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Central Nervous System Cancers

Clinical Practice Guidelines in Oncology

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Overview

In 2010, an estimated 22,020 new cases of primary brain and other nervous system neoplasms were diagnosed in the United States,[1] and approximately 13,140 deaths occurred from these tumors. The incidence of primary malignant brain tumors has been increasing over the past 30 years, especially in elderly persons.[2] Metastatic disease to the central nervous system (CNS) occurs much more frequently, with an estimated incidence approximately 10 times that of primary brain tumors. Between 20% and 40% of patients with systemic cancer will develop brain metastases.[3]

NCCN Clinical Practice Guidelines in Oncology for Central Nervous System Cancers

Key Words

NCCN Clinical Practice Guidelines, NCCN Guidelines, angiogenesis, astrocytoma, bevacizumab, brain metastases, brain tumor, chemotherapy, glioblastoma, irinotecan, temozolomide, spinal tumors, medulloblastoma, PTEN *(JNCCN* 2011;9:352–400)

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g., randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

The full NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Central Nervous System Cancers are not printed in this issue of *JNCCN*, but can be accessed online at www.NCCN.org.

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

Please Note

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

Disclosures for the NCCN Guidelines Panel for Central Nervous System Cancers

At the beginning of each NCCN Guidelines panel meeting, panel members disclosed any financial support they have received from industry. Through 2008, this information was published in an aggregate statement in *JNCCN* and online. Furthering NCCN's commitment to public transparency, this disclosure process has now been expanded by listing all potential conflicts of interest respective to each individual expert panel member.

Individual disclosures for the NCCN Guidelines for Central Nervous System Cancers panel members can be found on page 400. (The most recent version of these guidelines and accompanying disclosures, including levels of compensation, are available on the NCCN Web site at www.NCCN.org.)

These guidelines are also available on the Internet. For the latest update, please visit www.NCCN.org.

NOTE: This manuscript highlights only a portion of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Central Nervous System Cancers. Please refer to www.NCCN.org for the complete NCCN Guidelines.

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 may have a malignancy that is either highly responsive or 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, and venous thromboembolism, which can seriously impact quality of life. Involvement of an interdisciplinary team, including neurosurgeons,

Text continues on p. 380

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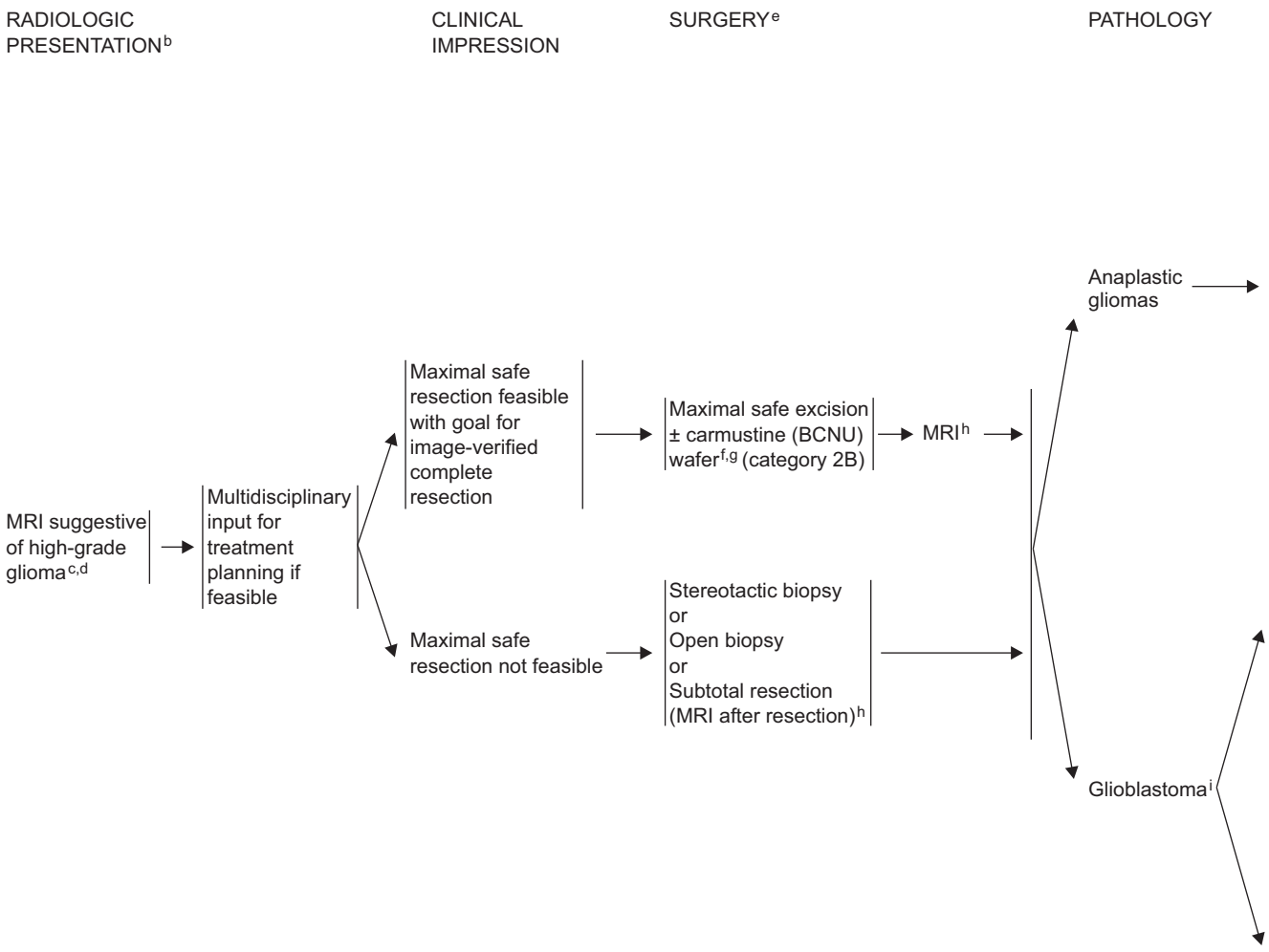
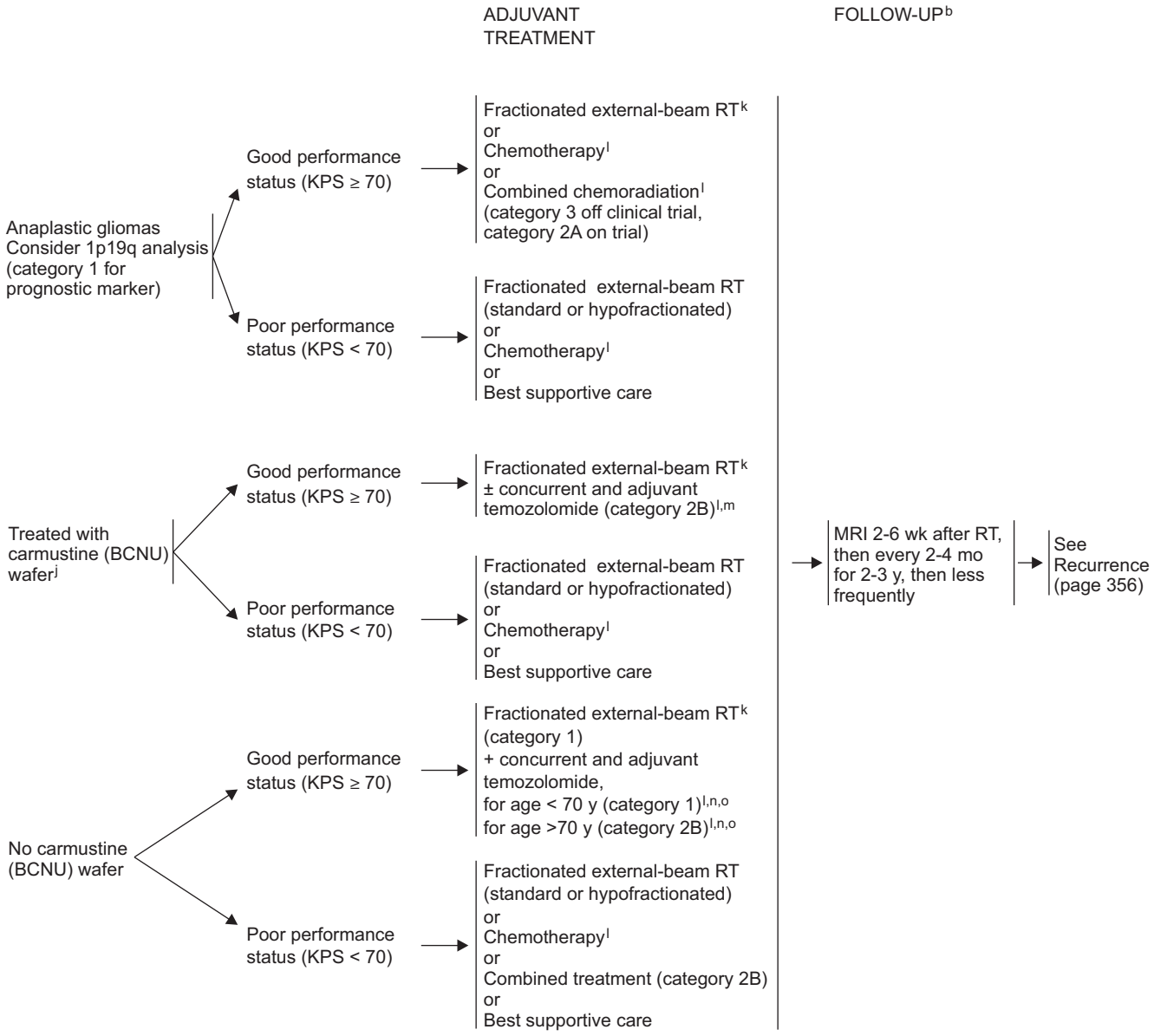
Subcommittees: [a]Meningiomas; [b]Metastatic Spine Tumors; [c]PCNSL Review; [d]Adult Medulloblastoma; [e]Primary Spinal Cord Tumors; [f]Principles of Imaging; [g]Principles of Systemic Therapy; [h]Principles of Radiation Therapy; [i]Principles of Brain Tumor Management (Please note: Underlining denotes the lead of the subcommittee)

Specialties: †Medical Oncology; ‡Hematology/Hematology Oncology; §Radiotherapy/Radiation Oncology; ΨNeurology/Neuro-Oncology; ¶Surgery/Surgical Oncology; ¥Patient Advocacy

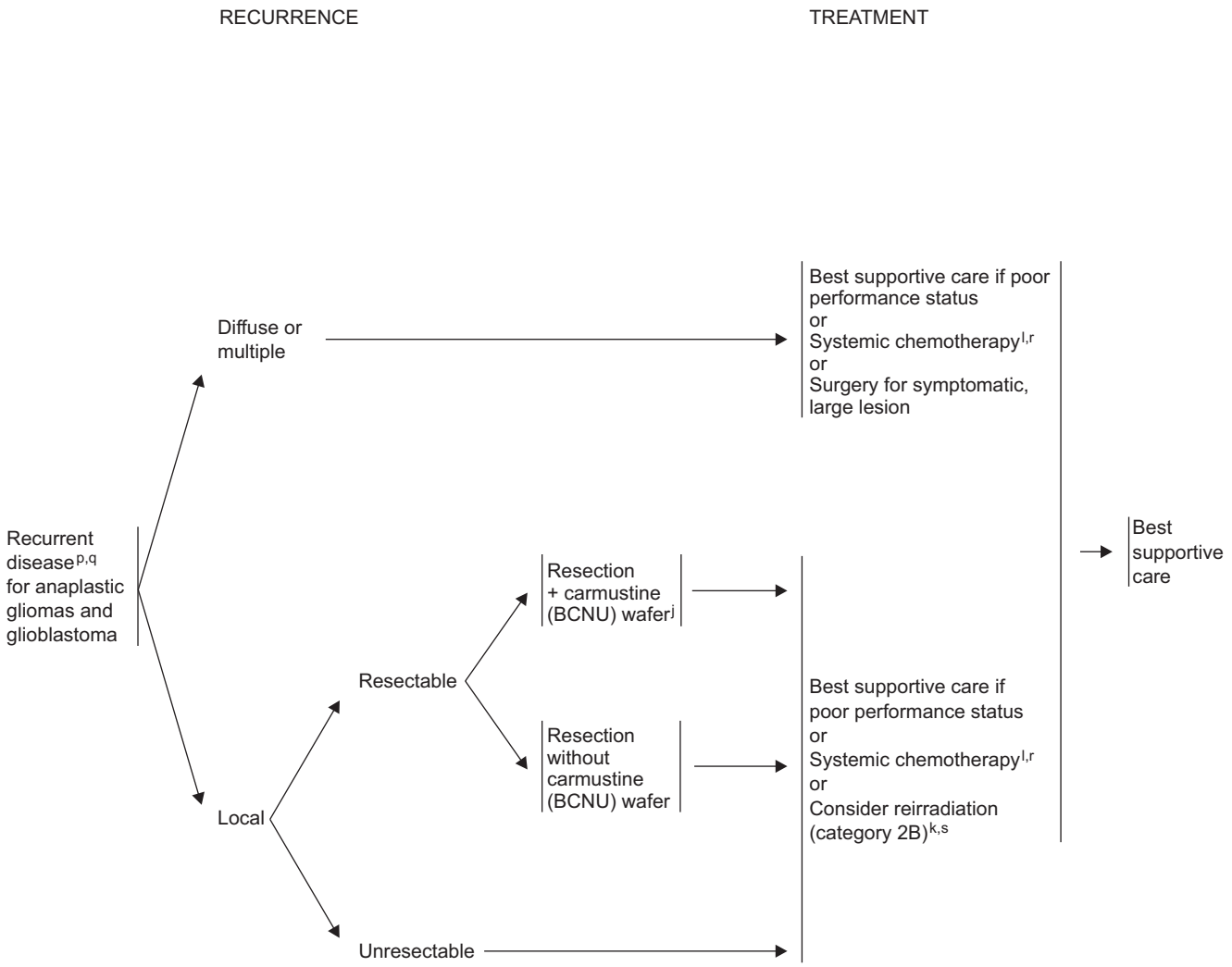


[a] This pathway includes the classification of mixed anaplastic oligoastrocytoma (AOA), anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), and other rare anaplastic gliomas.
[b] See Principles of Brain Tumor Imaging (page 374).
[c] Biopsy first if MRI compatible with CNS lymphoma.
[d] Consider a multidisciplinary review in treatment planning, especially once pathology is available (see Principles of Brain Tumor Management [pages 378 and 379]).
[e] See Principles of Brain Tumor Surgery (page 374).
[f] If frozen section diagnosis supports high-grade glioma.
[g] Treatment with carmustine (BCNU) wafer may impact enrollment in some adjuvant clinical trials.
[h] Postoperative MRI should be performed within 72 hours after surgery.
[i] This pathway also includes gliosarcoma.

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



[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 (page 374).
[j] Treatment with BCNU wafer, reirradiation, or multiple prior systemic therapies may impact enrollment in some adjuvant clinical trials.
[k] See Principles of Brain Tumor Radiation Therapy (page 375).
[l] See Principles of Brain Tumor and Spinal Cord Systemic Therapy (pages 376 and 377).
[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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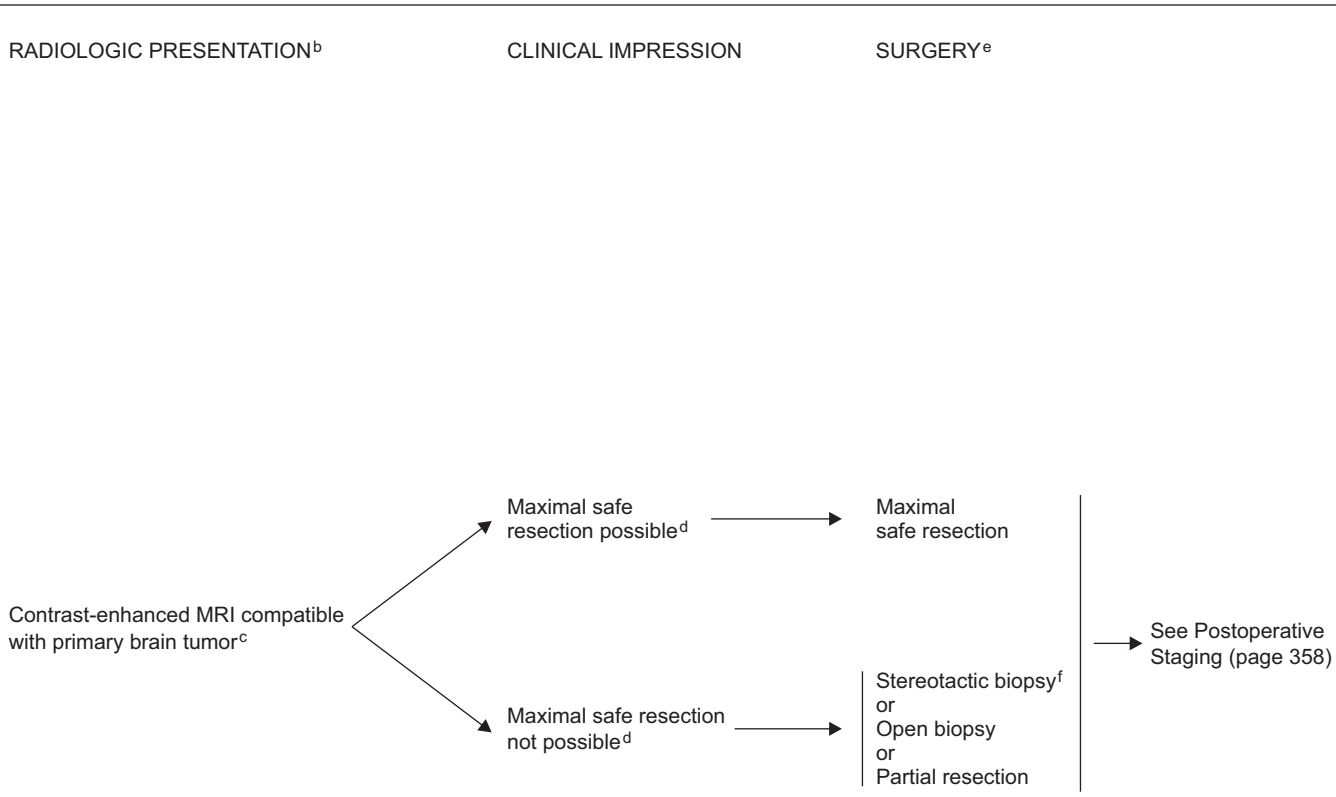
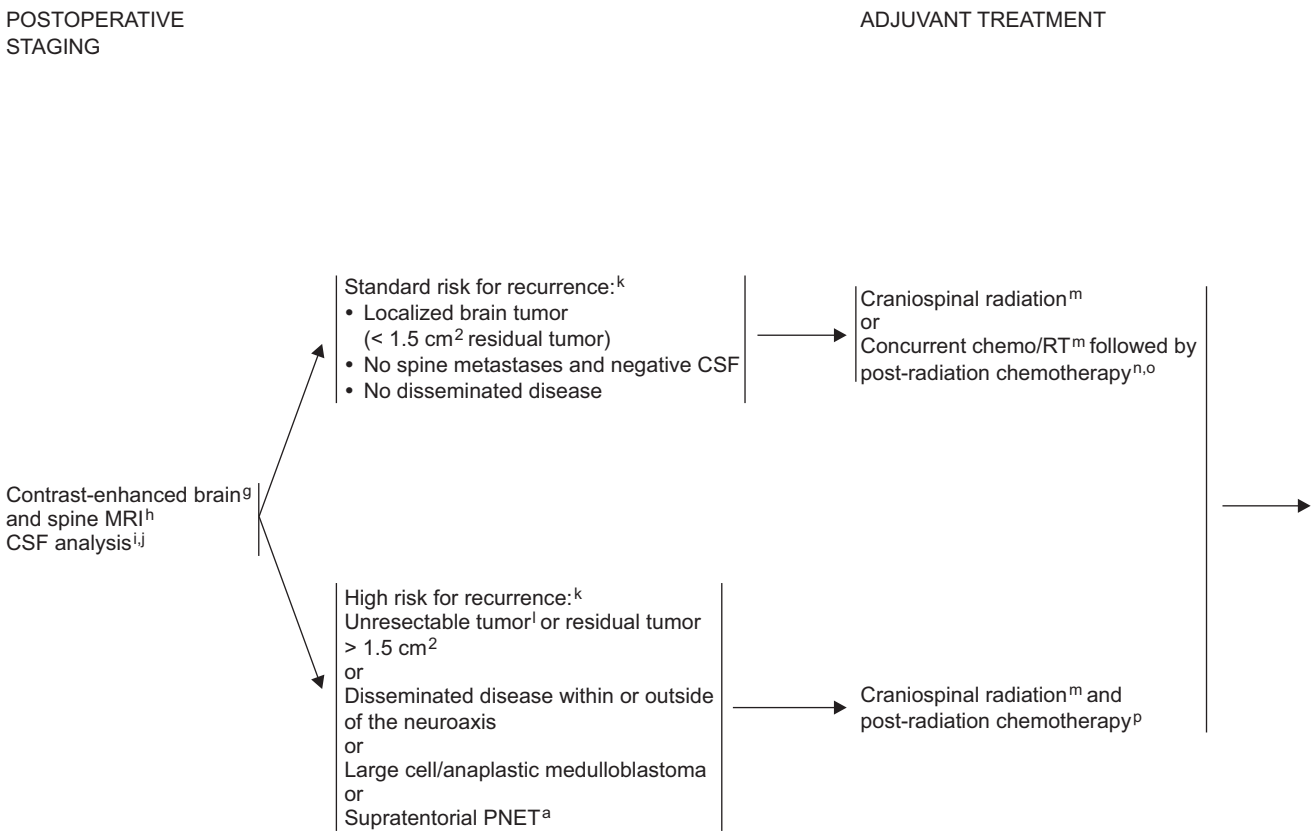
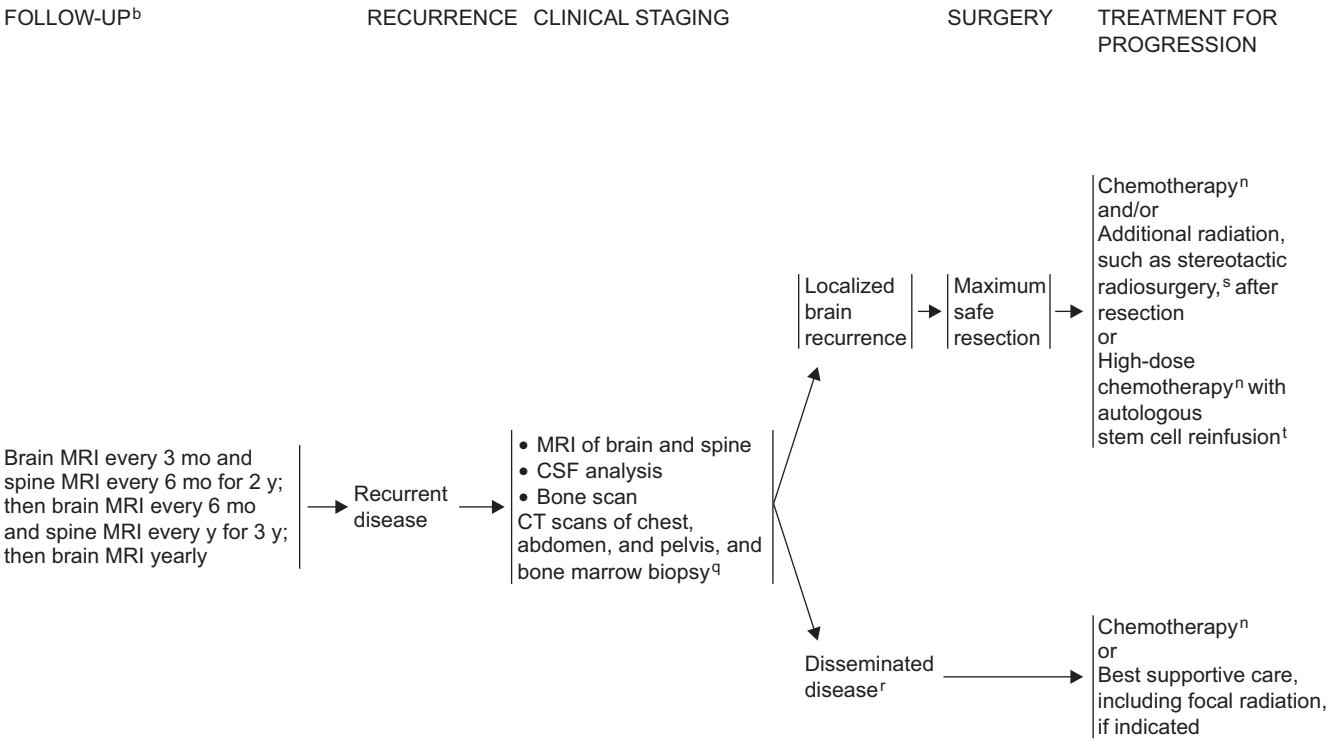
[j] Treatment with BCNU wafer, reirradiation, or multiple prior systemic therapies may impact enrollment in some adjuvant clinical trials.
[k] See Principles of Brain Tumor Radiation Therapy (page 375).
[l] See Principles of Brain Tumor and Spinal Cord Systemic Therapy (pages 376 and 377).
[p] Consider 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 months of the end of RT.
[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 good response to prior RT.



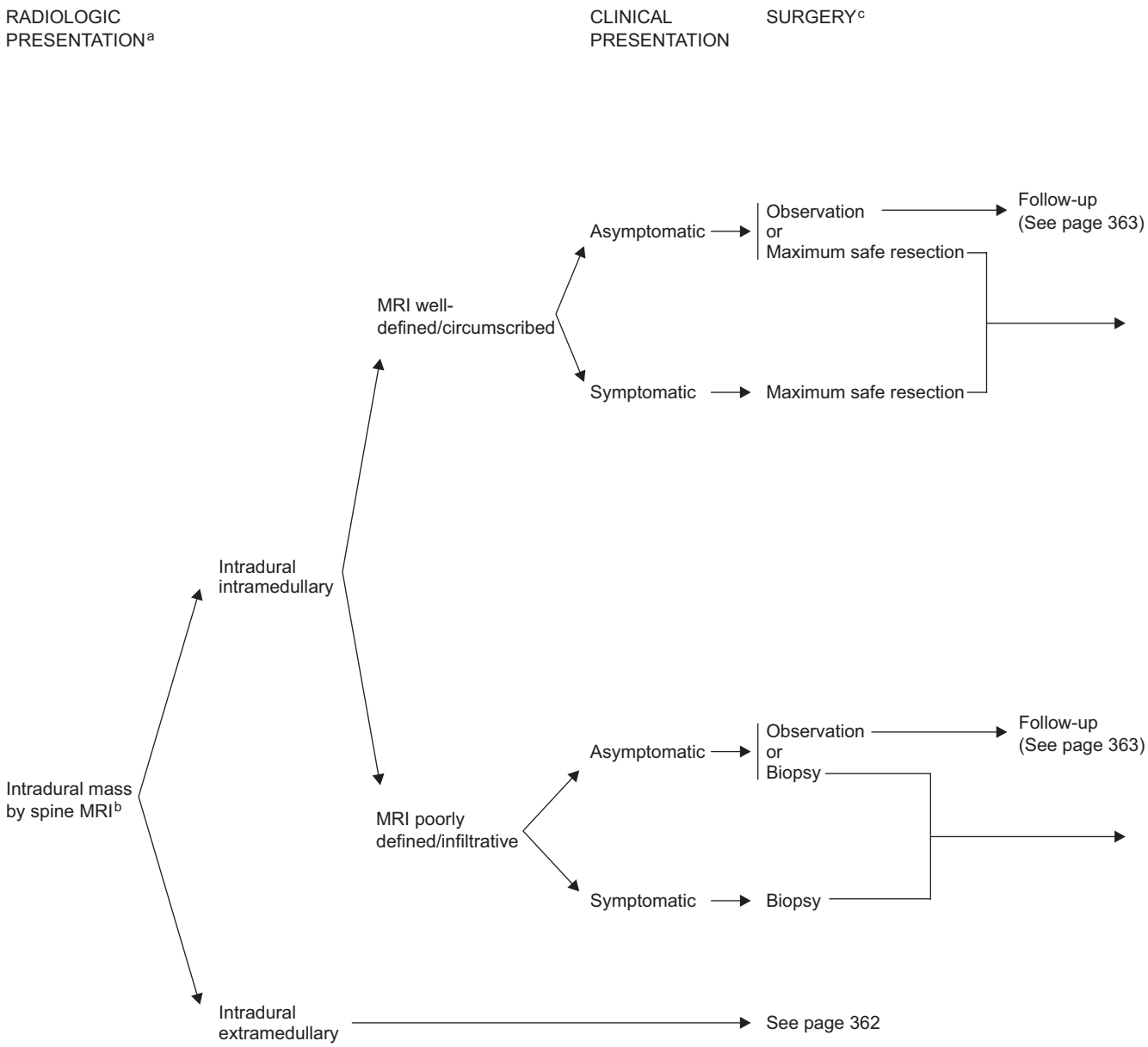
[a] Excluding pineoblastomas and esthesioneuroblastoma.
[b] See Principles of Brain Tumor Imaging (page 374).
[c] Consider a multidisciplinary review in treatment planning, before surgery and once pathology is available (see Principles of Brain Tumor Management [pages 378 and 379]).
[d] Placement of ventriculoperitoneal (VP) shunt for management of hydrocephalus is acceptable if needed.
[e] See Principles of Brain Tumor Surgery (page 374).
[f] Strongly recommend referring patient to a brain tumor center to be evaluated for possible further, more complete surgical resection.



[a] Excluding pineoblastomas and 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 performed 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 Jr. An operative staging system and a megavoltage radiotherapeutic technic for cerebellar medulloblastomas. Radiology 1969;93:1351-1359, and Cohen ME, Duffner PK, eds. Brain Tumors in Children, 2nd ed. New York, NY: McGraw-Hil; 1994:187.)
[l] If only biopsy is possible, consider preirradiation chemotherapy followed by an attempt at resection.
[m] See Principles of Brain Tumor Radiation Therapy (page 375).
[n] See Principles of Brain Tumor and Spinal Cord Systemic Therapy (pages 376 and 377).
[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 examinations.
[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".



[a] Excluding pineoblastomas and esthesioneuroblastoma.
[b] See Principles of Brain Tumor Imaging (page 374).
[n] See Principles of Brain Tumor and Spinal Cord Systemic Therapy (pages 376 and 377).
[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 Neurosurg 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 reinduction chemotherapy.



[a] See Principles of Brain Tumor Imaging (page 374).
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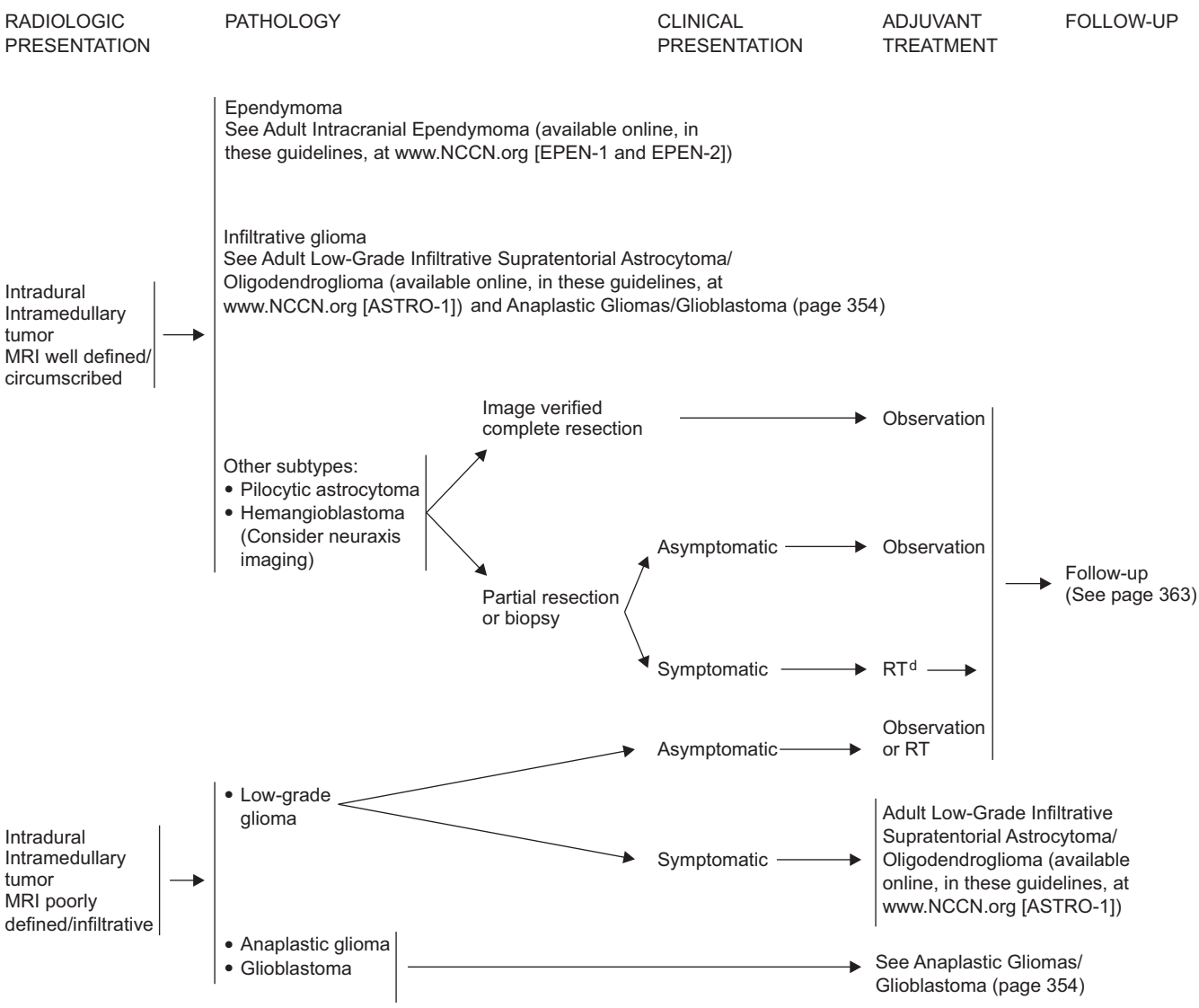
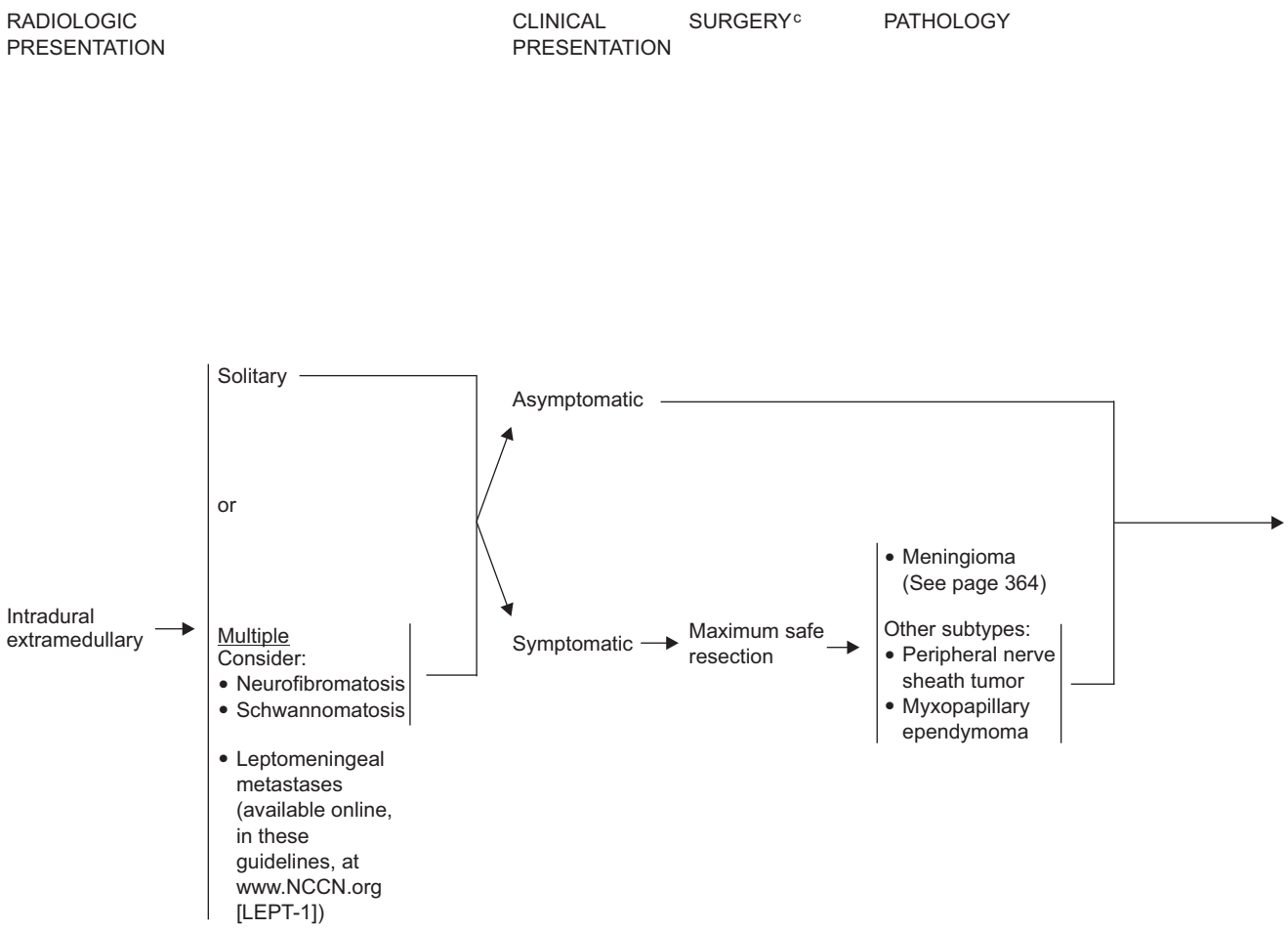
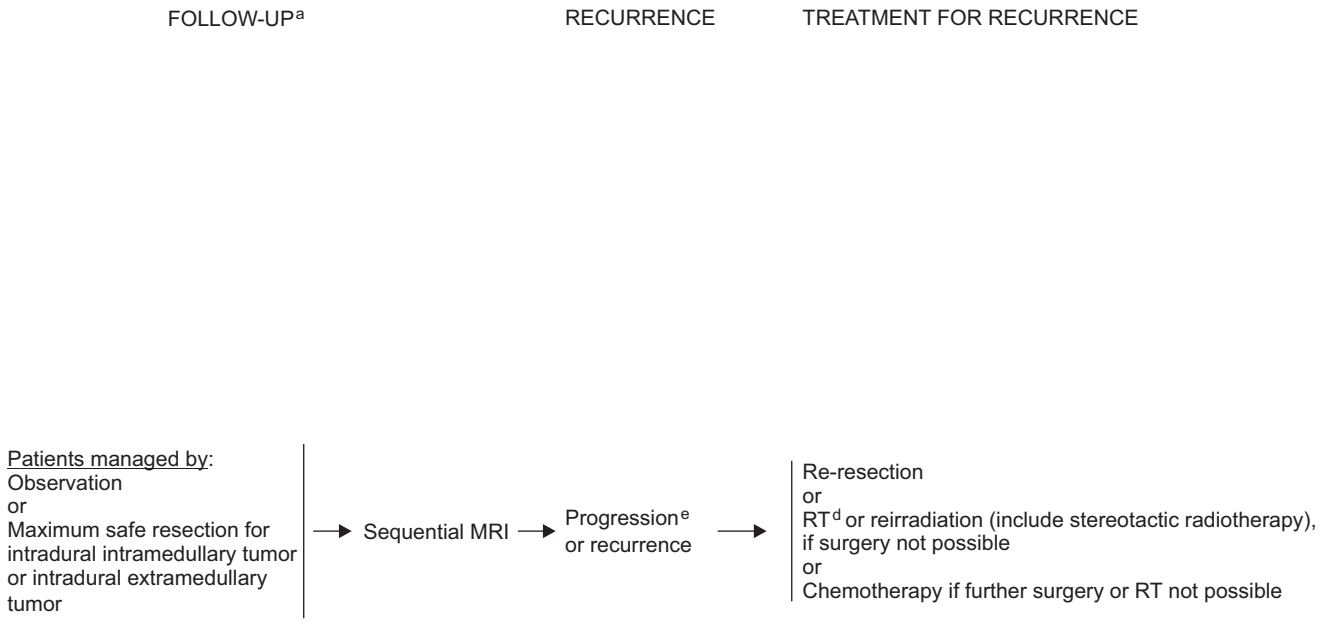
[c] See Principles of Brain Tumor Surgery (page 374).



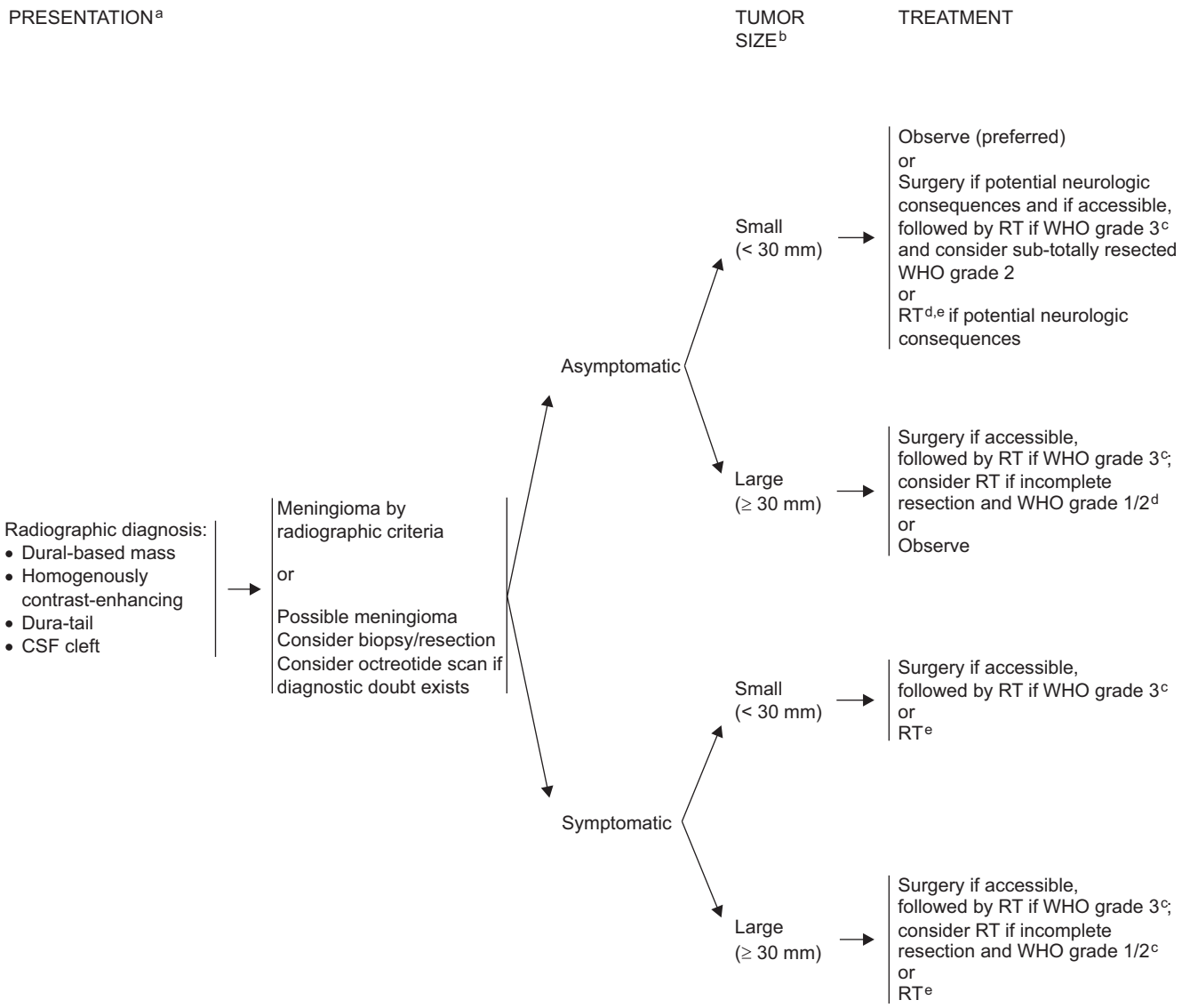
[d] See Principles of Brain Tumor Radiation Therapy (page 375).



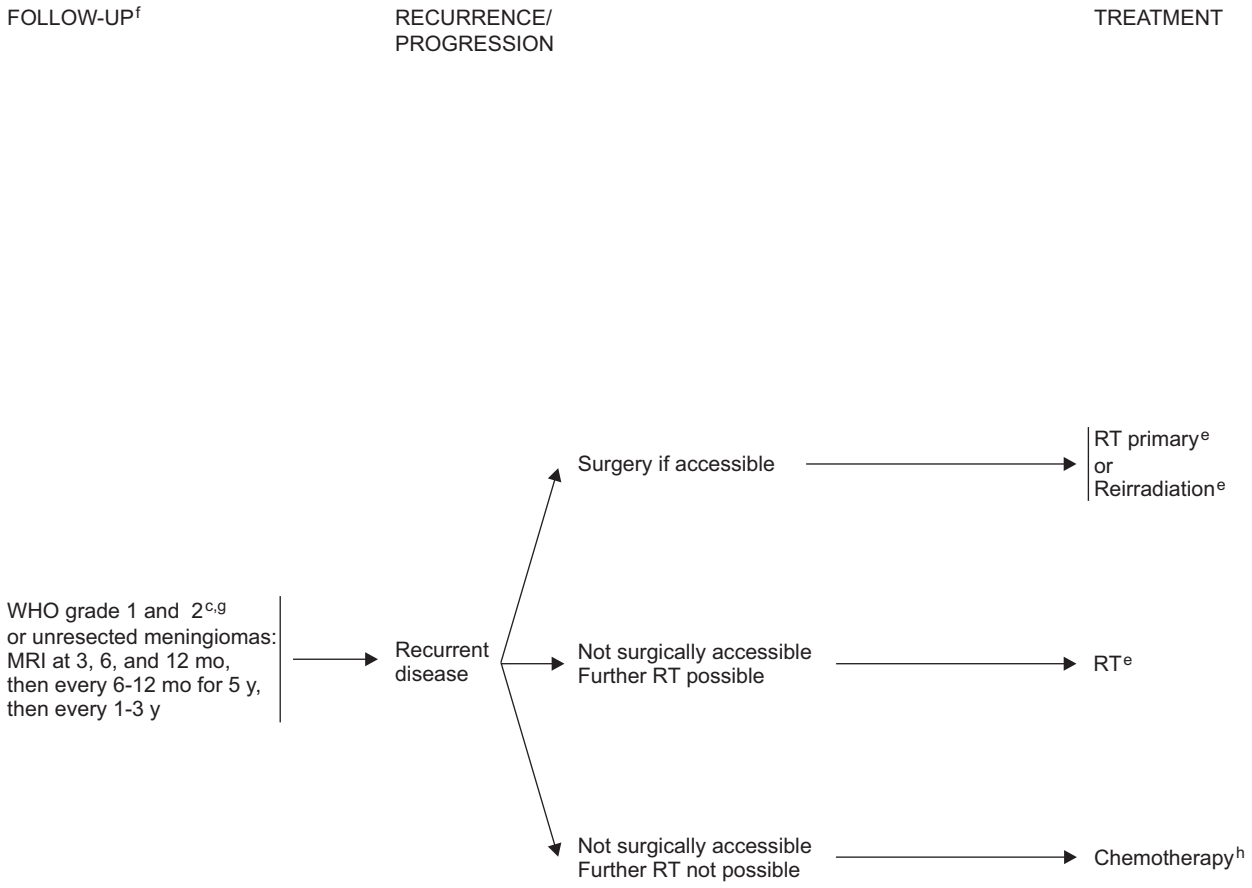
[c]See Principles of Brain Tumor Surgery (page 374).



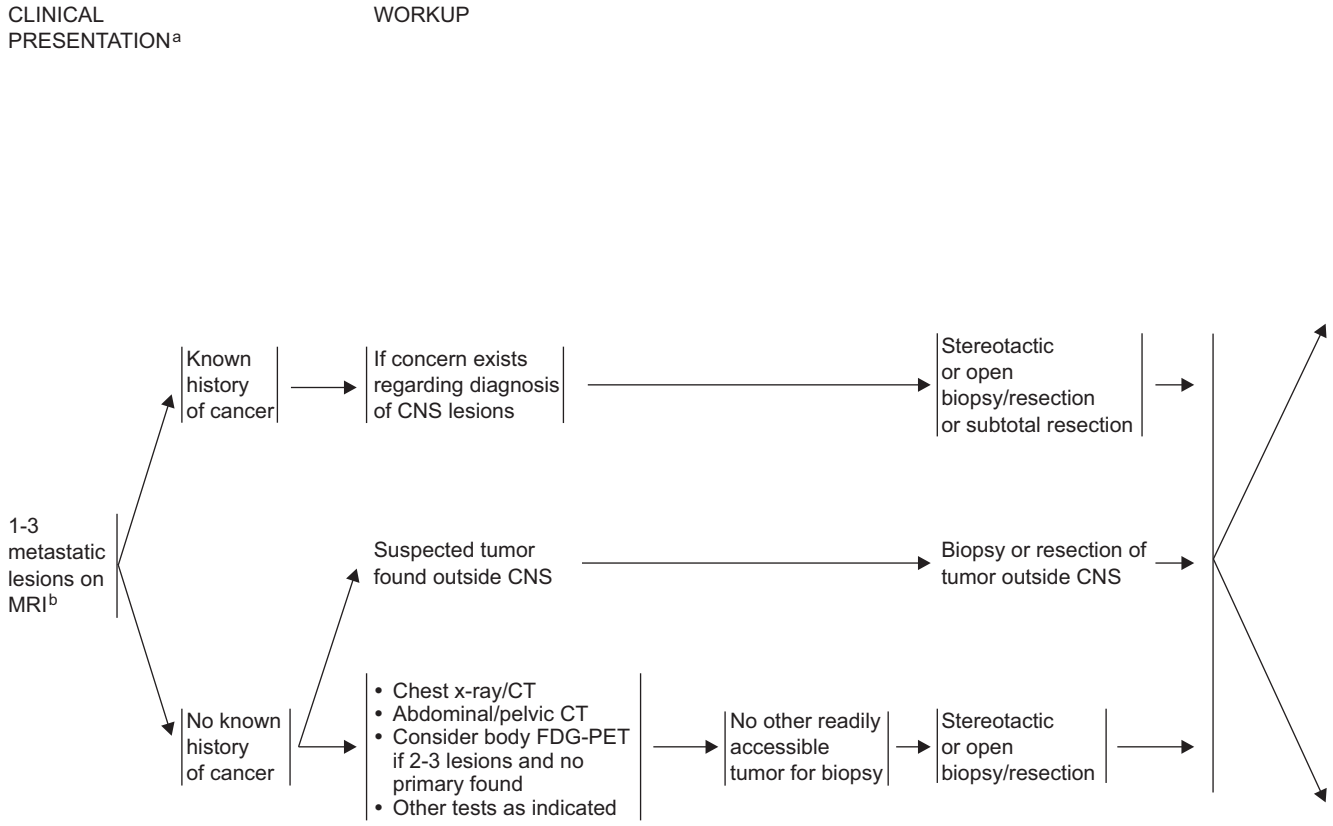
[a]See Principles of Brain Tumor Imaging (page 374).
[d]See Principles of Brain Tumor Radiation Therapy (page 375).
[e]New or worsening symptoms or radiographic progression.



[a] Multidisciplinary input for treatment planning if feasible.
[b] The median growth rate for meningiomas is 4 mm 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 (page 375).



[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 (page 375).
[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 and Spinal Cord Systemic Therapy (pages 376 and 377).



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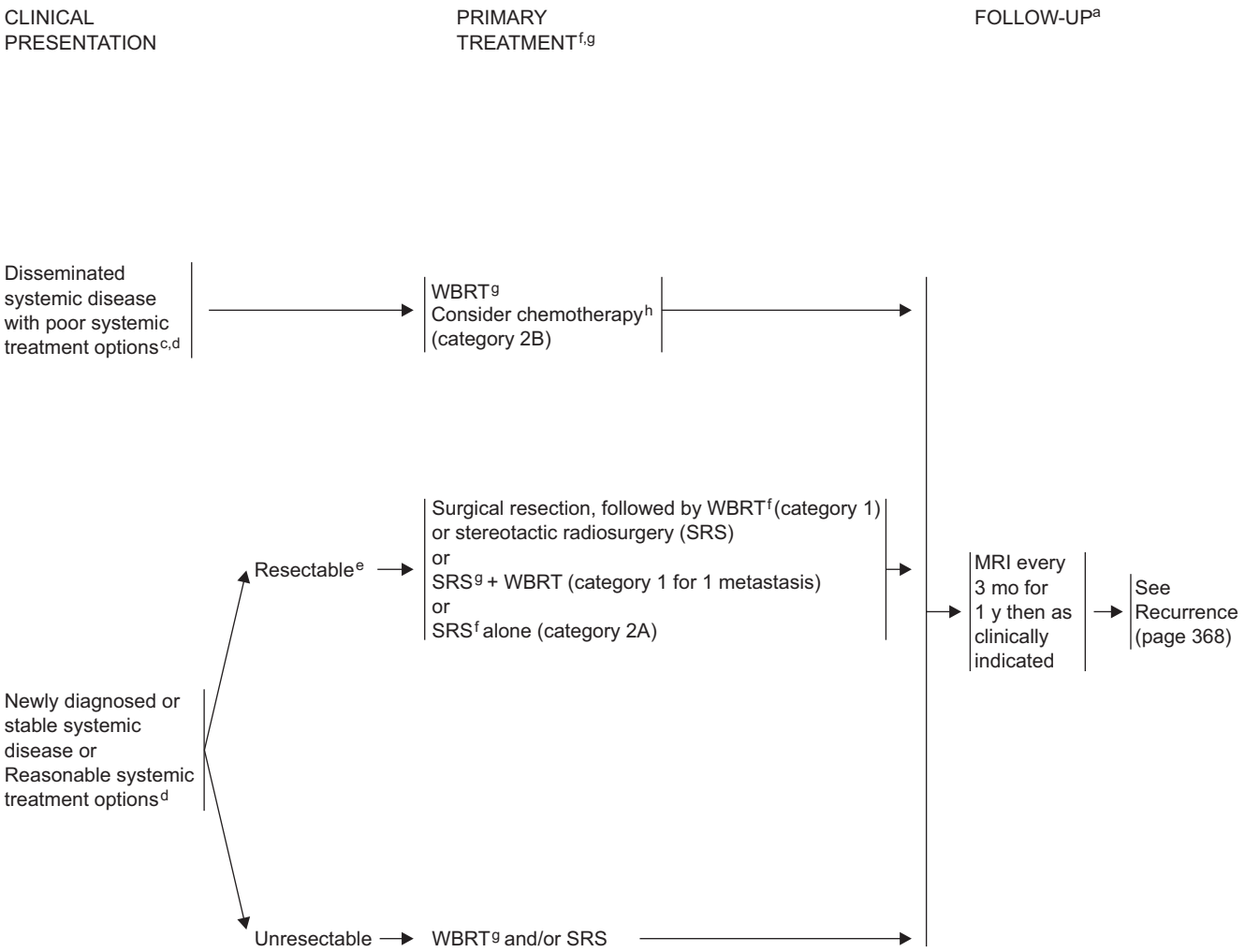
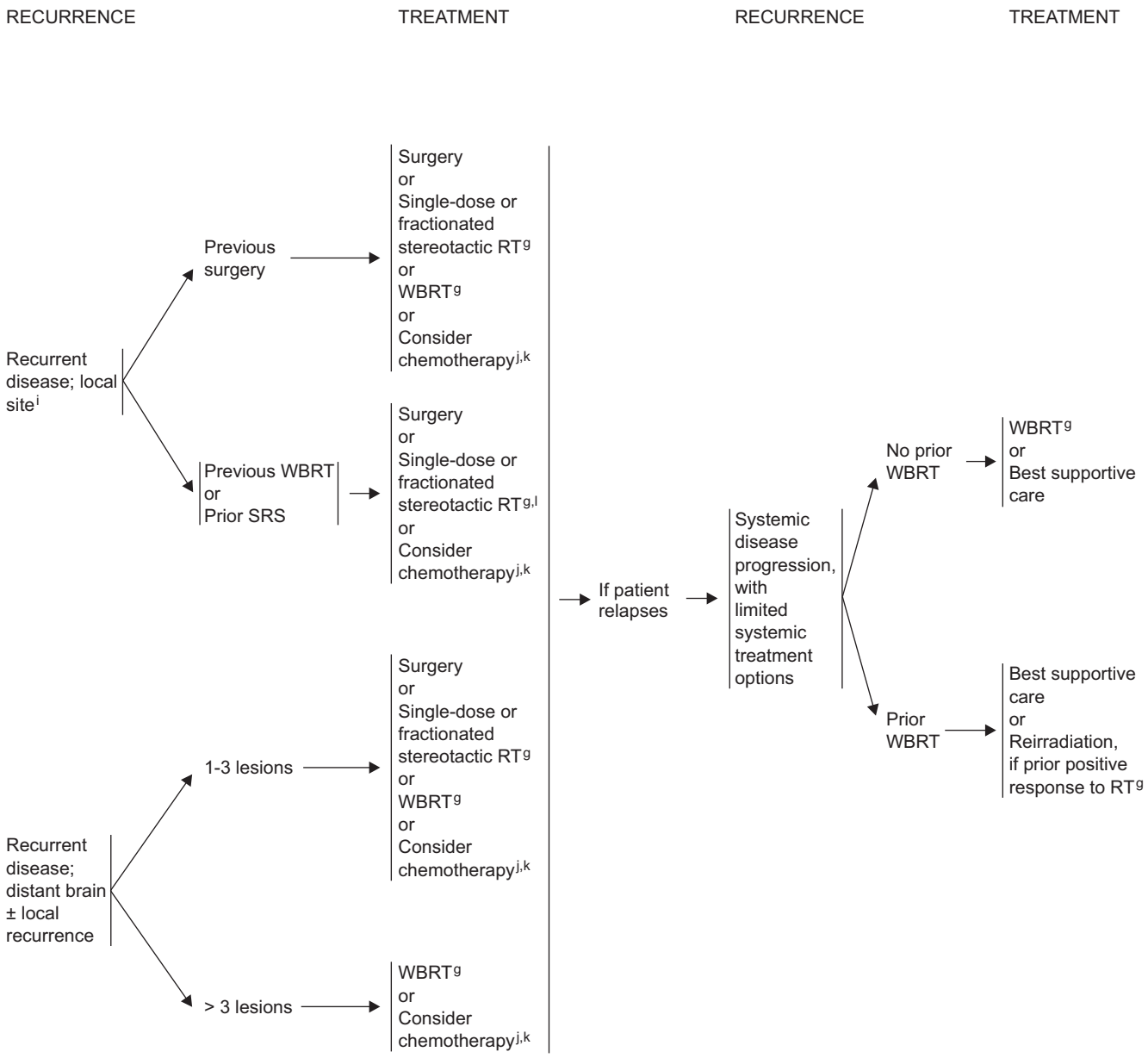
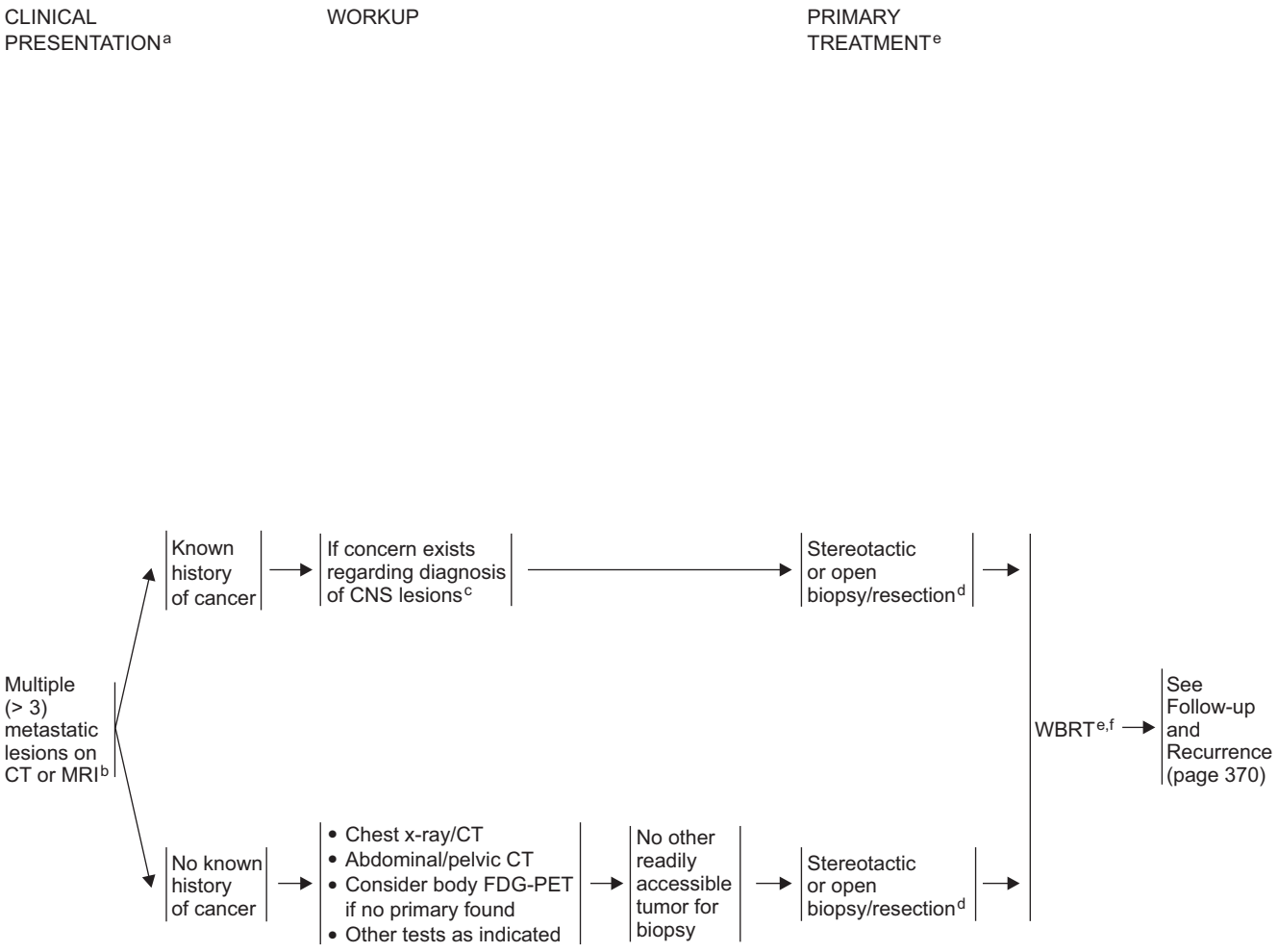


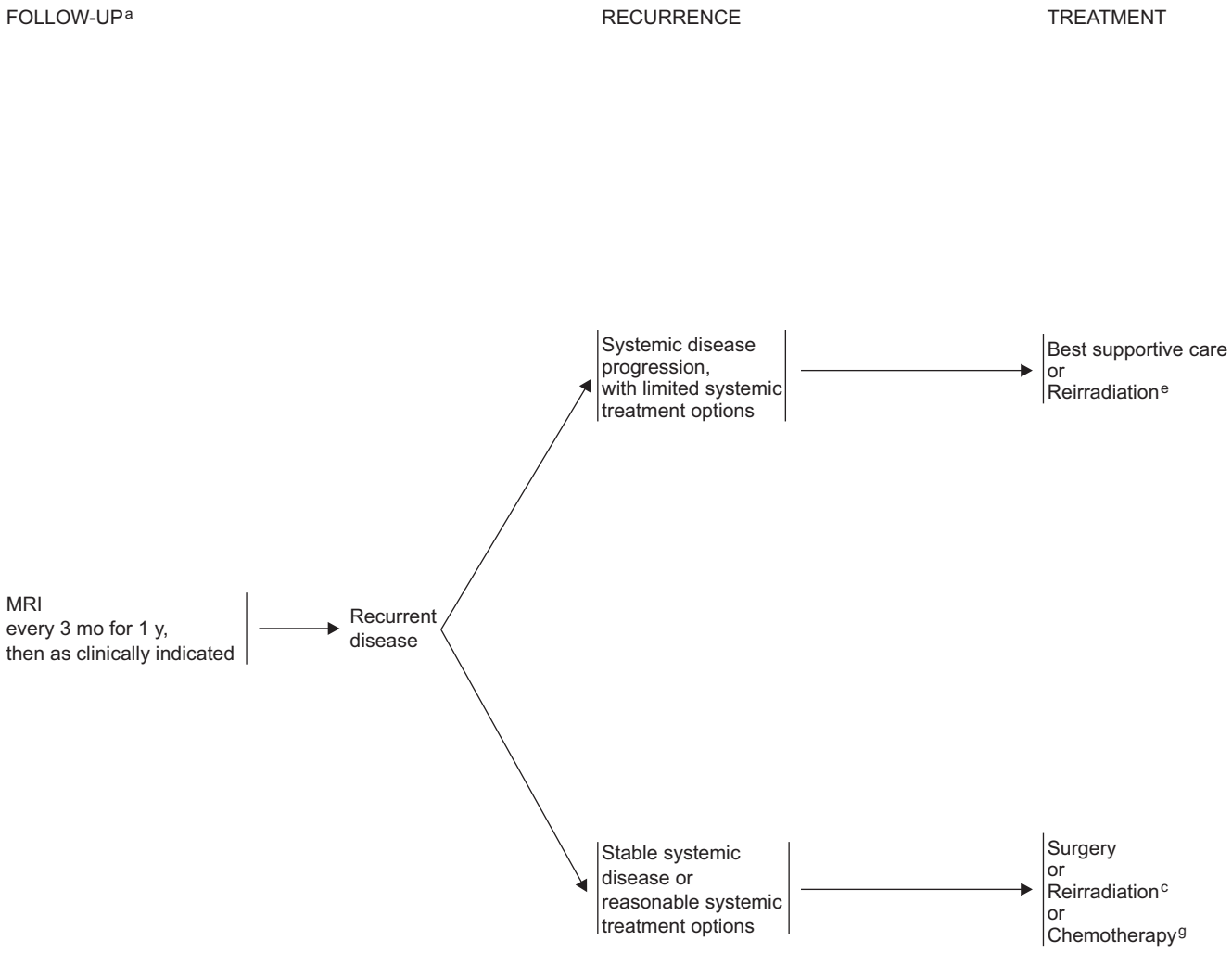
[a]See Principles of Brain Tumor Imaging (page 374).
[c]Consider surgery to relieve mass effect.
[d]Solid brain metastases with systemic nonprimary CNS lymphoma are not well defined, but treatment may include systemic treatment, WBRT, or focal RT.
[e]The decision to resect a tumor may depend on the need to establish histologic diagnosis, the size of the lesion, its location, and institutional expertise. For example, smaller (< 2 cm), deep, asymptomatic lesions may be considered for treatment with SRS versus larger (> 2 cm), symptomatic lesions that may be more appropriate for surgery. (Ewend MG, Morris DE, Carey LA, et al. 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 (page 374).
[g]See Principles of Brain Tumor Radiation Therapy (page 375).
[h]Chemotherapy may be considered in select patients (e.g., 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.



[g] See Principles of Brain Tumor Radiation Therapy (page 375).
[i] Recurrence on radiograph can be confounded by treatment effects. Strongly consider tumor tissue sampling if there is a high index of suspicion of recurrence.
[j] See Principles of Brain Tumor and Spinal Cord Systemic Therapy (pages 376 and 377).
[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.



[a] See Principles of Brain Tumor Imaging (page 374).
[b] Consider a multidisciplinary review in treatment planning, especially once pathology is available (See Principles of Brain Tumor Management [pages 378 and 379]).
[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 (page 375).
[f] SRS should only be considered in selected cases (e.g., limited number of lesions).



[a]See Principles of Brain Tumor Imaging (page 374).
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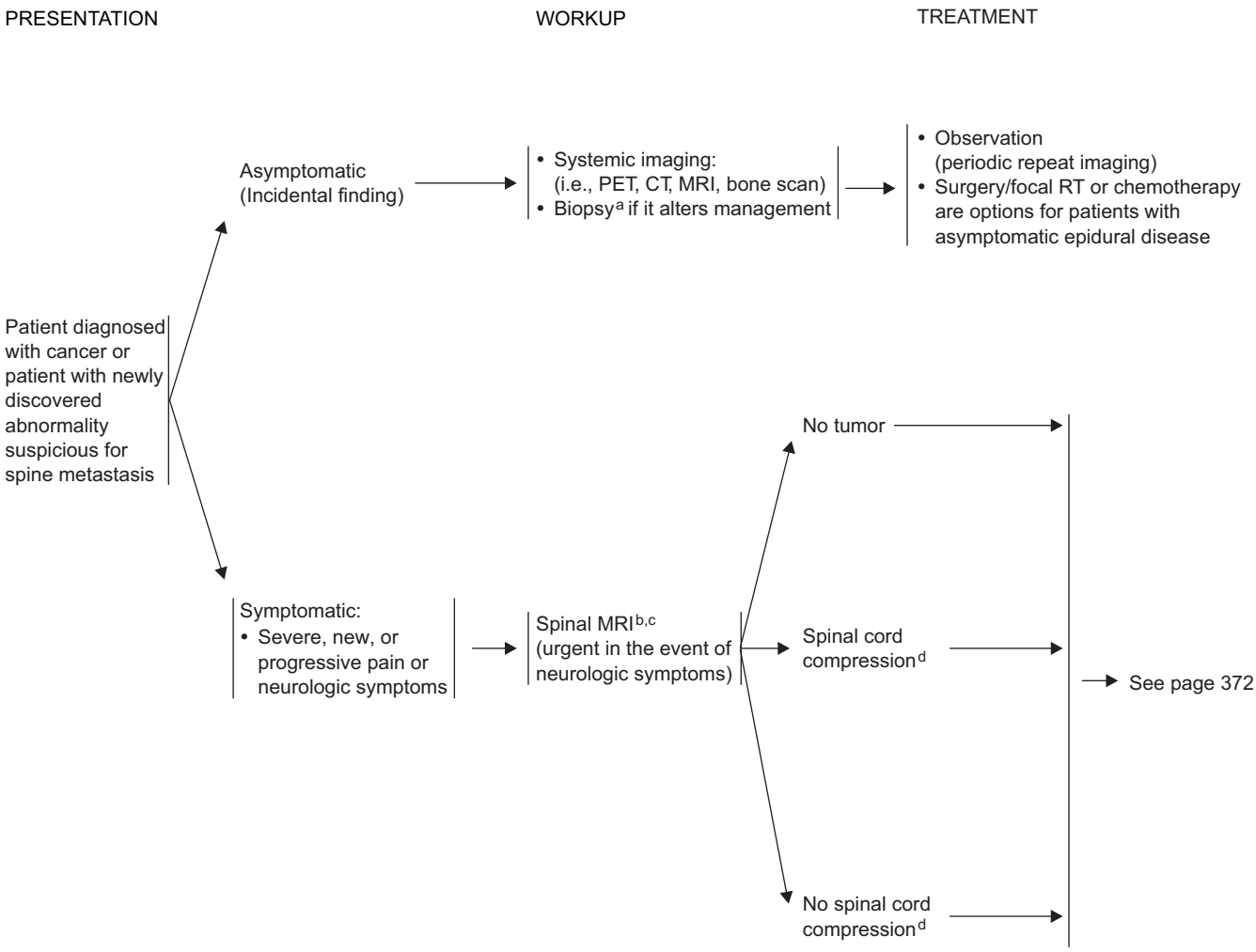
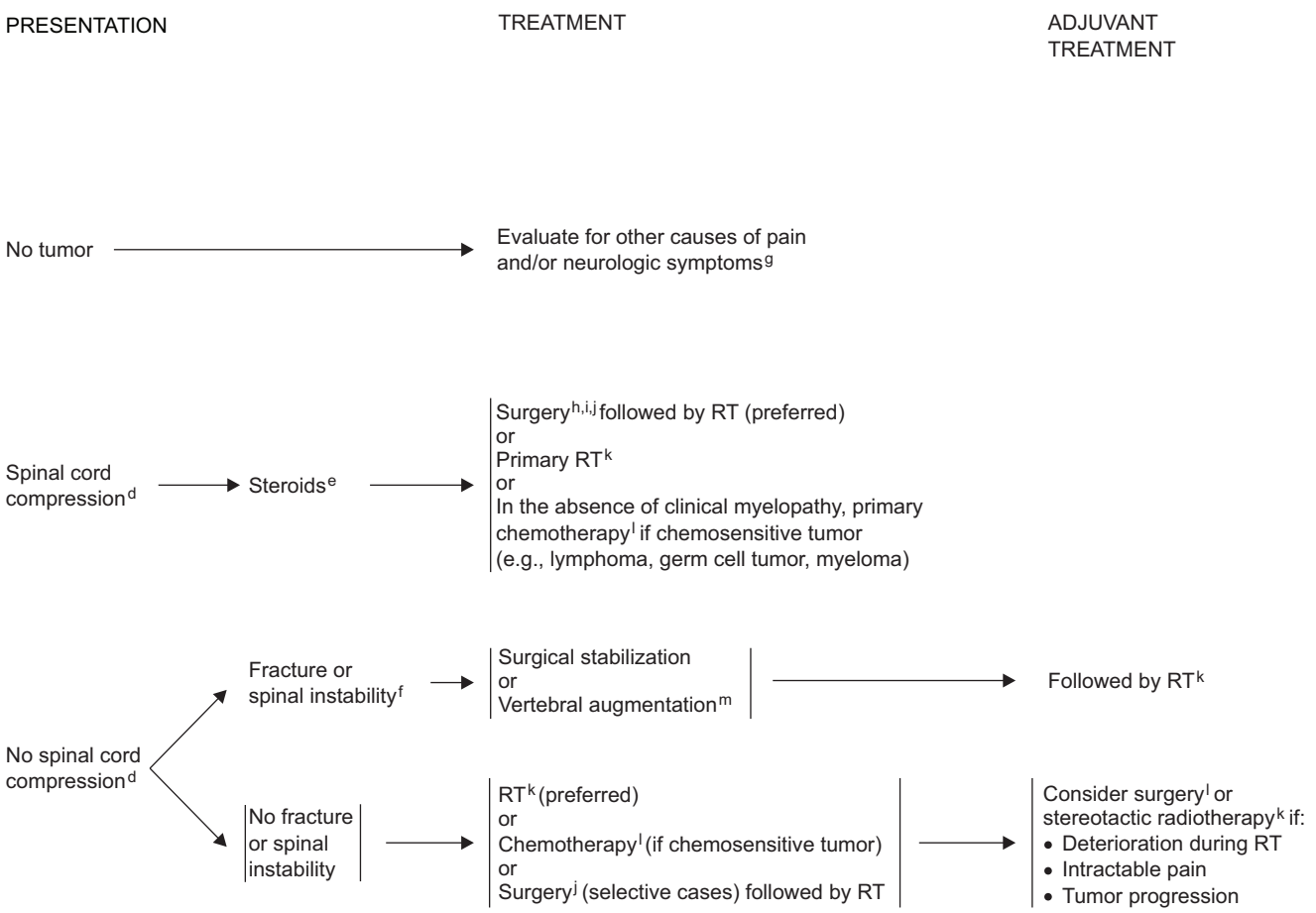
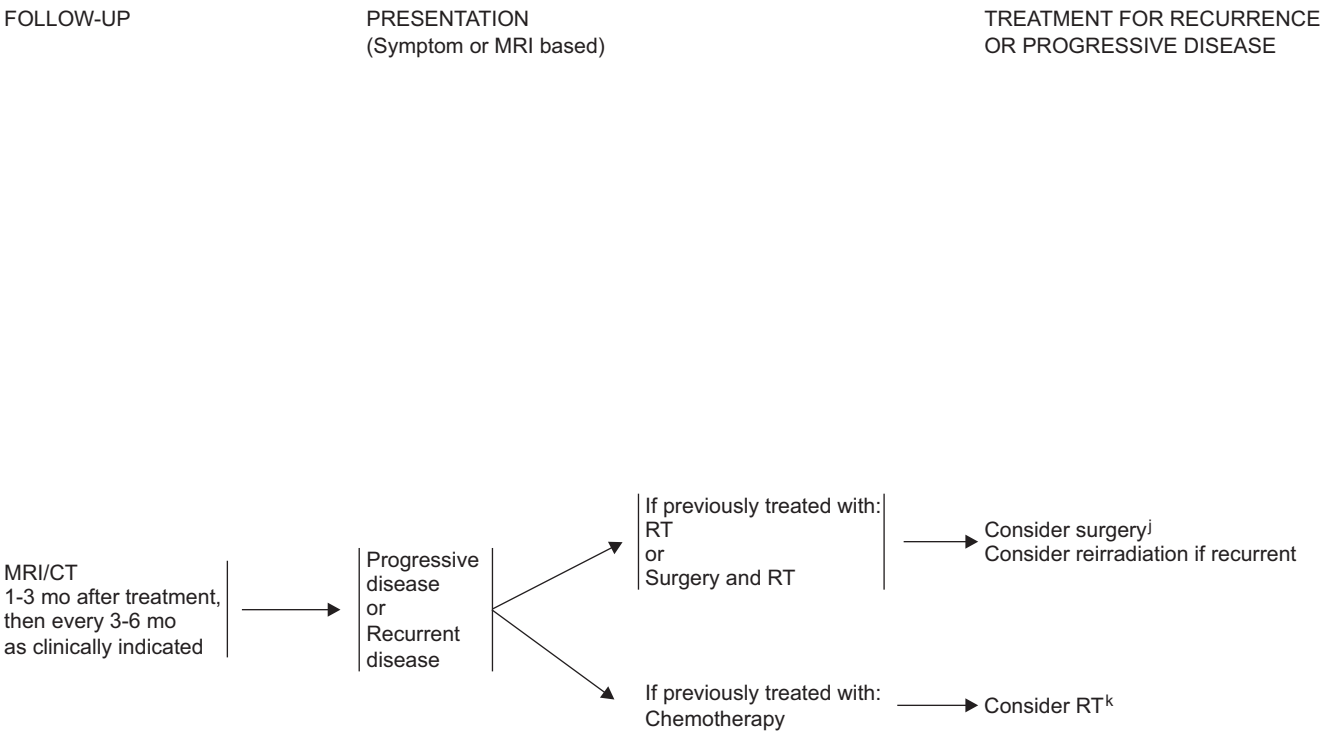


[a]Biopsy if remote history of cancer.
[b]If the patient is unable to have an MRI, then a CT myelogram is recommended.
[c]15%-20% of patients have additional lesions. Highly recommend complete spine imaging.
[d]Includes cauda equina syndrome.



[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 S, Helweg-Larsen S, Mouridsen H, Hansen HH. Effect of high-dose dexamethasone in carcinomatous metastatic spinal cord compression treated with radiotherapy: a randomised trial. Eur J Cancer 1994;30A:22-27).
[f] Spinal instability is grossly defined as the presence of significant kyphosis or subluxation (deformity) or significantly retropulsed bone fragment.
[g] Consider alternative diagnosis of leptomeningeal disease (see LEPT-1, available online, in these guidelines, at www.NCCN.org).
[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, Tibbs PA, Regine WF, et al. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomized trial. Lancet 2005;366:643-648.)
- 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 (page 374).
[k] See Principles of Brain Tumor Radiation Therapy (page 375).
[l] See Principles of Brain Tumor and Spinal Cord Systemic Therapy (pages 376 and 377).
[m] Vertebral augmentation: vertebroplasty, kyphoplasty.



[j] See Principles of Brain Turmor Surgery (page 374).
[k] See Principles of Brain Tumor Radiation Therapy (page 375).

PRINCIPLES OF BRAIN TUMOR IMAGING[1]

- Enhanced MRI of the brain and spine:
  - Gold standard
  - Provides a "static" picture of tumors
  - Benefits: Provides a reasonably good delineation of tumors. Higher grade tumors usually enhance, as does brain leptomeningeal metastasis
  - Limitations: Sensitive to movement, metallic objects cause artifact, patients with implantable devices cannot have an MRI, claustrophobia may be an issue

- Enhanced CT of the brain and spine:
  - 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
  - Optimal use is to differentiate 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 helpful 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 radiolabeled tracers
  - Optimal use is 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, because 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.

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 vs. 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

TISSUE
- Maximum to pathologist
- 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.

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- to 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)

- Tumor volume is best defined using pre- and postoperative imaging, by enhanced T1 or FLAIR/T2 when suspicious for tumor rather than edema. The GTV is expanded by 2-3 cm (CTV) to account for subdiagnosstic tumor infiltration. Fields are usually shrunk for the last phase of the treatment (boost). Although this is the practice in some institutions (i.e., MDACC and UCSF), many follow guidelines from RTOG protocols. There, the initial tumor volume, GTV1, includes any FLAIR or T2 signal abnormality. A CTV expansion of 2 cm is applied. Fields are shrunk to GTV2 to exclude likely edema.
- 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 and 50 Gy.

Adult Medulloblastoma and Supratentorial PNET

- Craniospinal radiation:
  - Standard risk for recurrence: 30-36 Gy with boosting primary brain site* to 55.8 Gy
    OR
    Craniospinal radiation 23.4 Gy with boosting primary brain site to 55.8 Gy[1]
  - High risk for recurrence: 36 Gy with boosting primary brain site* to 55.8 Gy†

Primary Spinal Cord Tumors

- Doses of 45-50.4 Gy are recommended using fractions of 1.8 Gy. In tumors below the conus medularis (i.e., 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- to 2.0-Gy fractions.
- Small WHO grade 1 meningiomas may also be treated with stereotactic radiosurgery doses of 12-15 Gy in a single fraction.

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]

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.

*For posterior fossa tumors, a radiation boost is given to the entire posterior fossa.
†Regimen supported by data from pediatric trials only.

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

[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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PRINCIPLES OF BRAIN AND SPINAL CORD TUMOR SYSTEMIC THERAPY

Anaplastic Gliomas
- Adjuvant Treatment
  - Temozolomide or PCV with deferred RT[1,2]
- Recurrence/Salvage Therapy
  - Temozolomide[3,4]
  - Nitrosourea
  - Combination PCV[5]
  - Bevacizumab[6-8]
  - Bevacizumab + chemotherapy (irinotecan,[9] BCNU,[10] temozolomide)
  - Irinotecan[11,12]
  - Cyclophosphamide[13]
  - Platinum-based regimens*
  - Etoposide[14]

Glioblastoma
- Adjuvant Treatment
  - Concurrent (with RT) temozolomide[15] 75 mg/m^2 daily
  - Post RT temozolomide 150-200 mg/m^2 5/28 schedule
- Recurrence/Salvage Therapy
  - Bevacizumab†[,6,16-18]
  - Bevacizumab + chemotherapy (irinotecan,[16-20] BCNU,[10] temozolomide)
  - Temozolomide[15,21,22]
  - Nitrosourea[23]
  - Combination PCV
  - Cyclophosphamide[13]
  - Platinum-based regimens*

Meningiomas
- Hydroxyurea
- Alpha-interferon[24]
- Somatostatin analogue[25]

Limited (1-3) Metastatic or Multiple (> 3) Metastatic Lesions
- Recurrent Disease‡
  - Treatment as per the regimens of the primary tumor
- Temozolomide 5/28 schedule
- Organ specific therapy
  - High dose methotrexate, cyclophosphamide (breast[26] and lymphoma)
  - Capecitabine, cisplatin, etoposide (breast)[27-33]
  - Topotecan (lung)

Metastatic Spine Tumors
- Use regimen for disease-specific site

Adult Medulloblastoma and Supratentorial PNET
- Adjuvant Treatment
  - Weekly vincristine§ during craniospinal radiation therapy followed by either of the following regimens:
    - Cisplatin, cyclophosphamide, and vincristine§,[34]
    - Cisplatin, lomustine, and vincristine§,[34]
- 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[35] 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[36,37]
    - Temozolomide[38] ± 13-cis retinoic acid
    - High-dose chemotherapy with autologous stem cell reinfusion[35] in patients who achieve a complete response with conventional doses of salvage chemotherapy or have no residual disease after re-resection

*Platinum-based regimens include cisplatin or carboplatin.
†Discontinuation of bevacizumab after progression may be associated with rapid neurologic deterioration and bevacizumab may be continued in these circumstances.
‡Use agents active against primary tumor.
§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 examinations.

See references (facing page)

PRINCIPLES OF BRAIN TUMOR AND SPINAL CORD SYSTEMIC THERAPY
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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 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 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, and 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 practitioner 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 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.

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 24 hours before RT. Patients with high risk of gastrointestinal (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 side effects from steroids.[3]

2. Antiepileptic Drugs

- Seizures are frequent in patients with primary or metastatic brain tumors. Despite this, studies have shown that the use of older, “traditional” antiepileptic drugs (AEDs), 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.
- Many AEDs have significant effects on the cytochrome P450 system, and may have effects on the metabolism of numerous chemotherapeutic agents, such as irinotecan, gefitinib, erlotinib, and temsirolimus. Where possible, these enzyme-inducing AEDs (EIAEDs) should be avoided (phenytoin, phenobarbital, carbamazepine), and non-EIAEDs should be used instead (levetiracetam, topiramate, valproic acid). Patients should be closely monitored for any adverse effects of the AEDs or chemotherapeutic agents.

[1]Depending upon local referral patterns and available expertise, this physician may be a neurosurgeon, neurologist, medical oncologist, or radiation oncologist.
[2]An exception to this rule is in the case of suspected CNS lymphoma. Steroids should be avoided where possible (see PCNS-1 [available online, in these guidelines, at www.NCCN.org]) 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.

PRINCIPLES OF BRAIN TUMOR MANAGEMENT (cont.)

Medical Management---continued

3. Endocrine disorders

- Endocrinopathies are common with brain tumor patients. This may be affected by concomitant steroid use and 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 for thyroid and gonad function.

4. Fatigue (also see the NCCN Clinical Practice Guidelines in Oncology for Cancer-Related Fatigue; to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org)

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

5. Psychiatric disorders (also see the NCCN Clinical Practice Guidelines in Oncology for Distress Management; to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org)

- 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 nontumor patients. If less severe, strong support from behavioral health allies and other qualified counselors is also extremely beneficial. Physicians and other members of the health care team should be sensitive to these symptoms and inquire about them in follow-up visits to determine if the patient may be a candidate for psychological or psychiatric treatment. Communication among 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

- See the NCCN Clinical Practice Guidelines in Oncology for Venous Thromboembolic Disease (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).

Allied Services

- Physical therapy, occupational therapy, and speech therapy may be helpful for many patients with CNS tumors, either benign or malignant. Surgical intervention is not a prerequisite for referral, and these therapies should not be withheld from patients because of the uncertain course of certain malignant tumors. Many patients with aggressive, malignant primary brain tumors or CNS metastases can benefit from inpatient rehabilitation.
- Practitioners are encouraged to serve as a resource 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 to help educate patients and families that involvement of these services does not indicate a state of hopelessness, no further treatment, or abandonment.

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radiation therapists, oncologists, neurologists, and neuroradiologists, is a key factor in the appropriate management of these patients. For any subtype of malignant brain lesions, the panel encourages thorough multidisciplinary review of each patient case once the pathology is available. Further discussion of multidisciplinary care and allied services, and guidelines on medical management of various disease complications, can be found in Principles of Brain Tumor Management on pages 378 and 379.

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) time since last surgery in patients with recurrent disease.[4]

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 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 RT (EBRT) is the most common approach, whereas hypofractionation is emerging as an option for select patients. RT for patients with primary brain tumors usually involves only the tumor volume and margins, whereas whole-brain RT (WBRT) and SRS are used for brain metastases.

Clinicians are advised to consult Principles of Brain Tumor Imaging and Principles of Brain Tumor Surgery (page 374) 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 on page 375. Appropriate chemotherapeutic and biologic regimens for each tumor subtype are listed under Principles of Brain Tumor Systemic Therapy on page 376.

Tumor Types

These NCCN Guidelines focus on management of adult CNS cancers, such as 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 2010 and 2011, specific guidelines on managing meningiomas, primary spinal cord tumors, medulloblastomas, and supratentorial primitive neuroectodermal tumors were 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

Information on low-grade infiltrative astrocytomas and oligodendrogliomas can be found in the full NCCN Guidelines for Central Nervous System Cancers, available online at www.NCCN.org.

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.[5] Glioblastoma is the deadliest brain tumor, with only a third of patients surviving for 1 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 1578 patients were histologic diagnosis, age, and PS.[6]

High-grade astrocytomas diffusely infiltrate sur-

rounding tissues and frequently cross the midline to involve the contralateral brain. Patients with these neoplasms often present with symptoms of increased intracranial pressure or 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 on image studies and 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.

The results of therapy are difficult to assess with CT 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 (e.g., surgery, radiation, 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.[7] This distinct histologic subtype has a much better prognosis than anaplastic astrocytomas and glioblastomas because of its marked sensitivity to chemotherapy[8]; half of the patients are alive at 5 years.[5]

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 gliomas showed that aggressive surgery is a strong prognostic factor compared with biopsy alone ($P < .0001$).[9] Retrospective analyses also suggest that gross total resection lengthens survival and is especially effective in patients with good PS.[10–12] Unfortunately, the infiltrative nature of high-grade astrocytomas frequently renders gross total removal difficult. However, total resection is often possible for oligodendrogliomas, because most occur in the frontal lobes and the tumors are frequently well demarcated.

Unfortunately, nearly all glioblastomas recur. When this occurs, reoperation may improve the outcome for selected patients.[13] According to an analysis by Park et al.,[14] 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 2 randomized trials conducted in the 1970s, which showed increased survival. Walker et al.[15] compared postoperative supportive care, carmustine (BCNU), radiation, and radiation plus BCNU in 303 patients, and reported median survivals of 14, 18.5, 35, and 34.5 weeks, respectively. Another trial of 118 patients also found a benefit in median survival with RT after surgery compared with no RT (10.8 vs. 5.2 months).[16] The typical dose is 60 Gy in 1.8- to 2.0-Gy fractions. Use of abbreviated courses of radiation (total 40–50 Gy) in older patients has been shown to be efficacious.[17,18]

The Radiation Therapy Oncology Group (RTOG) conducted a randomized trial of conventional radiotherapy to 60 Gy plus BCNU alone or preceded by a radiosurgery boost (to 15–24 Gy) in patients with glioblastoma of 4 cm or less.[19] 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 of EBRT with or without temporary 125I seed implant to 60 Gy also failed to show any survival benefit with a brachytherapy boost.[20]

Chemotherapy/Systemic Therapy: Traditionally, chemotherapy was believed to be of marginal value in the treatment of patients with newly diagnosed high-grade gliomas, but this perception is beginning to change. Most earlier trials studied nitrosourea-based chemotherapy regimens. In the largest randomized trial of adjuvant chemotherapy in high-grade gliomas[21] the Medical Research Council randomized 674 patients to either radiation alone or radiation plus procarbazine, lomustine, and vincristine (PCV). No survival benefit was seen with the addition of PCV, even in patients with anaplastic astrocytomas.

In contrast, 2 meta-analyses that reviewed

data from randomized trials of patients with high-grade gliomas both found a modest survival benefit when chemotherapy was added to postoperative radiation.[22,23] Specifically, the Glioma Meta-Analysis Trialists Group reviewed 12 studies involving approximately 3000 patients and reported an absolute increase in 1-year survival rate from 40% to 46% and a 2-month increase in median survival when chemotherapy was added to postoperative radiation (hazard ratio [HR], 0.85; 95% CI, 0.78–0.91; $P < .0001$).[22] In an earlier analysis of 16 randomized trials, Fine et al.[23] also found a 10% and 9% increase in survival at 1 and 2 years, respectively.

Other routes of drug delivery have been evaluated. Local administration of BCNU using a biodegradable polymer (wafer) placed intraoperatively in the surgical cavity showed a statistically significant improvement in survival for patients with recurrent high-grade gliomas (31 vs. 23 weeks; adjusted HR, 0.67; $P = .006$).[24] As a result, the FDA approved the BCNU wafer for this indication. A phase III placebo-controlled study in 32 patients with malignant glioma showed a statistically significant prolongation of survival when the BCNU polymer was used as initial therapy in combination with RT.[25] A larger phase III trial in 240 patients with newly diagnosed 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 groups treated with the BCNU wafer.[26] This benefit was maintained 2 and 3 years after implantation.[27] Based on these studies, the FDA extended the approval of the BCNU polymer wafers for use in malignant gliomas as initial therapy. However, clinicians and patients should be aware that BCNU can potentially interact with other agents, resulting in increased toxicity. For example, whether it is safe to administer temozolomide (see later discussion) to patients treated with BCNU is still a matter of debate. Implantation of the wafer may also preclude future participation in clinical trials involving other adjuvant therapy. Therefore, the panel has considerable disagreement over the value of including the wafer as initial therapy (category 2B).

Temozolomide, an alkylating agent, is becoming a standard addition to postoperative RT for patients with glioblastoma (without carmustine wafer) who are younger and have good PS. In a phase III study assessing temozolomide in 573 patients with glioblastoma aged 70 years or younger with WHO PS of 2 or less, Stupp et al.[28] randomized subjects to either daily temozolomide administered concomitantly with postoperative RT followed by 6 cycles of adjuvant temozolomide, or radiotherapy alone. Side effects for temozolomide include hair loss, nausea, vomiting, headaches, fatigue, and anorexia. Because of the risk of lymphocytopenia and subsequent opportunistic infection, prophylaxis against *Pneumocystis carinii* pneumonia (PCP) is required when the agent is administered with radiotherapy. A later study by Stupp et al.[29] showed that the chemoradiation arm resulted in a statistically better median survival (14.6 vs. 12.1 months) and 2-year survival (26.5% vs. 10.4%) than RT. Final analysis confirmed the survival advantage at 5 years (10% vs. 2%). However, the study design does not illuminate which is responsible for the improvement: temozolomide administered with radiation, following radiation, or both. This trial used a dosage of 75 mg/m^2 daily of concurrent temozolomide during the course of radiotherapy, then 150 to 200 mg/m^2 post-RT on a 5-day schedule every 28 days. Alternate schedules, such as a 21/28 dose-dense or a 50 mg/m^2 continuous daily regimen, have been explored in a phase II trial for newly diagnosed glioblastoma.[30] 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.

The panel disagreed about the adjuvant use of temozolomide in patients with an implanted BCNU wafer and those older than 70 years but with good performance (category 2B). For the latter group, some evidence from small studies suggests the usefulness of temozolomide in addition to adjuvant radiation despite old age.[31,32] Another approach is to administer temozolomide alone. A retrospective review of patients aged 70 or older with mean Karnofsky score of 70 found no survival difference between those receiving radiation alone and those taking monthly temozolomide only.[33] Given the susceptibility of elderly patients to radiation-induced neurotoxicity, especially when the PS is poor, chemotherapy alone seems to be a reasonable option.

Research suggests that MGMT (O-6-methylguanine-DNA methyltransferase) status may determine which patients will benefit from adjuvant temozolomide therapy.[34] MGMT is a DNA repair enzyme that may cause resistance to DNA-alkylating drugs. Oligodendrogliomas frequently exhibit MGMT hyper-

methylation and low expression levels, which may explain its high chemosensitivity.[35]

In terms of adjuvant treatment for anaplastic astrocytomas, postoperative chemotherapy is an alternative to radiation. In a phase III trial of sequential radiochemotherapy in 318 patients with anaplastic gliomas, Wick et al.[36] randomized patients to 1 of 3 arms: RT, PCV, or temozolomide. At progression, patients in arm 1 received PCV or temozolomide, whereas patients in arms 2 and 3 were irradiated. The 3 strategies resulted in comparable time-to-progression and survival. No published data directly compare the benefit of postoperative combined chemoradiation plus temozolomide with that of a nitrosourea in patients with newly diagnosed anaplastic astrocytomas. This study is currently underway through the RTOG (RTOG 9813). Adjuvant chemoradiation within a trial is a recommended option. However, its use outside a clinical trial received strong objection from some panelists (category 3).

Unfortunately, currently available chemotherapy does not provide cures. Patients with malignant gliomas eventually recur or progress. In addition to temozolomide[37–39] and the nitrosoureas,[24] regimens that are commonly used as second-line or salvage chemotherapy include combination PCV,[40] cyclophosphamide,[41] and platinum-based regimens.[42] Anaplastic gliomas may also be treated by irinotecan[43] or etoposide.[44]

Bevacizumab, an antiangiogenic agent, received accelerated approval in 2009 for recurrent glioblastoma based on 2 phase II studies. AVF 3708g randomized 167 patients to bevacizumab with or without irinotecan; MRI-defined objective response was seen in 28% and 38% of patients, respectively.[45] Median survival was around 9 months, similar to that seen in a previous phase II trial.[46] A published report of the other pivotal study (NCI 06-C-0064E) recorded a median survival of 31 weeks in 48 heavily pretreated patients.[47] Bevacizumab alone or in combination with chemotherapy has also shown activity in anaplastic gliomas.[48–53] Although 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. However, 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 PS of the patient. In the case of anaplastic gliomas, patients with a good Karnofsky score (≥ 70) can choose between fractionated EBRT, chemotherapy, or chemoradiation in the context of a clinical trial. Chemoradiation outside of a trial is controversial (category 3). Patients with a poor PS (< 70) can be managed with radiation, chemotherapy, or best supportive care.

If glioblastoma is diagnosed, the options for a patient with poor performance include radiation, chemotherapy, best supportive care, or chemoradiation (category 2B) only if no BCNU wafer was implanted. BCNU-naïve patients with favorable PS should undergo postoperative radiation (category 1); addition of concurrent and adjuvant temozolomide is a category 1 recommendation for younger patients (age < 70 years) but category 2B for older patients. If a BCNU wafer was used, addition of temozolomide is also a category 2B recommendation for patients with good performance.[54]

Follow-Up and Recurrence: Patients should be followed up 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 no actual tumor progression has occurred. 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."[55]

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, patients with poor performance should undergo best supportive care without further active treatment. If PS is favorable, systemic chemotherapy may be administered (especially for anaplastic oligodendrogliomas); reirradiation is a category 2B option if prior radiation produced a good/durable response. For diffuse or multiple recurring lesions, the options are best supportive care for patients with poor performance; systemic chemotherapy; or surgery to relieve mass effect. All patients should receive best supportive care.

Intracranial Ependymomas

Information on intracranial ependymomas can be found in the full NCCN Guidelines for Central Nervous System Cancers, available online at www.NCCN.org.

Medulloblastoma and Supratentorial Primitive Neuroectodermal Tumors

Cranial primitive neuroectodermal tumors (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 histologic variants.[56] 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).[57] Overall, PNETs represent only 1.8% of all brain tumors, although they are the most common type among pediatric brain malignancies.

Approximately half of the affected patients will present with elevated intracranial pressure. Headache, ataxia, and nausea are commonly observed symptoms.[58] All PNETs of the brain are WHO grade IV because they are invasive and rapidly growing. They also have the tendency to disseminate through the CSF. Larger retrospective case series of adult patients reported 10-year survival rates of 48% to 55%, with frequent recurrence beyond 5 years, commonly in the posterior fossa.[59,60]

Treatment Overview

Surgery: Evidence in adult patients is meager for this rare disease and no randomized trial data are available, but general consensus is 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[58,61,62] and is associated with improved survival.[61,63] In addition, surgical placement of a ventriculoperitoneal shunt can be used to treat hydrocephalus.

Radiation Therapy: Adjuvant radiation after surgery is the current standard of care, although most studies are based on the pediatric population. The traditional dose of craniospinal RT is 30 to 36 Gy with a boost to a total of 55 Gy to the primary brain site.[61,63] 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,[59,64,65] although one randomized trial found an increased relapse risk with dose reduction.[66] Recently, SRS demonstrated safety and efficacy in a small series of 12 adult patients with residual or recurrent disease.[67]

Systemic Therapy: The use of postirradiation chemotherapy to allow radiation dose reduction is becoming increasingly common especially for children,[64,65] but optimal use of adjuvant chemotherapy is still unclear for adult patients.[58–60,68,69] A phase III study that enrolled more than 400 patients between 3 and 21 years of age to receive postirradiation cisplatin-based chemotherapy regimens recorded an encouraging 86% 5-year survival.[70]

Several regimens are in use in the recurrence setting, most of which include etoposide.[71–73] High-dose chemotherapy in combination with autologous stem cell transplantation is a feasible strategy for patients who have had good response with lower doses.[73,74]

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.[59,60,69] Multidisciplinary consultation before treatment initiation is advised. Maximal safe resection is recommended wherever possible. Contrast-enhanced brain MRI should be performed within 24 to 72 hours after surgery, but spinal MRI should be delayed by 2 to 3 weeks. Because of the propensity of PNET to CSF seeding, CSF sampling through lumbar puncture after spine imaging is also necessary for staging. Medulloblastoma should be staged according to the modified Chang system using information from both imaging and surgery.[75,76]

Adjuvant Therapy: Patients should be stratified according to recurrence risk for planning of adjuvant therapy (reviewed by Brandes et al.[77]). The panel agrees that patients with large cell or anaplastic medulloblastoma, supratentorial PNET, disease dissemination, unresectable tumors, or residual tumors larger than 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: No robust data support an optimal follow-up schedule. 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 after resection or conventional reinduction chemotherapy. On disease progression, options include chemotherapy alone, radiation alone (including SRS), and chemoradiation. Patients with metastases should be managed with chemotherapy or best supportive care, such as palliative radiation.

Primary CNS Lymphomas

Information on primary CNS lymphomas can be found in the full NCCN Guidelines for Central Nervous System Cancers, available online at www.NCCN.org.

Primary Spinal Cord Tumors

Spinal tumors are classified according to their anatomic location as extradural, intradural–extramedullary, and intradural–intramedullary. Extradural tumors are primarily caused by metastatic disease and are discussed in Metastatic Spinal Tumors (page 391). 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%.[78] Extramedullary lesions, most commonly benign meningiomas, account for 70% to 80% of spinal cord tumors.[79] 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 NCCN Guidelines for further details regarding these subtypes because intracranial and spinal lesions are biologically similar.

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

Because 70% of primary spinal cord tumors are low-grade and slow-growing,[78] it is common for patients to experience pain for months to years before diagnosis. Pain that worsens at night is a classic symptom of 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 up with observation without immediate intervention.

Surgery: Surgery is preferred for symptomatic tumors. 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 re-

section is the goal. En bloc total resection yielded excellent local control rates greater than 90%.[80–83]

Gross total resection is seldom feasible with grade II or higher astrocytomas, because these tumors are infiltrative and poorly circumscribed. In a study of 202 patients with intramedullary tumors, more than 80% of grade I astrocytomas were completely resected, whereas total resection was achieved in only 12% of grade II tumors.[84] Nevertheless, Benes et al.[85] conducted a review of 38 studies on spinal astrocytomas and concluded that maximal safe resection should be attempted whenever possible based on reports of survival benefit.

Radiation Therapy: RT is not recommended as primary therapy because of limited response, unknown histology without surgery, and low radiation tolerance of the spinal cord. RT is also not advisable after gross total resection, because tumors that can be excised completely have a low local recurrence rate. A large retrospective analysis involving more than 1700 patients with primary spinal gliomas found an association between RT and worse cause-specific and overall survival, although these results may reflect a bias because patients who received radiation may have had more adverse risk factors.[86] The role of adjuvant RT after incomplete excision or biopsy is controversial.[85,87,88] However, EBRT is considered a viable option at disease progression or recurrence. SRS has also shown safety and efficacy in several series.[89–91]

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 when surgery and radiation fail, but no consensus exists on the best regimen. Chemotherapy is best given in the setting of a clinical trial.

NCCN Recommendations

MRI is the gold standard for diagnosing spinal cord lesions. Asymptomatic patients may be observed (especially for suspected low-grade lesions) or resected, whereas all symptomatic patients should undergo some form of surgery. The surgical plan and outcome are influenced by whether a clear surgical plane is available.[92] Whenever possible, maximal safe resection should be attempted. In most cases, postoperative adjuvant radiation is not recommended. However, if symptoms persist after incomplete resection or biopsy, radiation should be administered.

All patients should be followed up with sequential MRI scans. At progression or recurrence, re-resection is the first choice. If this is not feasible, conventional external-bean RT or SRS is the next option. Chemotherapy is reserved for when 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 mid to late adult life, and have a female predominance. The annual incidence for men and women reported by CBTRUS are 1.8 and 3.4 per 100,000 people, respectively.[57] 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).[93] Small tumors are often asymptomatic, incidental findings.[94] Seizure is a common presenting symptom occurring in 27% of patients.[95]

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.[96]). 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 noncontrast CT scan. Nonetheless, MRI reveals several imaging characteristics highly suggestive of meningioma and has been used to operationally define pathology in recent stereotactic radiotherapy articles. These MR findings include a tumor that is dural-based and isointense with gray matter and shows prominent and homogeneous enhancement (> 95%), frequent CSF/vascular clefts, and often an enhancing dural tail (60%). However, approximately 10% to 15% of meningiomas have an atypical MRI appearance mimicking metastases or malignant gliomas. In particular, secretory meningiomas may have a significant amount of peritumoral edema. Cerebral angiography is occasionally performed, often for surgical planning, because meningiomas are vascular tumors prone to intraoperative bleeding. In some instances, preoperative embolization is helpful for operative hemostasis management. Angiographic findings consistent with a meningioma include a dual vascular supply with dural arteries sup-

plying the central tumor and pial arteries supplying the tumor periphery. A "sunburst effect" may be seen because of 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 pathologically define an extra-axial lesion.[97–99] Octreotide imaging with radiolabeled indium or, more recently, gallium may be particularly useful in distinguishing residual tumor from postoperative scarring in subtotally resected/recurrent tumors.

Treatment Overview

Observation: Studies examining the growth rate of incidental meningiomas in otherwise asymptomatic patients suggest that many asymptomatic meningiomas may be followed up safely with serial brain imaging until either the tumor enlarges significantly or becomes symptomatic.[100,101] These studies confirm the tenet that many meningiomas grow very slowly and that a decision not to operate is justified in selected asymptomatic patients. Because 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 on patient-related (e.g., age, PS, medical comorbidities) and treatment-related factors (e.g., reasons for symptoms, resectability, goals of surgery). Most patients diagnosed with surgically accessible symptomatic meningioma undergo surgical resection to relieve neurologic symptoms. Complete surgical resection may be curative and is therefore the preferred treatment. Both the tumor grade and the extent of resection impact the rate of recurrence. In a cohort of 581 patients, the 10-year progression-free survival rate was 75% after gross total resection, but dropped to 39% for patients undergoing subtotal resection.[102] Short-term recurrences reported for grade I, II, and III meningiomas were 1% to 16%, 20% to 41%, and 56% to 63%, respectively.[103–105] The Simpson classification scheme that evaluates meningioma surgery based on extent of resection of the tumor and its dural attachment (grades I–V in decreasing degree of completeness) correlates with local recurrence rates.[106] First proposed in 1957, it is still being widely used by surgeons.

Radiation Therapy: Safe gross total resection is sometimes not feasible because of tumor location. In this case, subtotal resection followed by adjuvant EBRT has been shown to be associated with similar comparable long-term survival rates as gross total resection (86% vs. 88%, respectively), compared with only 51% after incomplete resection alone.[107] Of 92 patients with grade I tumors, Soyuer et al.[108] found that radiation after subtotal resection reduced progression compared with incomplete resection alone, but has no effect on overall survival.

Because high-grade meningiomas have a significant probability of recurrence even after gross total resection,[109] postoperative high-dose EBRT (> 54 Gy) has become the accepted standard of care for these tumors to improve local control.[110] A review of 74 patients showed that adjuvant RT improves survival in patients with grade III meningioma and in those with grade II disease with brain invasion.[111] The role of RT after gross total resection 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 RT (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 comorbidities.

A study of approximately 200 patients compared surgery with SRS as primary treatment for small meningiomas.[112] The SRS arm had similar 7-year progression-free survival rates as gross total resection, and superior survival over incomplete resection. In another study, Kondziolka et al.[113] followed a cohort of 972 patients with meningiomas managed with SRS over 18 years. Half of the patients underwent 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 modestly successful in patients

with recurrent meningiomas.[114] Targeted therapies that have shown partial efficacy in refractory meningiomas are somatostatin analogues[115] and alpha interferon.[116]

NCCN Recommendations

Initial Treatment: Meningiomas are typically diagnosed with 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 with observation. If neurologic impairment is imminent, surgery (if accessible) or RT (EBRT or SRS) is feasible. Asymptomatic tumors 30 mm or larger should be surgically resected or observed. Symptomatic disease requires active treatment with surgery whenever possible. Nonsurgical candidates should undergo radiation.

Regardless of tumor size and symptom status, all patients with surgically resected grade III meningioma (even after gross total resection) should receive adjuvant radiation to enhance local control. After 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 patients should be followed up based on individual clinical conditions. Generally, malignant or recurrent meningiomas are followed up 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 to 10 years.

After recurrence is detected, the lesion should be resected whenever possible and then the patient should undergo radiation. Nonsurgical candidates should undergo radiation. Chemotherapy is reserved for patients with an unresectable recurrence refractory to radiotherapy.

Brain Metastases

Metastases to the brain are the most common intracranial tumors in adults and occur 10 times more frequently than primary brain tumors. More recent population-based data report that 8% to 10% of people with cancer develop symptomatic metastatic tumors in the brain.[117,118] A much higher incidence on autopsy has been reported. Because of advances in 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.[119]

Almost 80% brain metastases occur in the cerebral hemispheres, an additional 15% occur in the cerebellum, and 5% occur in the brainstem.[120] 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. Most cases have multiple brain metastases evident on MRI scans. The presenting signs and symptoms of metastatic brain lesions are similar to those of other mass lesions in the brain, such as headache, seizures, and neurologic impairment.

Treatment Overview

Surgery: 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 1988 through 1990 to 2.3% in 1997 through 2000.[121] High-volume hospitals and surgeons produced superior outcomes.

Patchell et al.[122] randomized 95 patients with single intracranial metastases to complete resection alone or surgery plus adjuvant WBRT, and found postoperative radiation was associated with dramatic reduction in tumor recurrence (18% vs. 70%; $P < .001$) and likelihood of neurologic deaths (14% vs. 44%; $P = .003$). No difference was seen in the secondary end point of overall survival. Surgery plus WBRT versus WBRT alone is discussed later.

For 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 with good prognosis who had up to 3 metastatic sites.[123,124]

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.[125] 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 with SRS alone (7.5 vs. 8.0 months, respectively).[126] However, 1-year brain recurrence rate was lower in the WBRT plus SRS arm (47% vs. 76%; $P < .001$). This likely served to decrease the need for salvage therapy in this group (10 of 65 patients) compared with patients receiving no upfront WBRT (29 of 67 patients).

Retrospective comparative studies showed that SRS plus WBRT resulted in equivalent if not better survival compared with surgery and WBRT.[127–129] SRS also conferred a significant improvement in local control, especially for patients with radiosensitive tumors or solitary brain lesions. Muacevic et al.[130] compared SRS alone with resection plus WBRT in a randomized controlled trial. The study was stopped prematurely because of 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 was associated with a higher rate of distant relapse.

Small patient series have shown local control rates greater than 70% with SRS in the recurrence setting for patients with good PS and stable disease who have received prior WBRT.[131–135]

WBRT: 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.[136] showed that surgery followed by WBRT lengthened overall survival (40 vs. 15 weeks in WBRT arm; $P < .01$) and functional dependence (38 vs. 8 weeks; $P < .005$), and decreased recurrence (20% vs. 52%; $P < .02$) compared with radiation alone. Similarly, Vecht et al.[137] showed that combined treatment led to longer survival and functional independence in another randomized study (n = 63). The greatest difference was observed in patients with stable disease; median survival was 12 versus 7 months and functional independence was 9 versus 4 months. A third study of 84 patients found no difference in survival between the strategies; however, patients with extensive systemic disease and lower performance levels were included, which likely resulted in poorer outcomes in the surgical arm.[138]

The impact of SRS in addition to WBRT was evaluated in 2 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.[139] 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; $P = .04$) when a single lesion was involved; this was not observed in patients with multiple lesions. A much smaller trial of 27 patients with 2 to 4 lesions found no significant difference in survival, although SRS did extend time to local failure (36 vs. 6 months; $P = .0005$).[140]

Based on these results, WBRT in conjunction with surgery or SRS leads to better clinical outcomes than WBRT alone for patients with good performance and 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.[141–143]

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 with radiation alone,[144,145] although there have been reports of increase in progression-free survival or radiologic response with temozolomide.[145,146] 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 blood–brain barrier is an additional concern. Therefore, chemotherapy is usually considered a last line of therapy for recurrent disease when other options have been exhausted (surgery, SRS, radia-

tion). The choice of agent depends on the histology of the primary tumor.

Among various agents, temozolomide may be useful in some patients with previously untreated brain metastases from metastatic melanoma.[147] Temozolomide, given on a prolonged schedule, plus thalidomide was tested in a phase II study of patients with brain metastases, but the high toxicity and lack of response rendered the regimen inappropriate.[148]

In a study of high-dose methotrexate in patients mostly diagnosed with breast cancer, 56% experienced disease control.[149] Other agents shown to have activity in breast cancer include platinum plus etoposide,[150,151] and capecitabine.[152]

A phase I/II study of topotecan plus WBRT showed a 72% response rate in 75 patients with brain metastases.[153] Unfortunately, a follow-up phase III trial was closed early because of slow accrual.[154]

NCCN Recommendations

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

Treatment for Limited (1–3) Metastatic Lesions: For patients with limited systemic disease or who have reasonable options for systemic treatment, aggressive management should be strongly considered. For surgical candidates, a high level of evidence supports category 1 recommendations for surgical resection plus postoperative WBRT, and for SRS plus WBRT if only one brain lesion is involved. SRS alone or after 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 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), but it may be considered in select patients using regimens specific to the primary cancer.

Patients should be followed up with MRI every 3 months for 1 year and then as clinically indicated. Recurrence on radiograph can be confounded by treatment effects. Tumor tissue sampling should be strongly considered if there is a high index of suspicion of recurrence. When recurrent disease is detected, 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 previously treated with surgery have the option of undergoing surgery, SRS, WBRT, or chemotherapy. However, patients who previously received WBRT or SRS should not undergo WBRT at recurrence. SRS should be reconsidered in patients who had previous SRS with a durable response for greater than 6 months if imaging supports active tumor and not necrosis. The algorithm for distant brain recurrences branches depending on whether patients have either 1 to 3 lesions or more than 3 lesions. In both cases, patients may undergo WBRT or consider local/systemic chemotherapy, but patients with 1 to 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 PS) if it 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.[155]

If systemic CNS disease progression occurs in the setting of limited systemic treatment options, WBRT should be administered in patients who were not previously irradiated. For patients who received prior WBRT, reirradiation is an option only if they had a positive response to the first course of RT treatment. Best supportive care is also an option for either case.

Treatment for Multiple (> 3) Metastatic Lesions: All patients diagnosed with more than 3 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 on survival was reported with variations in fractionation and dosing according to a meta-analysis of 9 randomized trials.[156] 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 (e.g., with 4 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 systemic disease progression with limited systemic treatment options, or stable systemic disease or reasonable systemic treatment options. For patients with systemic disease progression, options include best supportive care or reirradiation. For patients with stable systemic disease, options include surgery, reirradiation, or chemotherapy.

Leptomeningeal Metastases

Information on leptomeningeal metastases can be found in the full NCCN Guidelines for Central Nervous System Cancers, available online at www.NCCN.org.

Metastatic Spinal Tumors

Bone metastases are a growing problem among cancer patients because of increasing life expectancy, with the spine being the most frequently affected site. In a report of 832 patients who died of malignancies, vertebral involvement was found in 36% on autopsy.[157] Spinal metastases primarily arise from breast, lung, prostate, and renal cancers.[158,159] Extradural lesions account for approximately 95% of spinal tumors, mostly in the thoracic region.

Some patients are found to have vertebral involvement as an asymptomatic, incidental finding. However, for most affected patients, pain is the primary presenting symptom preceding neurologic dysfunction. Three types of pain have been classically defined: local, mechanical, and radicular. Local pain from 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. Although seldom responsive to steroids, mechanical pain can be alleviated with surgical stabilization. Radicular pain is a sharp or stabbing sensation that occurs when nerve roots are compressed by the tumor. Patients may experience any or a combination of these types of pain.

Spinal cord compression is the most debilitating complication of spine metastases. It affects 5% to 10% of all patients with cancer, with more than 20,000 cases diagnosed each year in the United States.[160] Most patients initially complain of progressive radicular pain,[161] which is followed by neurologic symptoms such as motor weakness and sensory loss, and may even include autonomic bladder dysfunction. If left untreated, neurologic deficits rapidly progress to paralysis. Unfortunately, a study of 319 patients with cord compression showed significant delay in reporting of initial pain (3 months) and in diagnosis (2 months), which can lead to irreversible spinal cord damage.[162] Therefore, clinicians must watch for early suspicious signs and use MRI of the spine for prompt diagnosis. Once diagnosed, spinal cord compression is considered a medical emergency; intervention should be implemented immediately to prevent further neurologic decline.

Treatment Overview

Dissemination to the spinal column is largely incurable. Therefore, the goals of treatment are palliation and improvement of quality of life through preservation of neurologic function, pain relief, and stabilization of mechanical structure. One exception is slow-growing cancers (mainly renal cell carcinoma) with solitary spinal metastasis, for which surgery may achieve cure.[163]

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

Surgery: The general consensus is that a patient should have a life expectancy of at least 3 months to be a surgical candidate. Paraplegia for more than 24 hours is an exclusion criterion because of the low chances of improvement when prolonged neurologic deficits ex-

ist before surgery.[164] Patients with hematologic malignancies should also be excluded, because they are best managed with radiotherapy or chemotherapy. Because estimation of life expectancy can be difficult, several groups have developed prognostic scoring systems to help predict surgical outcomes.[165–168]

Posterior laminectomy has been widely used in the past but is now obsolete because of 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, either anterior, posterior, or combined/circumferential, is primarily determined by disease anatomy.[169,170]

Sundaresan et al.[163] reported favorable results using various surgical approaches in 80 patients with solitary spine metastases, with most patients experiencing improvement in both pain and mobility. Overall survival reached 30 months, with 18% surviving 5 years or more. The best outcomes were 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 patients with solid tumors. A meta-analysis involving 24 surgery cohort studies and 4 radiation studies found that patients are twice as likely to regain ambulatory function after surgery than after radiation alone.[171] However, data also showed 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 outcomes over radiation alone or laminectomy, achieving a 75% mean improvement in neurologic function, although a high surgical mortality rate (mean, 10%) was also reported.[172]

To date, only one relevant randomized trial has been reported.[173] Approximately 100 patients with metastatic spinal compression were randomized to surgery plus postoperative RT or RT alone. Compared with the radiation group, significantly more patients in the surgery group regained walking ability (84% vs. 57%; $P = .001$) and for a longer time (median, 122 days vs. 13 days; $P = .003$). The impressive results were obtained with strict eligibility criteria; the study excluded patients with radiosensitive tumors, neurologic deficits for 24 hours, multiple spinal tumors, lesions only compressing spinal roots, and prior RT to the vertebrae. Although studies have shown high efficacy of surgery, the formidable complications related to surgery cannot be overlooked. Using the National Inpatient Sample all-payor database, Patil et al.[174] reviewed data of more than 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 to achieve decompression or stabilization (see earlier discussion) but is routinely used as adjuvant therapy after surgery because wide negative margins are difficult to obtain. Given the potential impact of RT on wound healing, most studies suggested an interval of 1 to 3 weeks between resection and subsequent radiation.[175]

Marazano et al.[176] reported an excellent response to RT alone for spinal compression after randomizing 300 patients to a short-course (8 Gy × 2 days) or split-course (5 Gy × 3; 3 Gy × 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 patients with breast cancer recovered mobility compared with only 20% of those with hepatocellular carcinoma. In general, solid tumors are considered either moderately radiosensitive (e.g., breast and prostate cancers) or radioresistant (e.g., melanoma, osteosarcomas, and cancers of the thyroid, colon, and kidney).[177] However, hematologic malignancies such as lymphomas and multiple myelomas are highly responsive to RT. Hence, radiation alone is routinely used as therapy for these cancers, even in the presence of cord compression.

In the absence of compression, fracture, or instability, EBRT is effective in achieving local control as primary treatment. A mean 77% local control rate from 7 retrospective studies involving 885 patients

was found in a systematic review by Gerszten et al.[177] Radiation is also a mainstay of palliative treatment for patients with poor PS, significant comorbidities, or limited life expectancy (< 3–4 months). The meta-analysis by Klimo et al.[171] involving 543 patients treated with radiation revealed pain control rates of 54% to 83%. Unlike surgery, radiation has no immediate significant treatment-related complications and very few local recurrences. However, it increases surgical complications because it impairs wound healing.

The advent of SRS allowed precise high-dose targeting in 1 or 2 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 whom had previous conventional irradiation.[178] 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.[177] 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, whereas 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.[179] 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 produce 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 several theoretical benefits, including anti-inflammation, reduction in edema, short-term neurologic function improvement, and enhanced blood flow. However, the preference between high-dose (96 mg daily) and low-dose (10–16 mg daily) is still unclear.[180–182]

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

Workup: Initial workup depends on the presence or absence of symptoms. Patients with an incidental, asymptomatic metastatic lesion confirmed with 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, obtaining a spinal MRI for every incidental metastatic lesion seen on surveillance bone scans is not mandatory. 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 preexisting degenerative spine conditions. Immediate spinal MRI is warranted when neurologic symptoms occur, 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 no spinal radiculopathy or myelopathy correlates with the patient's symptoms. In this case, other causes should be considered (e.g., leptomeningeal disease). An abnormal neurologic examination includes motor abnormalities, sphincter abnormalities, or sensory deficits attributable to a dysfunction of nerve roots 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, and sensory deficits of a stocking/glove distribution are excluded.

Treatment: Once metastatic vertebral involvement is diagnosed, treatment is based on whether the patient is experiencing 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. Epidural tumors may occupy part of the spinal canal with or without partial obliteration of CSF around the spinal cord. Those cases are excluded because no cord deformation is present. For tumors occurring below L1, any canal compression of 50% or more should be considered equally as important 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 in the presence of spinal instability and no surgical contraindication. Primary EBRT alone is appropriate for patients with radiosensitive cancers (hematologic malignancies) and without evidence of spinal instability. Many fractionation schemes are available (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.[183,184] Primary chemotherapy is also an option for chemoresponsive tumors in the absence of clinical myelopathy.

Metastases to the spine without cord compression include the presence of tumor in the vertebral body, pedicles, 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 with 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 and 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 preferred treatment. Alternatives are chemotherapy for responsive tumors, or surgery plus adjuvant RT in select cases. Surgery or SRS should be considered in patients experiencing intractable pain or rapid neurologic decline during RT. 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 because of side effects.

Progression and Recurrence: Follow-up involves MRI or CT imaging within 1 to 3 months posttreatment, then every 3 to 6 months as indicated. When progression or recurrence is detected on imaging scans, the management strategy is based on previous treatment. Patients who underwent prior RT or surgery plus adjuvant RT may consider surgery or reirradiation to the recurred area. Patients previously treated by chemotherapy can consider salvage radiotherapy.

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Individual Disclosures for the NCCN Central Nervous System Cancers Panel

Panel Member	Clinical Research Support	Advisory Boards, Speakers Bureau, Expert Witness, or Consultant	Patent, Equity, or Royalty	Other	Date Completed
Philip J. Bierman, MD	Bradmer Pharmaceuticals	None	None	None	9/18/09
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Larry Junck, MD	Genentech, Inc.	Genentech, Inc.	None	None	11/16/09
Gerald P. Linette, MD, PhD	None	None	None	None	9/28/09
Jay S. Loeffler, MD	None	Genentech, Inc.; ProCure; and TransMolecular	None	None	9/30/10
Moshe H. Maor, MD	None	None	None	None	8/4/09
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