to chemotherapy and on the clinical judgment of the medical and radiation oncologists. WBRT may increase neurotoxicity, especially in patients older than 60 years, and may be withheld in the primary setting. If a patient is found to have malignant uveitis, radiation to the globe has been the standard recommendation

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.[152] Therefore, with a PCNSL patient who has asymptomatic ocular involvement, a reasonable strategy is to delay radiation to the globe in order to see if high-dose methotrexate is effective. Intraocular injection of chemotherapy (category 2B) is also an option. Additionally, if the patient is found to have a malignant pleocytosis in the CSF, direct intrathecal chemotherapy can be considered (category 2B).

Patients with KPS below 40 are too weak to undergo multi-modal treatment. However, these patients are potentially eligible for a change to more aggressive therapy if their performance status improves following steroid therapy. If the health condition remains poor, it is recommended that treatment consist of WBRT in order to rapidly induce a response, diminish neurologic morbidity, and optimize quality of life. Radiation to the globe is advised if ocular involvement is detected. Chemotherapy is also an option; non-methotrexate-based regimens may be used if the patient cannot tolerate methotrexate. If the lumbar puncture or spinal MRI is positive, consider intrathecal chemotherapy plus focal spinal RT.

Progressive Disease

For patients who are treated with prior WBRT and ultimately relapse, they may consider further chemotherapy (systemic and/or intrathecal), reirradiation, or palliative/best supportive care. High-dose therapy with stem cell rescue can also be considered (category 2B).

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 radiation 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 or involved-field RT, with or without chemotherapy.[186] In either case, palliative/best supportive care remains an option, or high-dose chemotherapy with stem cell transplantation may be considered (category 2B).

Primary Spinal Cord Tumors

Spinal tumors are classified according to their anatomic location as extradural, intradural-extramedullary, and intradural-intramedullary. 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%.[189] Extramedullary lesions, most commonly benign meningiomas, account for 70% to 80% of spinal cord tumors.[190] 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,[189] it is common for patients to suffer 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 above 90%.[191-194]

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.[195] Nevertheless, Benes et al[196] 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

Radiotherapy is not recommended as primary therapy because of limited response, unknown histology without surgery, and low radiation 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 1,700 patients with primary spinal gliomas found an association between radiotherapy and worse cause-specific and overall survival, although there may be a bias that patients who received radiation had more adverse factors.[197] The role of adjuvant radiotherapy following incomplete excision or biopsy is controversial.[196,198,199] 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.[200-202]

Systemic therapy

Unfortunately, evidence on efficacious chemotherapeutic agents for primary spinal cord tumors is too scant for specific recommendations. The panel agrees that salvage chemotherapy should be an option where surgery and radiation 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. 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.[203] Whenever possible, maximal safe resection should be attempted. In most cases, post-operative adjuvant radiation is not recommended. However, if symptoms persist after incomplete resection or biopsy, radiation should be administered.

All patients should be followed by sequential MRI scans. 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 radiation 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 CBTRUS are 1.8 and 3.4 per 100,000 people, respectively.[124] 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).[204] Small tumors are often asymptomatic, incidental findings.[205] Seizure is a common presenting symptom occurring in 27% of patients.[206]

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[207]). 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 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 recent stereotactic radiotherapy articles, MR has been used to operationally define pathology. These MR findings include a tumor which is dural-based and isointense with gray matter, demonstrates prominent and homogeneous enhancement (>95%), frequent CSF/vascular cleft(s) and often an enhancing dural tail (60%). However, approximately 10-15% of meningiomas have an atypical MRI appearance mimicking metastases or malignant gliomas. In particular secretory meningiomas may have 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 pre-operative embolization is helpful for operative hemostasis 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 allowing for the use of octreotide brain scintigraphy to help delineate extent of disease and to pathologically define an extra-axial lesion.[208-210] Octreotide imaging with radiolabeled indium or more recently, gallium, may be particularly useful in distinguishing residual tumor from post-operative 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.[211,212] 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 (age, performance status, medical co-morbidities) and treatment-related factors (reasons for symptoms, resectability and goals of surgery). Most patients diagnosed with surgically-accessible symptomatic meningioma undergo surgical resection to relieve neurological symptoms. Complete surgical resection may be curative and is therefore the treatment of choice. Both the tumor grade and the extent of resection impact the rate of recurrence. In a cohort of 581 patients, 10-year progression-free survival was 75% following GTR but dropped to 39% for patients receiving subtotal resection.[213] Short-term recurrences reported for grade I, II, and III meningiomas were 1% to 16%, 20% to 41%, and 56% to 63%, respectively.[214-216] The Simpson classification scheme that evaluates meningioma surgery based on extent of resection of the tumor and its dural attachment (grades I to V in decreasing degree of completeness) correlates with local recurrence rates.[217] 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, subtotal resection 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.[218] Of 92 patients with grade I tumors, Soyuer and colleagues found that radiation following subtotal resection reduced progression compared to incomplete resection alone, but has no effect on overall survival.[219]

Because high grade meningiomas have a significant probability of recurrence even following GTR,[220] postoperative high-dose EBRT (above 54 Gy) has become the accepted standard of care for these tumors to improve local control.[221] A review of 74 patients showed that adjuvant radiotherapy improves survival in patients with grade III meningioma and in those with grade II disease with brain invasion.[222] The role of post-GTR radiotherapy in benign cases remains controversial.

Technical advances have enabled stereotactic administration of radiotherapy by linear accelerator (LINAC), Leksell Gamma Knife™ or Cyberknife™ radiosurgery. The use of stereotactic radiotherapy (either single fraction or 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 (i.e. base of skull meningiomas) or in patients deemed poor surgical candidates because of advanced age or medical co-morbidities. A study of about 200 patients compared surgery with SRS as primary treatment for small meningiomas.[223] The SRS arm had similar 7-year progression-free survival compared to GTR and superior survival over incomplete resection. In another study, Kondziolka and colleagues followed a cohort of 972 meningioma patients managed by SRS over 18 years.[224] Half of the patients have undergone previous surgery. SRS provided excellent tumor control (93%) in patients with grade I tumors. For grade II and III meningiomas, tumor control was 50% and 17%, respectively. These results suggest that stereotactic radiation is effective as primary and salvage treatment for meningiomas smaller than 3.5 cm.

Systemic therapy

Notwithstanding limited data, hydroxyurea has been well-tolerated with modest activity in patients with recurrent meningiomas.[225,226] Targeted therapies that have shown partial efficacy in refractory meningiomas are somatostatin analogues[227] and alpha interferon[228].

NCCN Recommendations

Initial treatment

Meningiomas are typically diagnosed by CT or MRI imaging. Biopsy 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 (< 30 mm) are best managed by observation. If neurologic impairment is imminent, surgery (if accessible) or radiotherapy (EBRT or SRS) is feasible. Asymptomatic tumors 30 mm or larger should be surgically resected or observed. Symptomatic disease requires active treatment by surgery whenever possible. Non-surgical candidates should undergo radiation.

Regardless of tumor size and symptom status, all patients with surgically resected grade III meningioma (even after GTR) should receive adjuvant radiation to enhance local control. Following subtotal resection, radiation should be considered for small, asymptomatic grade II tumors and for large grade I and II tumors. SRS may be used in lieu of conventional radiation 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 meningiomas are followed more closely than grades 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. Less frequent imaging is required beyond 5-10 years.

Upon detection of recurrence, the lesion should be resected whenever possible, followed by radiation. Non-surgical candidates should receive radiation. Chemotherapy is reserved for patients with an unresectable recurrence refractory to radiotherapy. 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 occur ten times more frequently than do primary brain tumors. More recent population-based data reported that about 8% to 10% of cancer patients are inflicted by symptomatic metastatic tumors in the brain.[229,230] A much higher incidence upon autopsy has been reported. As a result of advances in the diagnosis and treatment, most patients improve with treatment and do not die 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 becoming more common in patients with breast cancer as therapy for metastatic disease is improving.[231]

Almost 80% brain metastases occur in the cerebral hemispheres, an additional 15% occur in the cerebellum, and 5% occur in the brainstem.[232] 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 neurological impairment.

Treatment Overview

Surgery

Advances in surgical technique have rendered upfront resection followed by WBRT the standard of care for solitary brain metastases. A retrospective analysis of 13,685 patients admitted for resection of metastatic brain lesions showed a decline in in-hospital mortality from 4.6% in the period 1988-1990 to 2.3% in the period 1997-2000.[233] High-volume hospitals and surgeons produced superior outcomes.

Patchell and his group conducted a study that randomized 95 patients with single intracranial metastases to complete resection alone or surgery plus adjuvant WBRT.[234] Postoperative radiation was associated with dramatic reduction in tumor recurrence (18% vs 70%; P<0.001) and likelihood of neurologic deaths (14% vs 44%; P=0.003). Overall survival, a secondary endpoint, showed no difference between the arms. Comparison of surgery plus WBRT versus WBRT alone is discussed in the WBRT section.

In the case of multiple lesions, the role of surgery is more restricted to obtaining biopsy samples or relieving mass effect. However, evidence from retrospective series suggested survival benefits from tumor resection for selected patients of good prognosis with up to three metastatic sites.[235,236]

Stereotactic radiosurgery

The advent of SRS offered a minimally invasive option as opposed to surgery. Patients undergoing SRS avoid the risk of surgery-related morbidity. Late side effects such as edema and radiation necrosis are uncommon.[237] SRS is mostly successful for small, deep tumors.

In a randomized Japanese study of 132 patients with 1 to 4 metastatic brain tumors smaller than 3 cm, addition of WBRT to SRS did not prolong median survival compared to SRS alone (7.5 months vs. 8.0 months, respectively).[238] However, 1-year brain recurrence rate was lowered in the WBRT plus SRS arm (47% vs. 76%; P<0.001). This likely served to decrease the need for salvage therapy in this group (10/65) compared to patients receiving no upfront WBRT (29/67).

Retrospective comparative studies showed that SRS plus WBRT resulted in equivalent if not better survival compared with surgery and WBRT.[239-241] SRS also conferred a significant improvement in local control, especially for patients with radiosensitive tumors or solitary brain lesions. SRS alone compared to resection plus WBRT was evaluated in a randomized controlled trial by Muacevic et al.[242] The study was stopped prematurely due to poor accrual. In the final analysis based on 64 patients with solitary brain metastases, radiosurgery alone was less invasive and resulted in equivalent survival and local control, but it was associated with a higher rate of distant relapse.

Small patient series have demonstrated local control rates above 70% with SRS in the recurrence setting for patients with good performance status and stable disease who have received prior WBRT.[243-247]

Whole brain radiation therapy

Historically, WBRT was the mainstay of treatment for metastatic lesions in the brain. It continues to play multiple roles in the modern era, as primary intervention where surgery or SRS are not feasible, as adjunctive therapy to prevent recurrence, and as treatment for recurrent disease.

Three randomized trials investigated the effectiveness of WBRT with or without surgery in patients with single brain metastases. In a study of

48 patients, Patchell et al[248] demonstrated that surgery followed by WBRT lengthened overall survival (40 vs. 15 weeks in WBRT arm; P<0.01) and functional dependence (38 vs 8 weeks; P<0.005), as well as decreased recurrence (20% vs. 52%; P<0.02) compared to radiation alone. Similarly, combined treatment led to longer survival and functional independence in another randomized study by Vecht and colleagues (n=63).[249] The greatest difference was observed in patients with stable disease; median survival was 12 months versus 7 months and functional independence was 9 months versus 4 months. 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.[250]

The impact of SRS in addition to WBRT was evaluated in two randomized controlled studies. A multi-institutional trial by RTOG (RTOG 9508) randomly assigned 333 patients with 1 to 3 brain metastases to WBRT plus SRS or radiation only.[251] Despite the inclusion of larger tumors (3-4 cm) that are not favorable to SRS, the authors found a significant survival benefit in the combined arm (6.5 vs. 4.9 months; P=0.04) when a single lesion was involved; this was not observed in patients with multiple lesions. A much smaller trial of 27 patients with 2-4 lesions found no significant difference in survival, although SRS did extend time to local failure (36 vs. 6 months; P=0.0005).[252]

Taken together, WBRT in conjunction with surgery or SRS leads to better clinical outcomes than WBRT alone for good performance patients with solitary metastatic intracranial lesions. However, many patients are not candidates for resection because of the inaccessibility of the tumor, extensive systemic disease, or other factors. WBRT is the main choice of primary therapy for this patient group.

No randomized data are available in the recurrent setting, but case series reported 31% to 70% of symptom-relieving response to irradiation.[253-255]

Systemic therapy

Systemic therapy is rarely used as primary therapy for brain metastases. In randomized studies, addition of carboplatin or temozolomide to WBRT did not improve overall survival compared to radiation alone,[256,257] although there have been reports of increase in progression-free survival or radiologic response with temozolomide.[257,258] Many tumors that metastasize to the brain are not very chemosensitive or have been already heavily pretreated with potentially effective agents. Poor penetration through the BBB is an additional concern. As such, chemotherapy is usually considered as a last line of therapy for recurrent disease when other options have been exhausted (surgery, SRS, radiation). The choice of agent depends on the histology of the primary tumor. Carmustine wafer implantation is a reasonable option at recurrence.[259]

Among various agents, temozolomide may be useful in some patients with previously untreated brain metastases from metastatic melanoma.[260] Temozolomide given on a prolonged schedule plus thalidomide has been tested in a phase II study of patients with brain metastases, but the high toxicity and lack of response rendered the regimen inappropriate.[261]

A study of high-dose methotrexate in patients mostly with breast cancer achieved disease control in 56% of patients.[262] Other agents shown to have activity in breast cancer include platinum plus etoposide,[263,264] and capecitabine with or without lapatinib.[265-267]

A phase I/II study of topotecan plus WBRT has shown a 72% response rate in 75 patients with brain metastases.[268] Unfortunately, a follow-up phase III trial was closed early due to slow accrual.[269]

NCCN Recommendations

Work-up

Patients who present with a single mass or multiple lesions on MRI or CT imaging suggestive of metastatic cancer to the brain, and do not have a known primary, require a careful systemic workup with chest x-ray or CT, abdominal or pelvic CT, or other tests as indicated. FDG-PET can be considered if there are one than one brain lesions, and no primary has yet been found. If no other readily accessible tumor is available for biopsy, a stereotactic or open biopsy resection is indicated to establish a diagnosis. Among patients with a known history of cancer, if there are concerns regarding the diagnosis of CNS lesions, a stereotactic or open biopsy resection or subtotal resection is also needed. Because brain metastases are often managed by multiple modalities, the NCCN panel encourages multidisciplinary consultation prior to treatment for optimal planning.

Treatment for limited (1-3) metastatic lesions

For patients with limited systemic disease or for whom reasonable systemic treatment options exist, aggressive management should be strongly considered. For surgical candidates, high level of evidence supports category 1 recommendations for surgical resection plus post-operative WBRT, and for SRS plus WBRT if only one brain lesion is involved. SRS alone or following resection are also reasonable options. Macroscopic total removal is the objective of surgery. The choice between open resection and SRS depends on multiple factors such as tumor size and location. The best outcome for SRS is achieved for small, deep lesions at institutions with experienced staff. If the tumor is unresectable, WBRT and/or radiosurgery can be used.

Patients with progressive extracranial disease whose survival is less than 3 months, should be treated with WBRT alone, but surgery may be considered for symptom relief. The panel did not reach a consensus on the value of chemotherapy (category 2B). It may be considered in select patients using regimens specific to the primary cancer.

Patients should be followed with MRI every 3 months for 1 year and then as clinically indicated. 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 can receive the following options: 1) surgery; 2) SRS; 3) WBRT; or 4) chemotherapy. However, patients who previously received WBRT or SRS should not undergo WBRT at recurrence. If the patient had previous SRS with a durable response for greater than 6 months, reconsider SRS if imaging supports active tumor and not necrosis. The algorithm for distant brain recurrences branches depending on whether patients have either 1-3 lesions or more than 3 lesions. In both cases, patients may receive WBRT or consider local/systemic chemotherapy, but patients with 1-3 recurrent tumors have the additional options of surgery or SRS.

WBRT should be used (30-45 Gy, given in 1.8 to 3.0 Gy fractions depending on the patient's performance status, if this modality was not used for initial therapy. Local or systemic chemotherapy may be considered for select patients, if the multiple lesions cannot be controlled by a combination of surgery and radiosurgery.[270]

If systemic CNS disease progression occurs in the setting of limited systemic treatment options and poor performance status, WBRT should be administered if the patients have not been previously irradiated. For patients who have received prior WBRT, re-irradiation is an option only if they had a positive response to the first course of RT treatment. Palliative/best supportive care is also an option in either case.

Treatment for multiple (>3) metastatic lesions

All patients diagnosed with more than three metastatic lesions should be treated with WBRT as primary therapy. The standard regimens for WBRT are 30 Gy in 10 fractions or 37.5 Gy in 15 fractions, but no significant impact to survival was reported with variations in fractionation and dosing according to a meta-analysis of nine randomized trials.[271] 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 (eg., four small lesions). Palliative neurosurgery should be considered if a lesion is causing a life-threatening mass effect, hemorrhage, or hydrocephalus.

After WBRT, patients should have a repeat contrast-enhanced MRI scan every 3 months for 1 year. If a recurrence is found, the algorithm branches depending on whether patients have (1) systemic disease progression with limited systemic treatment options; or (2) stable systemic disease or reasonable systemic treatment options. For patients with systemic disease progression, options include palliative/best supportive care or reirradiation. For patients with stable systemic disease, options include surgery, reirradiation, or chemotherapy.

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.[272] 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; melanoma has the highest rate of leptomeningeal spread.[273,274]

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, cerebral disturbances, mental changes, and motor weakness are among the most common presenting symptoms.[272] The median survival of patients diagnosed with this disorder is less than 3 months with death resulting from progressive neurologic dysfunction but may be extended by early detection and intervention.[273,274]

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. Unfortunately, there is a lack of standard treatments due to meager evidence in literature. Because treatment is palliative, aggressive chemotherapy should only be given to patients most likely to benefit (see “Patient stratification”).

Radiation therapy

Radiation is mainly given for symptom alleviation, CSF flow correction, or for debulking to facilitate chemotherapy.[274-276]

Surgery

The role of neurosurgery for leptomeningeal metastases is mainly to place an intraventricular catheter and subcutaneous reservoir for drug administration.[277] This is preferred over lumbar punctures because of improved drug delivery, safety, superior pharmacokinetics, lower inter-patient variability, and patient comfort.[278]

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 may be administered systemically in high doses. 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 performance status.

Agents used for intra-CSF therapy include methotrexate,[279-281] liposomal cytarabine,[280] cytarabine, thiotepa,[281], rituximab,[282] topotecan,[283] etoposide,[284] and interferon alfa.[285] Breast cancers[262] and lymphomas[286] are particularly responsive to high-dose methotrexate.

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 in 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 if intra-CSF chemotherapy is being considered. A definitive diagnosis is most commonly made by 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. The CSF cytology is positive approximately 50% of the time with the first lumbar puncture, and 90% of the time after repeated CSF examinations in affected patients.[276] 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 a low KPS; 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 a high KPS, no major neurologic deficits, minimal systemic disease, and reasonable systemic treatment options. Many patients fall in between these 2 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. Fractionated EBRT to symptomatic sites (for example, to the whole brain for increased intracranial pressure or to the lumbosacral spine for a developing cauda equina syndrome) can be considered.

Good-risk patients should receive fractionated EBRT to symptomatic sites and to areas of bulky disease identified on neuroimaging studies. A CSF flow scan should be strongly considered to ensure correct flow of chemotherapy.

For patients with a normal CSF flow scan and otherwise stable disease, induction intrathecal chemotherapy should be given for 4 to 6 weeks. Surgical implantation of a subcutaneous reservoir and ventricular catheter (SRVC) should be considered for intrathecal chemotherapy administration. Alternately, patients with breast cancer or lymphoma may receive high-dose methotrexate or craniospinal RT. The patient should be reassessed clinically and with a repeat CSF cytology. Because the cytology is much less likely to be positive from the SRVC than from the lumbar subarachnoid space, it is critical that it be sampled from the site where the cytology was originally positive. If the CSF cytology was originally negative, then reassess from the lumbar region. If the patient is clinically stable or improving 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 if the cytology has converted to negative. The CSF cytology status should be followed every month.

CSF flow abnormalities are common in patients with neoplastic meningitis and 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. CSF flow scans are easily performed in most nuclear medicine departments. Indium 111-DTPA is administered into the SRVC, and imaging of the brain and spine is performed immediately after injection and then imaging is done again at 4 and 24 hours. If significant flow abnormalities are seen, fractionated EBRT is administered to the sites of obstruction and a CSF flow scan is repeated. If CSF flow normalizes, which occurs most commonly in radiosensitive neoplasms, intrathecal chemotherapy commences. If significant flow abnormalities remain, then the patient should be treated as a poor-risk patient (that is, with supportive measures or RT).

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) radiation to symptom sites; (2) chemotherapy; or (3) palliative/best supportive care.

Metastatic Spinal Tumors

Bone metastases are a growing problem among cancer patients due to increasing life expectancy, with the spine being the most frequent affected site. In a report of 832 patients who died of malignancies,

vertebral involvement was found in 36% upon autopsy.[287] Spinal metastases primarily arise from breast, lung, prostate, and renal cancers.[288,289] 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 neurological 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 over 20,000 cases diagnosed each year in the United States.[290] The majority of patients initially complain of progressive radicular pain.[291] This is followed by neurological symptoms such as motor weakness, 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.[292] Therefore, it is paramount that the clinician watches for early suspicious signs and establish prompt diagnosis by spine MRI. Once diagnosed, spinal cord compression is considered a medical emergency; intervention should be implemented immediately to prevent further neurological 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 neurological 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.[293]

The type and aggressiveness of the primary tumor often dictates the choice of treatment as different cancers have varying sensitivities to systemic therapy and radiation. In addition, patient characteristics including performance status 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 three months to be a surgical candidate. Paraplegia for over 24 hours is an exclusion criterion due to low chances of improvement when prolonged neurological deficits exist before surgery.[294] Patients with hematological malignancies should also be excluded as they are best managed by radiotherapy or chemotherapy. Because estimation of life expectancy can be difficult, several groups have developed prognostic scoring systems to help predict surgical outcomes.[295-298]

Posterior laminectomy has been widely used in the past but is now obsolete due to frequent complications and lack of benefit. 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 improve reconstruction outcome. The surgical approach - anterior, posterior, or combined/circumferential - is primarily determined by disease anatomy.[299,300]

Sundaresan and colleagues[293] 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. Overall survival reached 30 months, with 18% 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 4 radiation studies found that patients are twice as likely to regain ambulatory function after surgery than radiation alone.[301] 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 radiation was associated with superior outcome over radiation alone or laminectomy, achieving 75% mean improvement in neurological function, but high surgical mortality rate (mean 10%).was also reported. [302]

To date, only one relevant randomized trial has been reported.[303] Approximately 100 patients with metastatic spinal compression were randomized to surgery plus postoperative RT or RT alone. Compared to the radiation group, significantly more patients in the surgery group regained walking ability (84% vs 57%; P = 0.001) and for a longer time (median 122 days vs 13 days; P = 0.003). The impressive results are obtained with strict eligibility criteria. The study excluded patients with radiosensitive tumors, neurological 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 National Inpatient Sample all-payor database, Patil et al[304] 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

Traditionally, EBRT has been the main form of treatment for spinal metastases. In the modern surgery era, radiation 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 one to three weeks between resection and subsequent radiation.[305]

An excellent response to RT alone for spinal compression was reported by Marazano and colleagues.[306] Three hundred patients were randomized to a short-course (8 Gy x 2 days) or split-course (5 Gy x 3; 3 Gy x 5) 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 is highly dependent on the histology: 70% of nonambulatory breast cancer patients recovered mobility compared to only 20% of hepatocellular carcinoma patients. In general, solid tumors are considered either moderately-radiosensitive (*e.g.*, breast and prostate cancers) or radioresistant (*e.g.,* melanoma, osteosarcomas, cancers of the thyroid, colon, and kidney).[307] On the

other hand, hematological malignancies such as lymphomas and multiple myelomas are highly responsive to RT. Hence, radiation 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.[307] Radiation is also a mainstay of palliative treatment for patients with poor performance status, significant comorbidities, and/or limited life expectancy (less than 3-4 months). Klimo's meta-analysis, including 543 patients treated by radiation, revealed pain control rates of 54% to 83%.[301] Unlike surgery, radiation has no immediate significant treatment-related complications and very few local recurrences. However, it increases surgical complications as it impairs wound healing.

The advent of SRS allowed precise high-dose targeting in one or two fractions while minimizing exposure of the surrounding cord. 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.[308] 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 suggest that SRS is safe and offers more durable response than conventional therapy.[307] However, robust randomized trials with long-term outcomes are still lacking.

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.[309] 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 neurological function improvement, and enhanced blood flow. However, the preference between high-dose (96 mg daily) and low-dose (10 to 16 mg daily) is still unclear.[310-312]

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

NCCN Recommendations

Work-up

Initial work-up 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 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 radiation is the preferred treatment where there is spinal instability and no surgical contraindication. Primary EBRT alone is appropriate for patients with radiosensitive cancers (hematological malignancies) and without evidence of spinal instability. Many fractionation schemes are available (20-37.5 Gy in 5-15 fractions over 1-3 weeks); the most common is a total of 30 Gy in 3-Gy daily fractions for 10 days.[313,314] Primary chemotherapy is also an option for chemo-responsive tumors in the absence of clinical myelopathy.

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, patient should undergo surgical stabilization or minimally-invasive vertebral augmentation to relieve pain. These procedures should be followed by adjuvant radiation to obtain local control.

If no fracture or instability is found, EBRT is the treatment of choice. Alternatives are chemotherapy for responsive tumors, or surgery plus adjuvant RT in select cases. Patients experiencing intractable pain or rapid neurological decline during RT should consider surgery or SRS. 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.

Progression and recurrence

Follow-up involves MRI or CT imaging within one to three months post-treatment, then every three to six months as 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. Patients previously treated by chemotherapy can consider salvage radiotherapy.

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