National Comprehensive Cancer Network

Clinical Practice Guidelines in Oncology – v.1.2003

Central Nervous System Cancers

Version 1.2003

Continue

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Multiple (>3) Metastatic Lesions (MU-1)
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- Radiation Therapy Guidelines (BRAIN-2)

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

To find clinical trials online at NCCN member institutions, click here: nccn.org/clinical_trials/physician.html

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

See NCCN Categories of Consensus

Adult Low-Grade Infiltrative Supratentorial Astrocytoma/Oligodendroglioma

(Excluding Pilocytic Astrocytoma)

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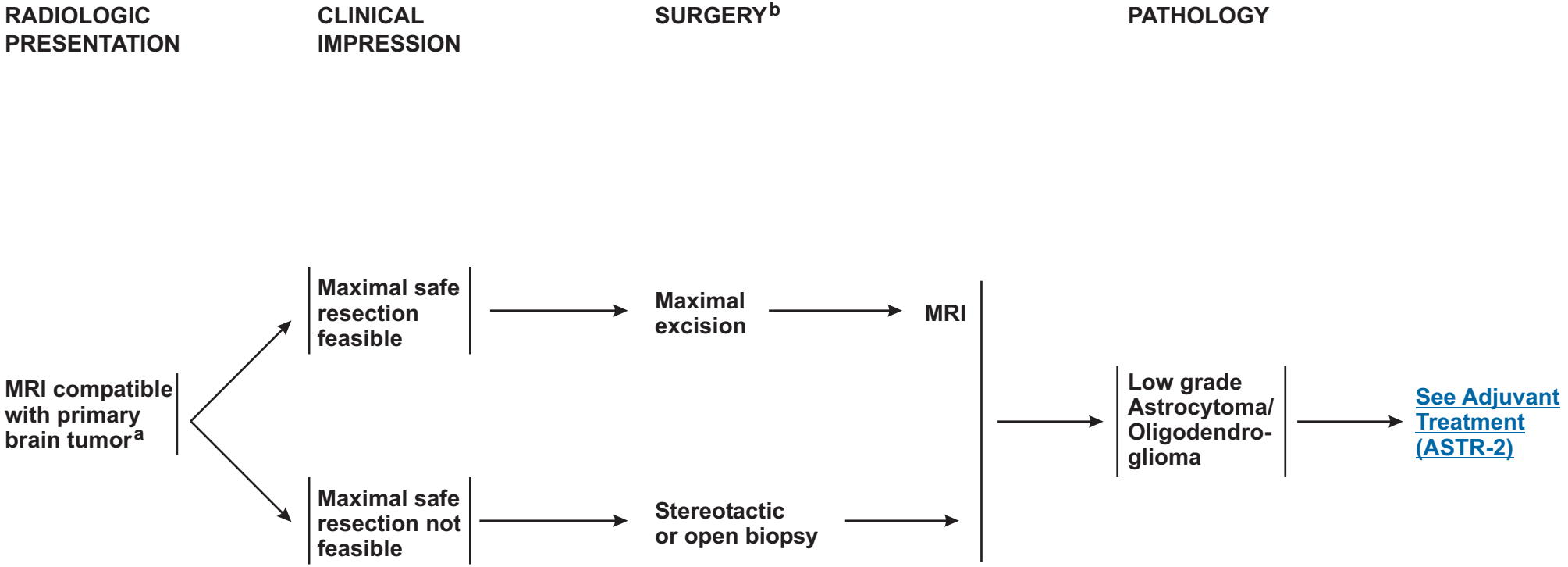

[a] Biopsy first if MRI compatible with CNS lymphoma.

[b] See Surgical Issues (BRAIN-1).

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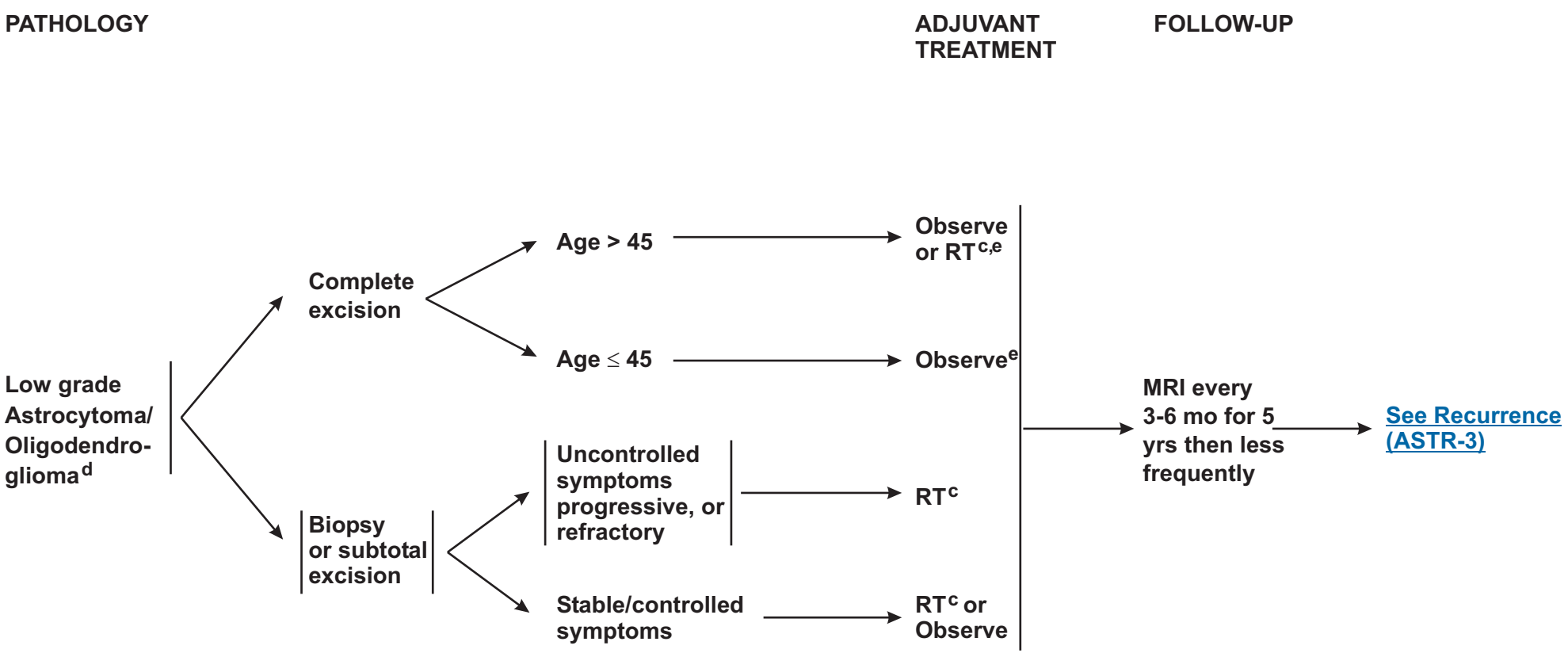
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Adult Low-Grade Infiltrative Supratentorial Astrocytoma/Oligodendroglioma

(Excluding Pilocytic Astrocytoma)



[c] See Radiation Therapy Guidelines (BRAIN-2).

[d] Oligodendrogliomas have been reported to be chemotherapy sensitive to treatment. Chemotherapy using PCV (procarbazine, lomustine, vincristine) or temozolamide may be appropriate adjuvant therapy.

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

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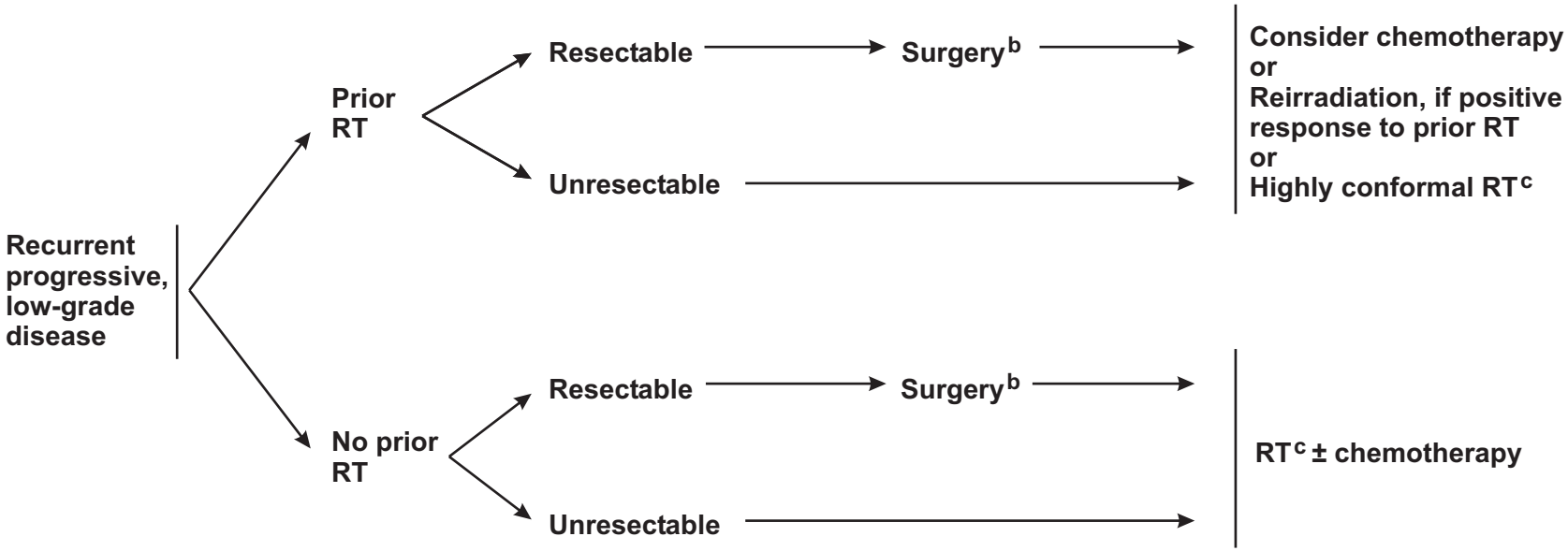
Adult Low-Grade Infiltrative Supratentorial Astrocytoma/Oligodendroglioma

(Excluding Pilocytic Astrocytoma)

RECURRENCE



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[b] See Surgical Issues (BRAIN-1).
[c] See Radiation Therapy Guidelines (BRAIN-2).

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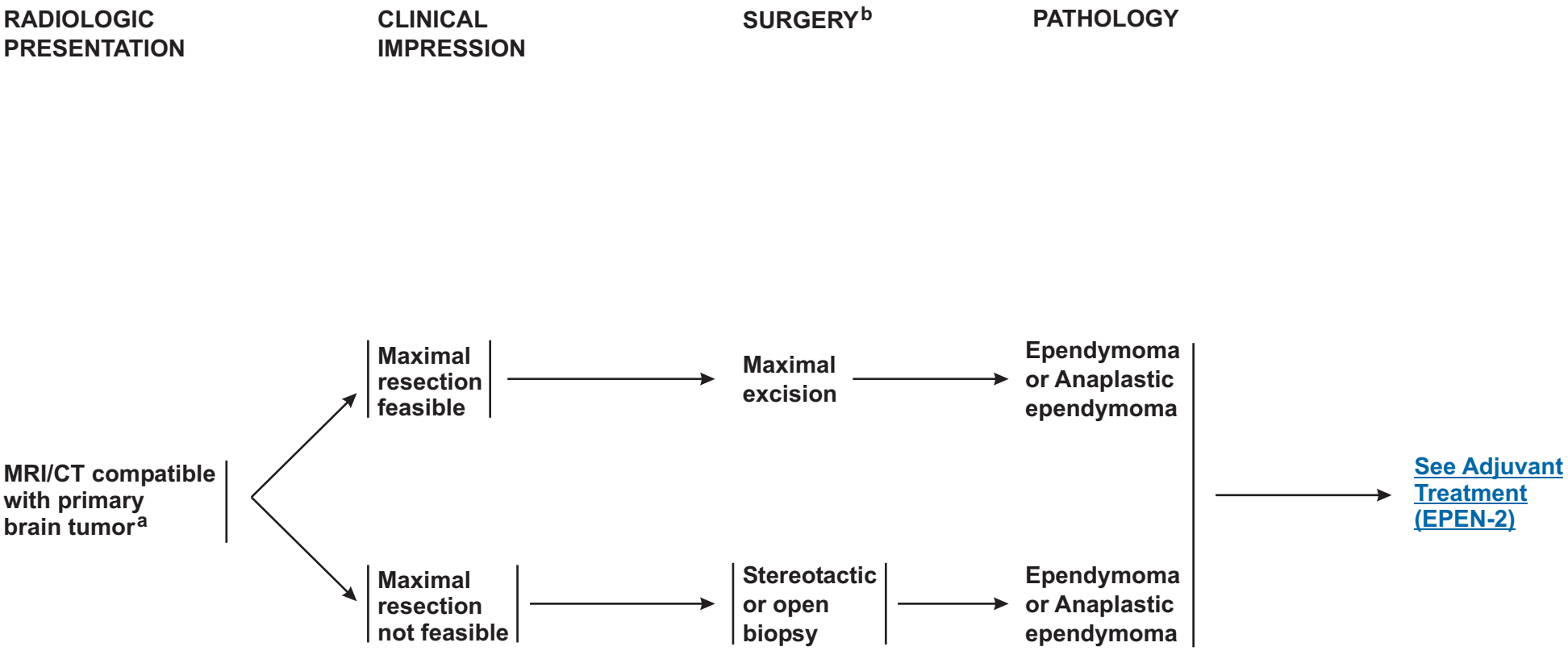
Adult Intracranial Ependymoma



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

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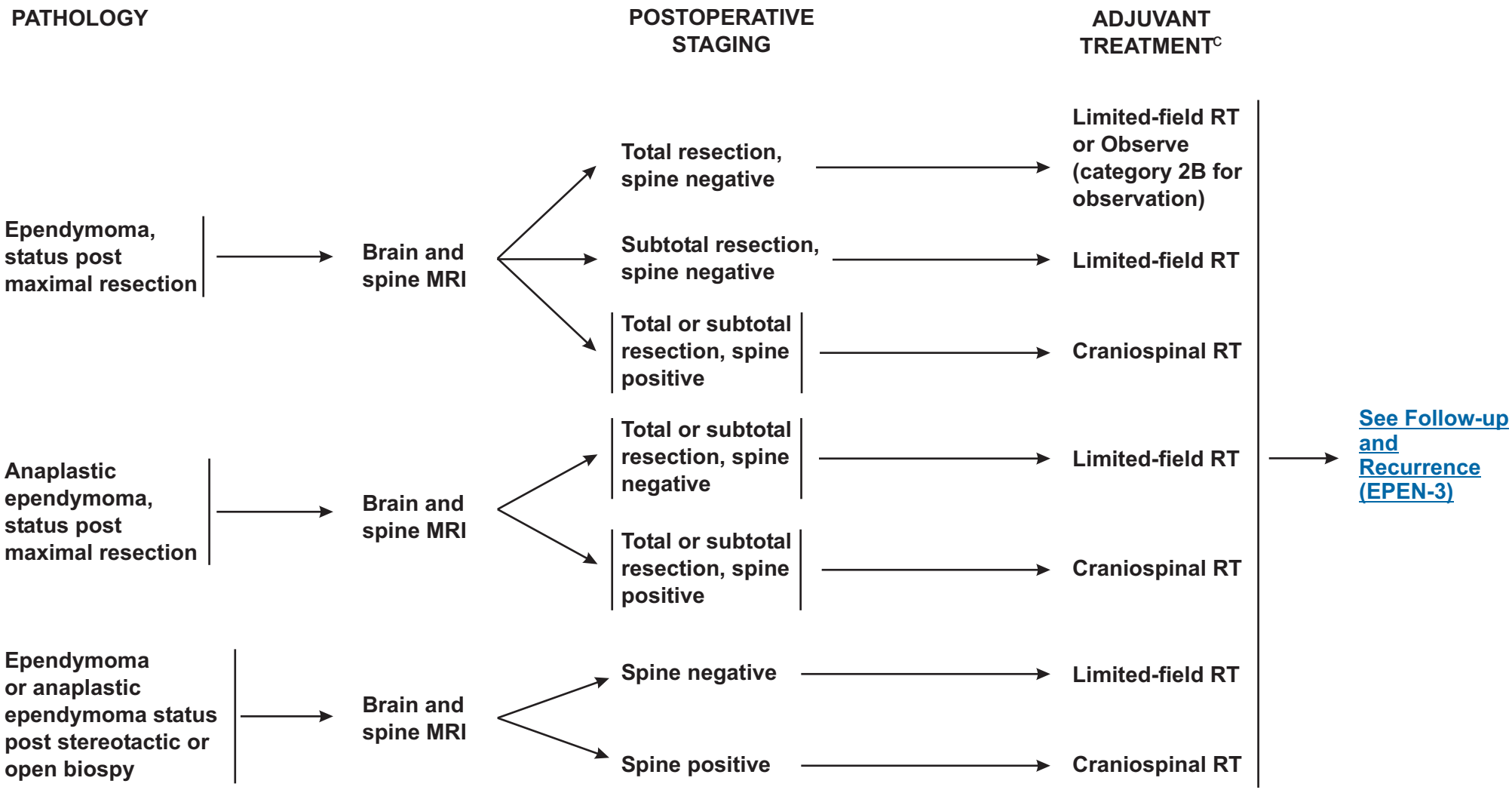

[C] See Radiation Therapy Guidelines (BRAIN-2).

Note: All recommendations are category 2A unless otherwise indicated.
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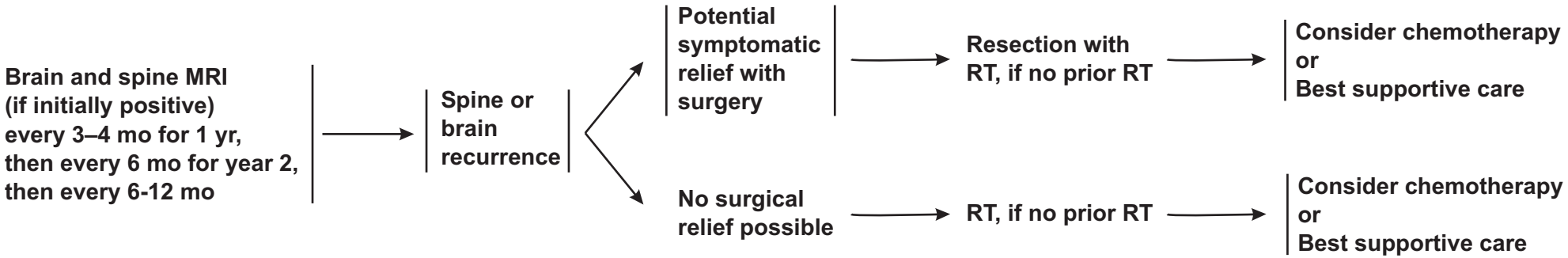
Adult Intracranial Ependymoma

FOLLOW-UP

RECURRENCE



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Note: All recommendations are category 2A unless otherwise indicated.
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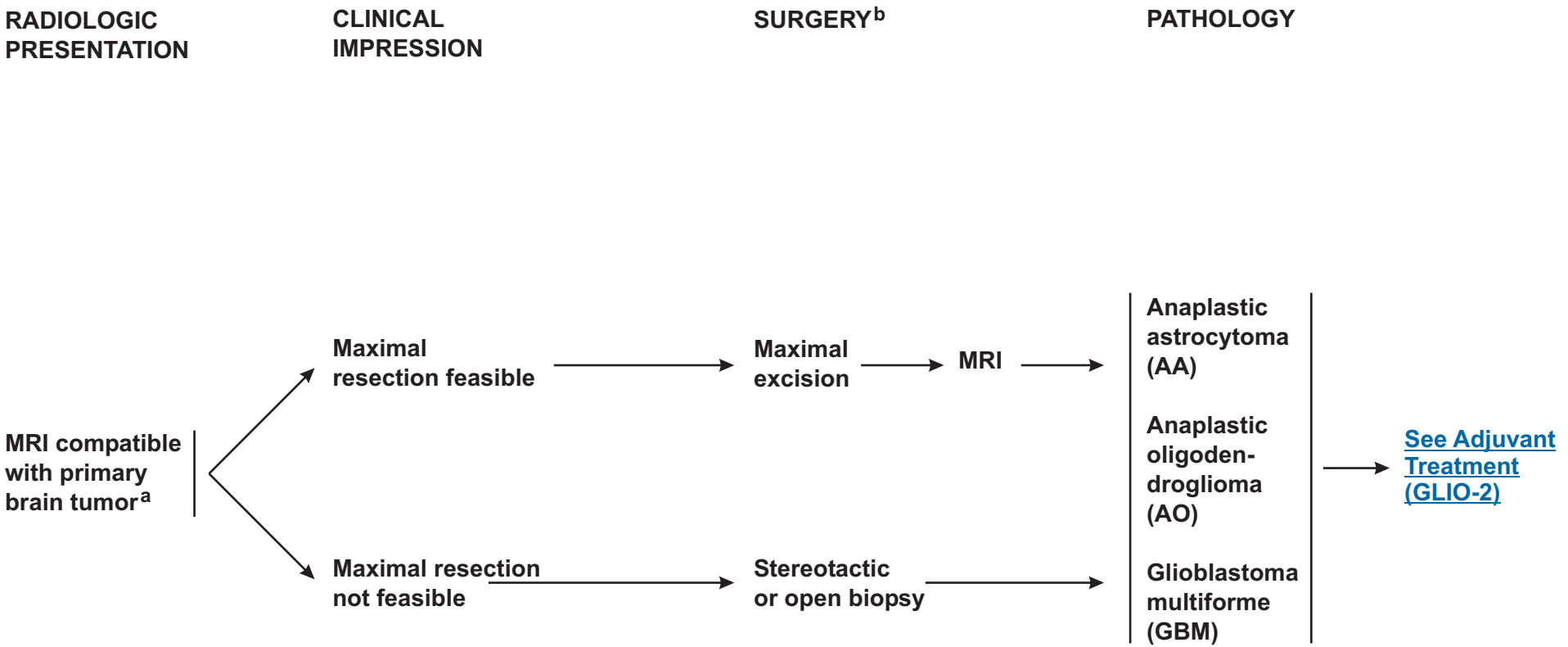
Anaplastic Astrocytoma/Anaplastic Oligodendroglioma/Glioblastoma Multiforme



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

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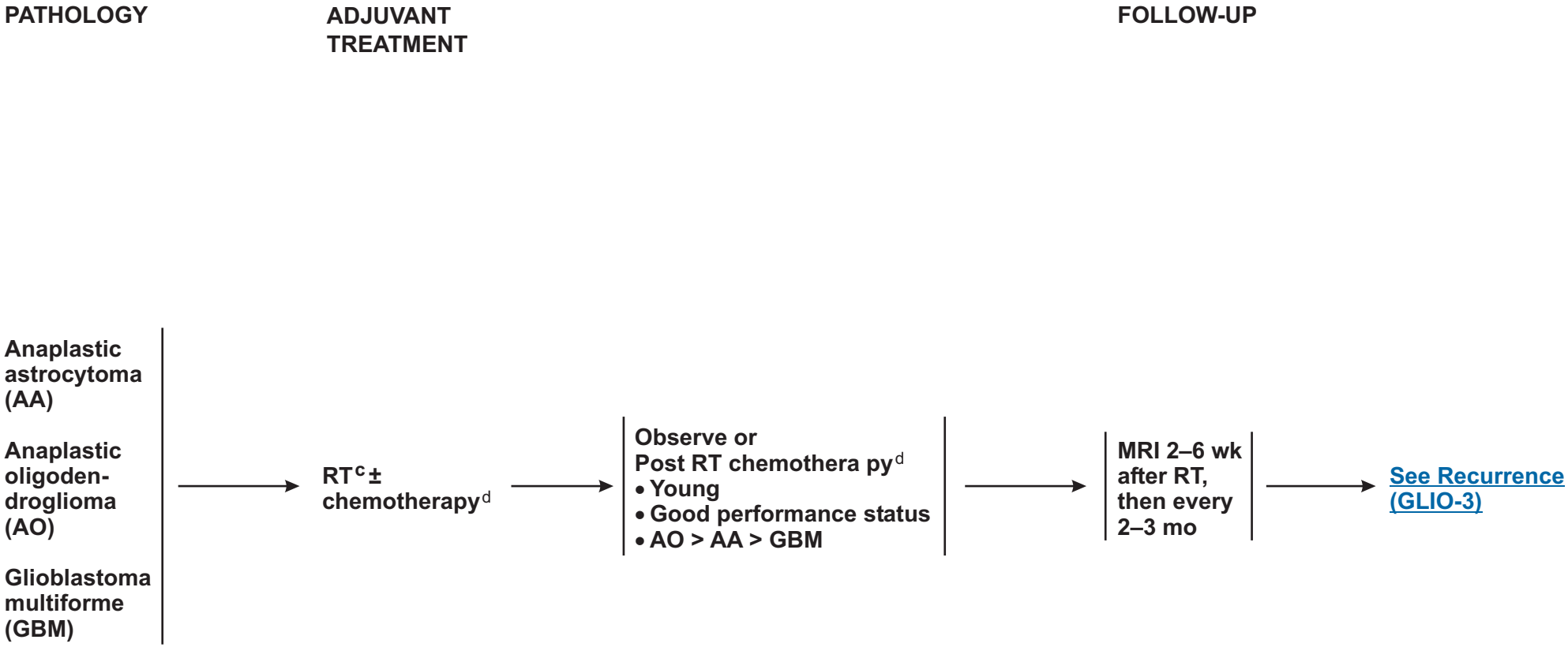

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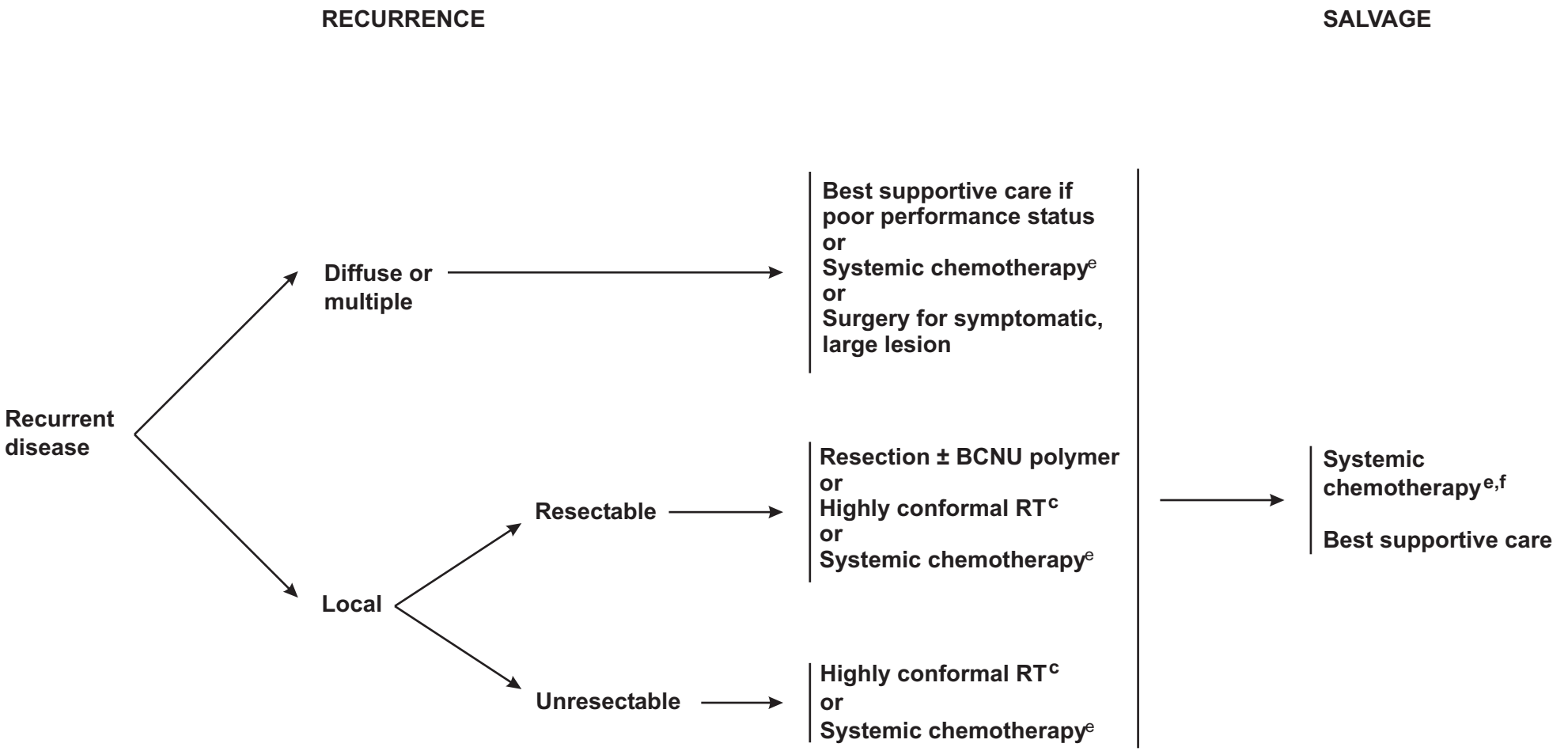

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[c] See Radiation Therapy Guidelines (BRAIN-2).

[e] Chemotherapy agents include: nitrosureas, temozolomide, procarbazine. See text for further discussion.

[f] A response after 2 consecutive failures is unlikely.

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

Limited (1-3) Metastatic Lesions

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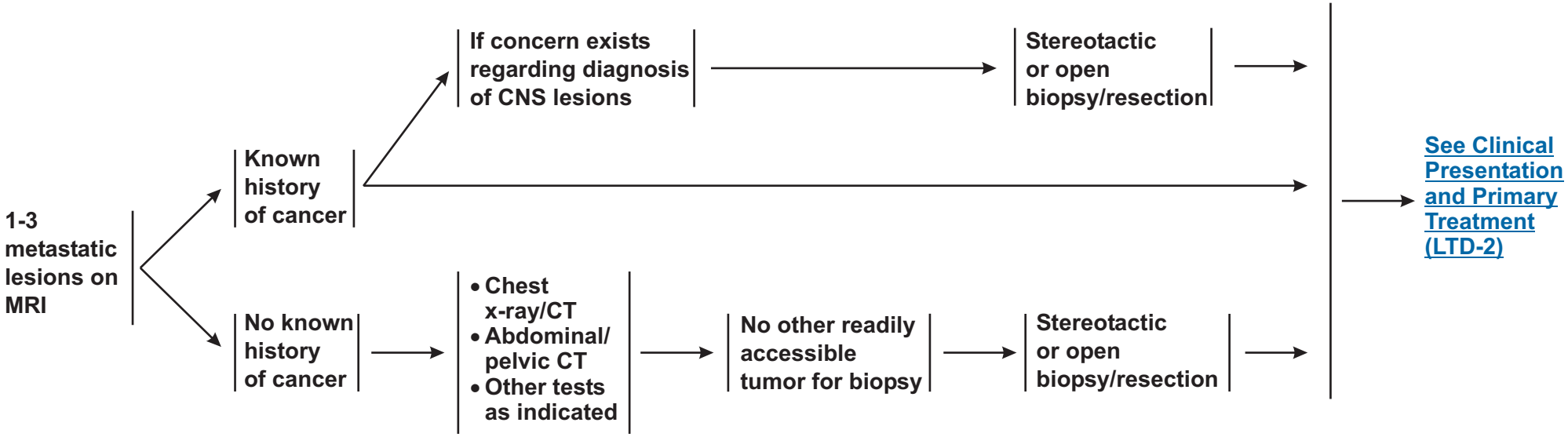
CLINICAL PRESENTATION **WORKUP**



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Limited (1-3) Metastatic Lesions

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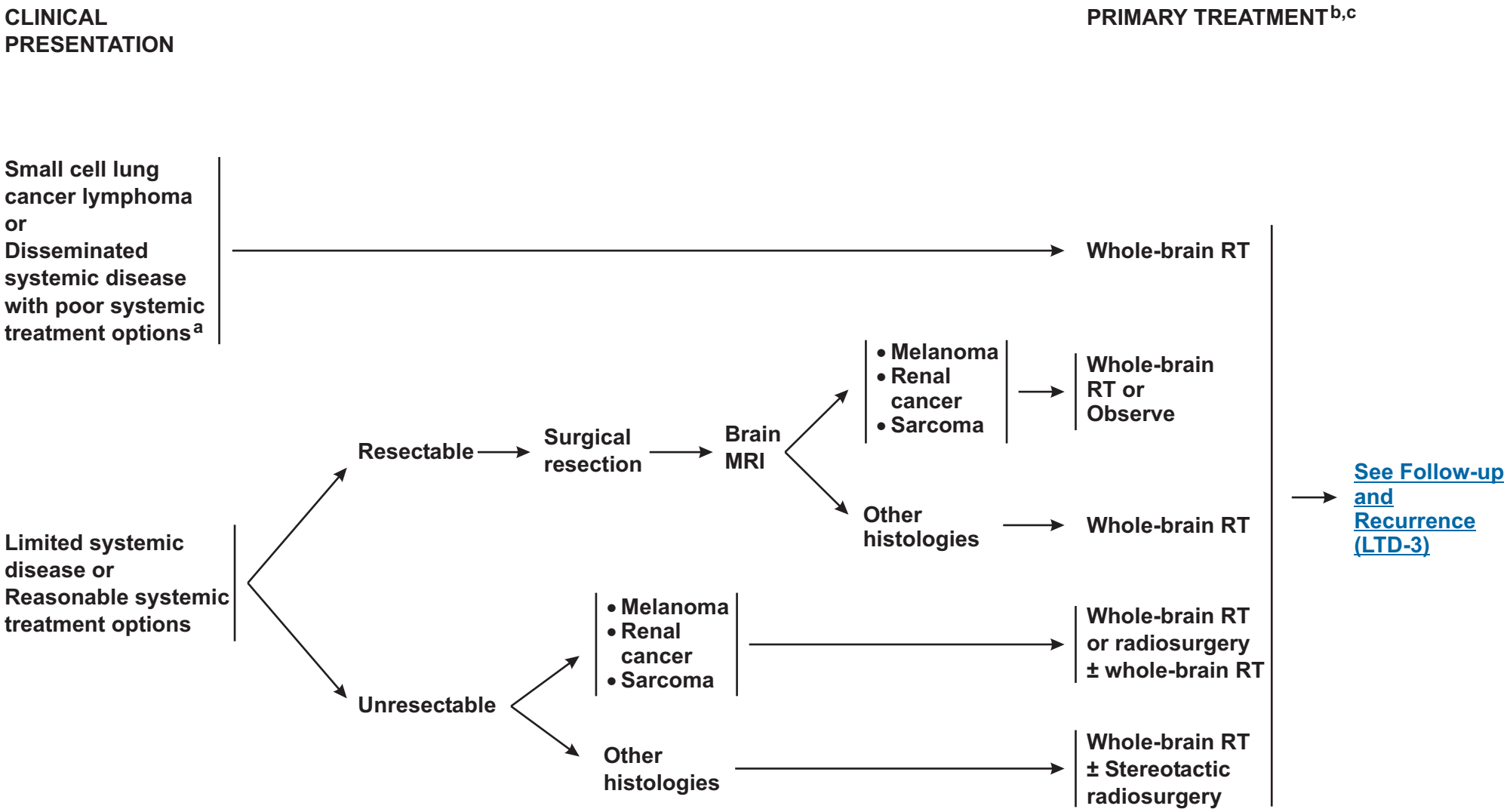

[a] Consider surgery to relieve mass effect.
[b] See Surgical Issues (BRAIN-1).
[c] See Radiation Therapy Guidelines (BRAIN-2).

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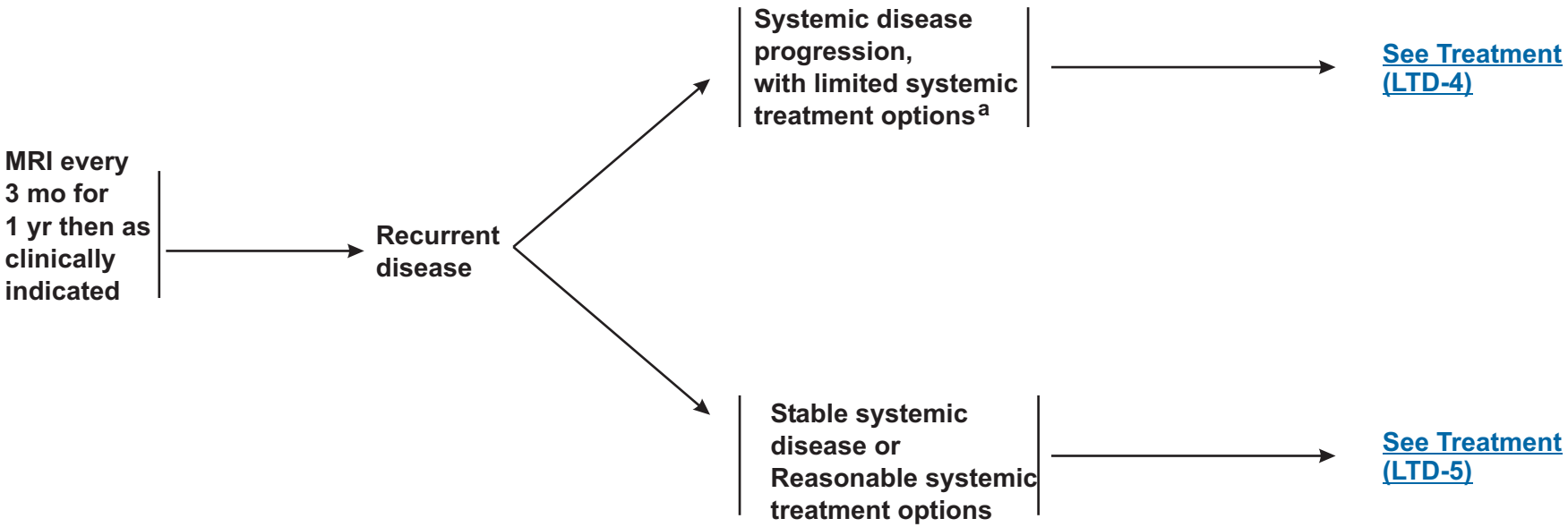
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Limited (1-3) Metastatic Lesions

FOLLOW-UP

RECURRENCE



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Limited (1-3) Metastatic Lesions

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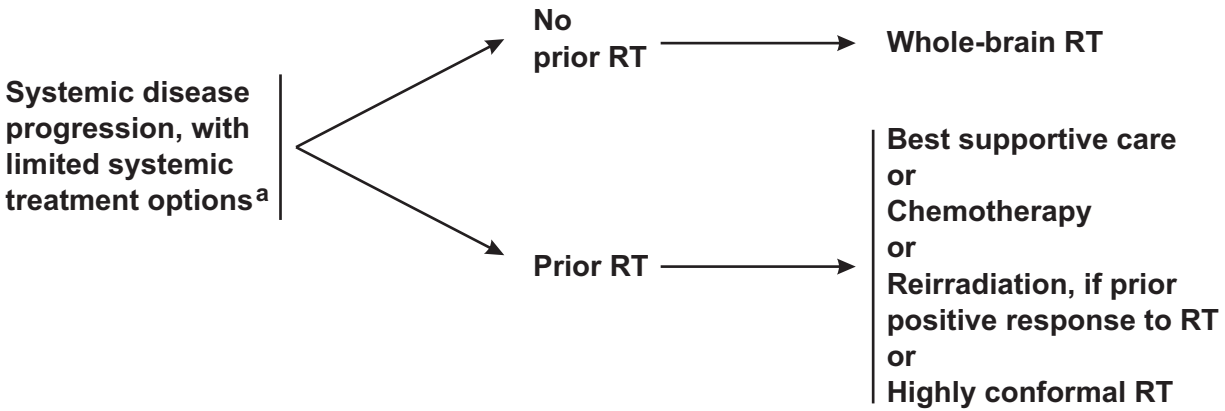

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[a]Consider surgery to relieve mass effect.
[c]See Radiation Therapy Guidelines (BRAIN-2).

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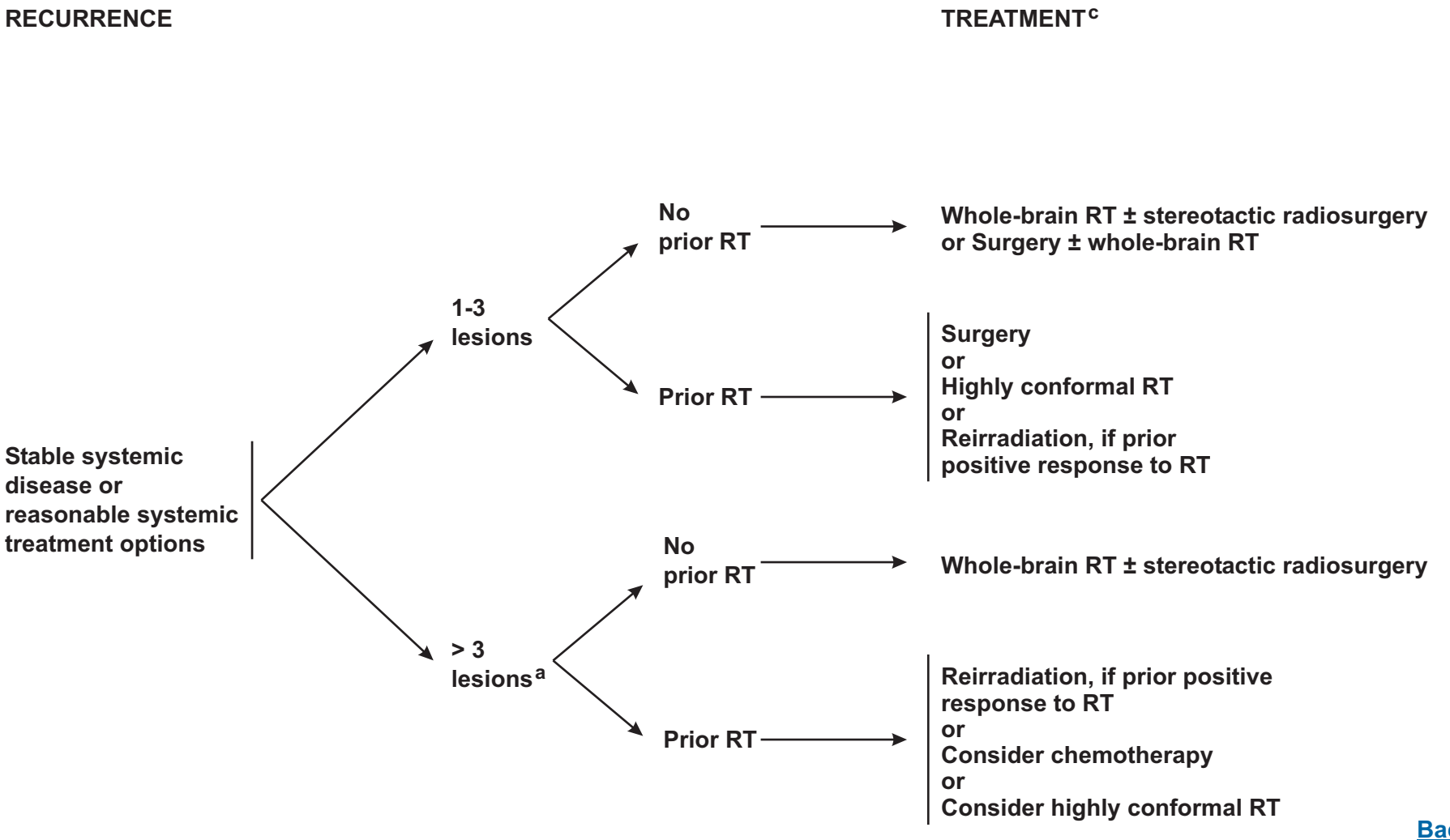
Limited (1-3) Metastatic Lesions



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[a]Consider surgery to relieve mass effect.

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Multiple (>3) Metastatic Lesions

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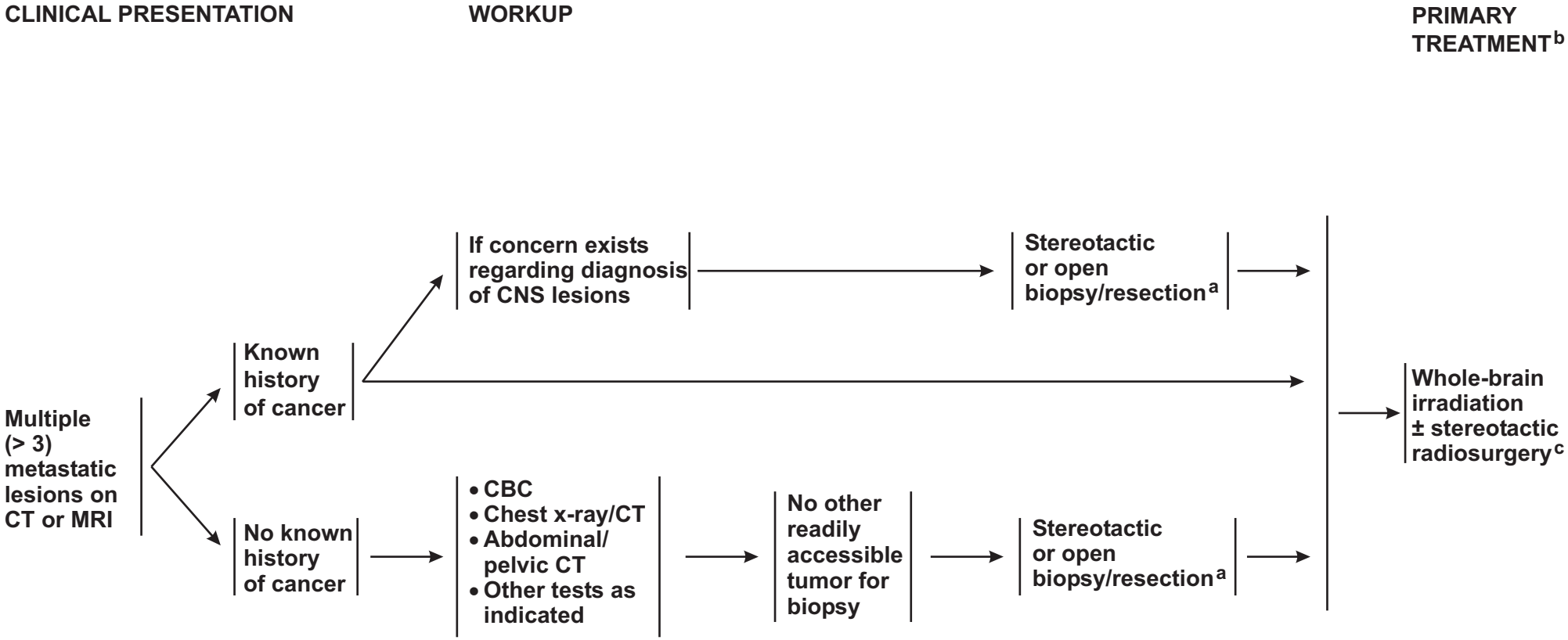

See Follow-up and Recurrence (MU-2)

[a] Consider surgery to relieve mass effect.

[b] See Radiation Therapy Guidelines (BRAIN-2).

[c] SRS should only be considered in selected cases (e.g., limited number of lesions).

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

Multiple (>3) Metastatic Lesions

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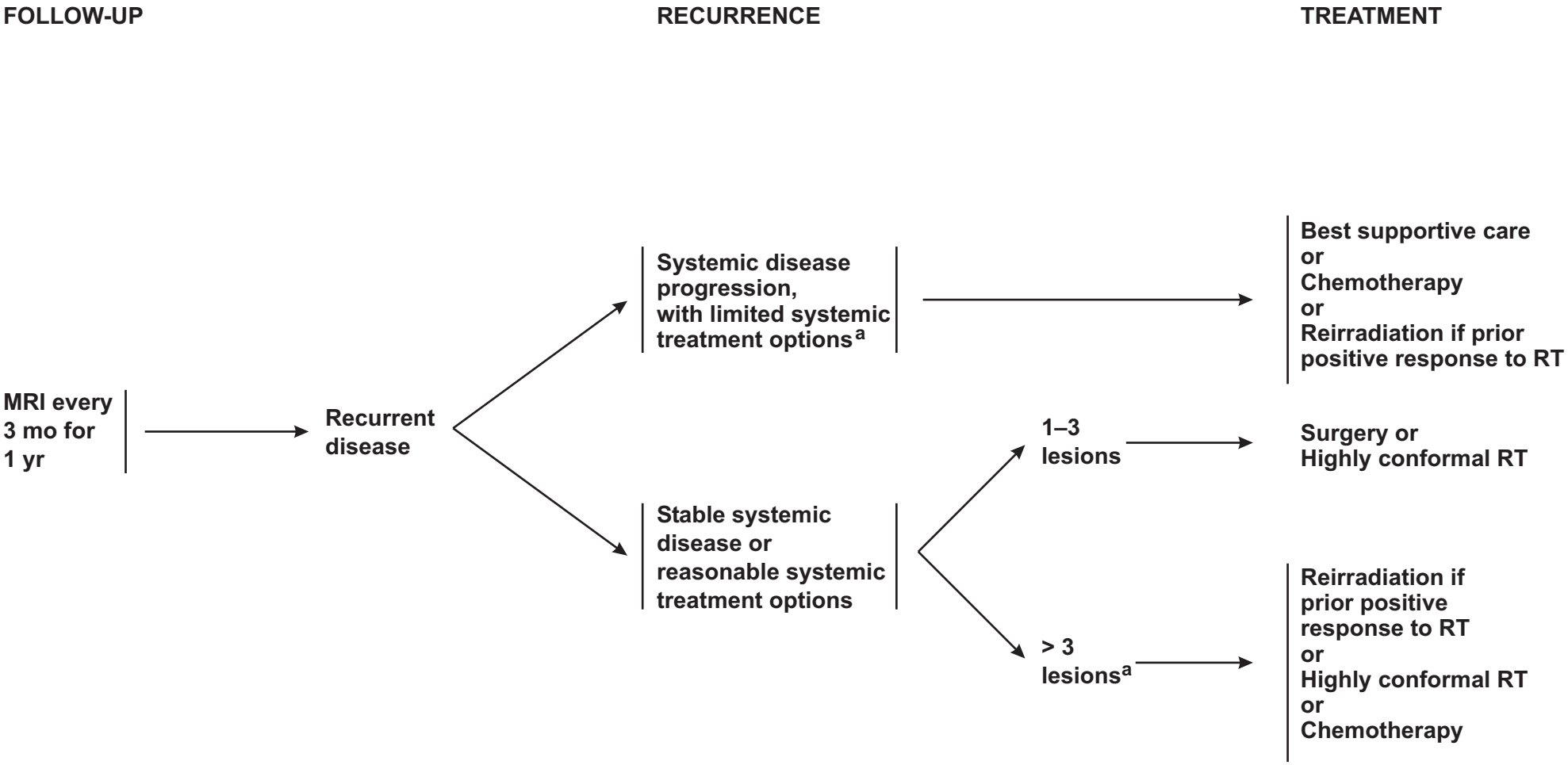

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[a]Consider surgery to relieve mass effect.

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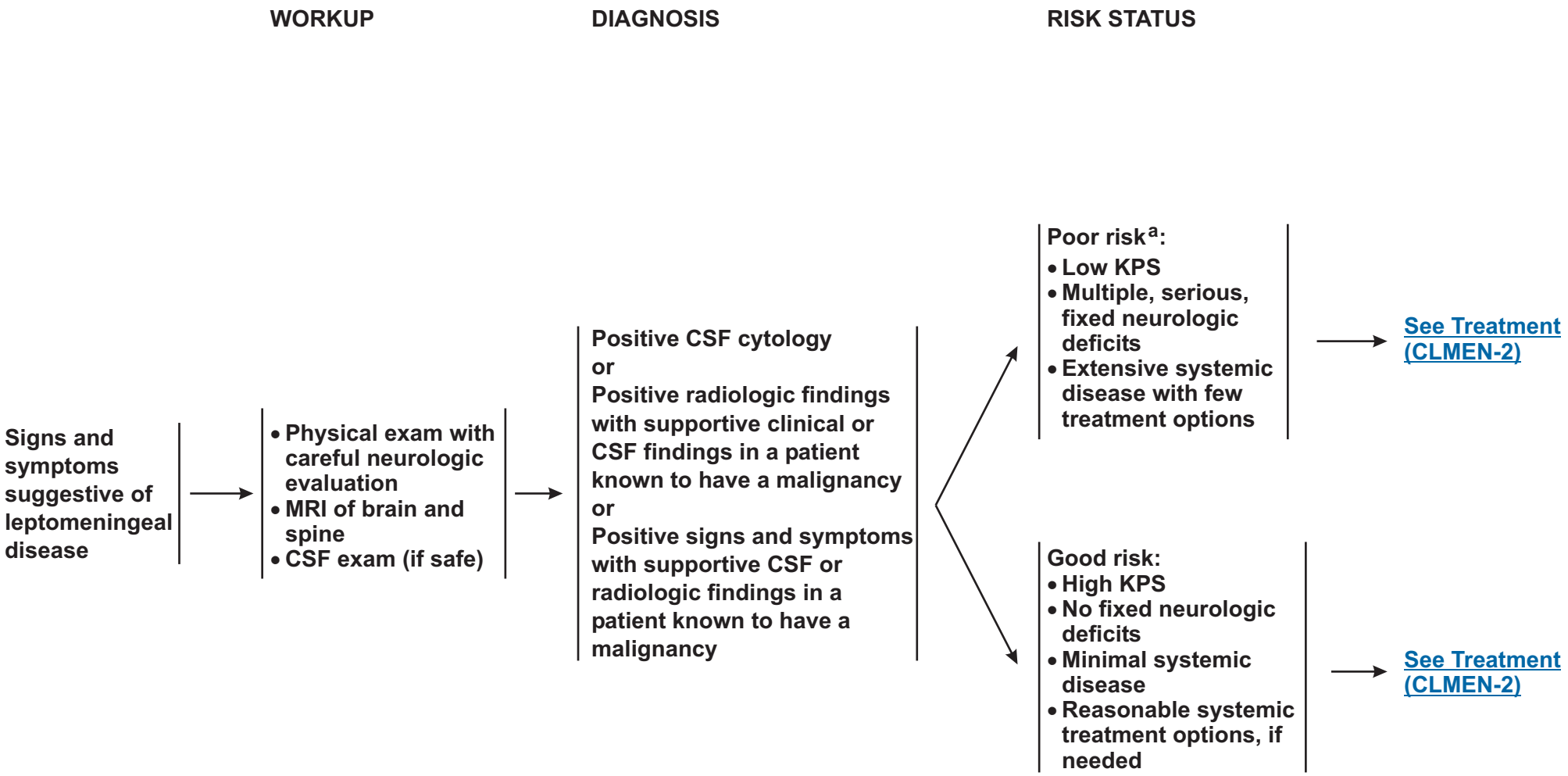
Carcinomatous/Lymphomatous Meningitis



[a]Patients with exceptionally chemosensitive tumors, e.g., SCLC, lymphoma; may be treated.

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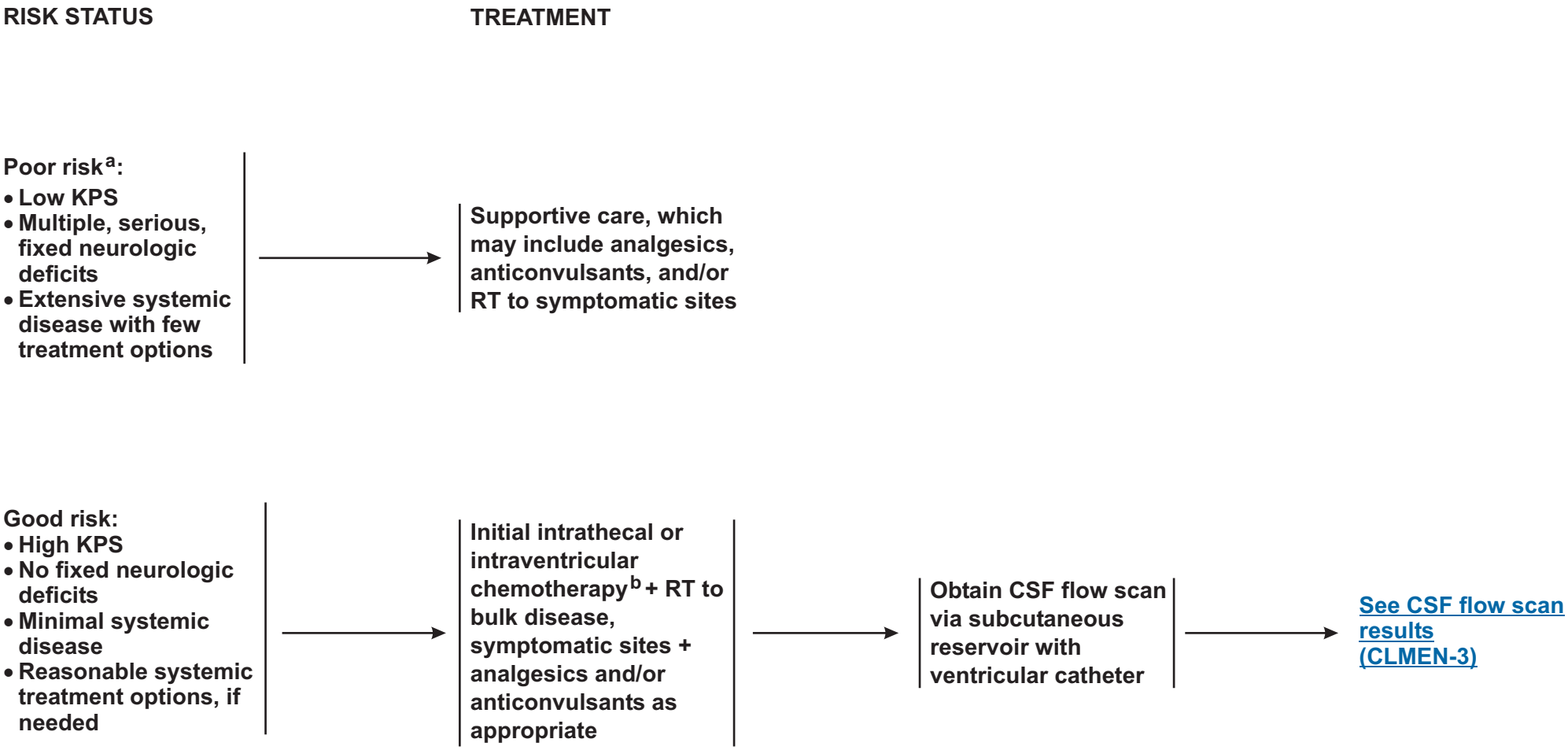
Carcinomatous/Lymphomatous Meningitis



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[a] Patients with exceptionally chemosensitive tumors, e.g., SCLC, lymphoma; may be treated.
[b] Initiation of chemotherapy should not be delayed for flow study.

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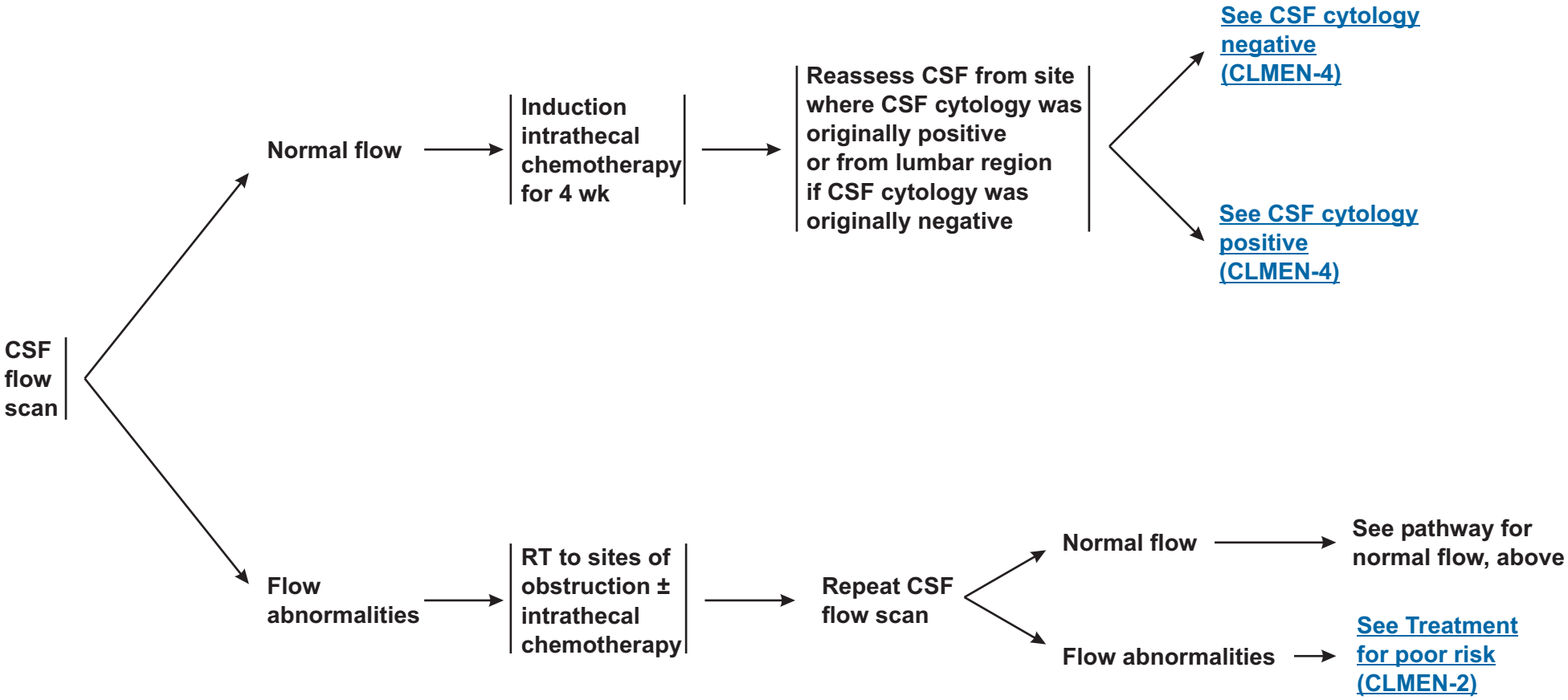
Carcinomatous/Lymphomatous Meningitis

PRIMARY TREATMENT



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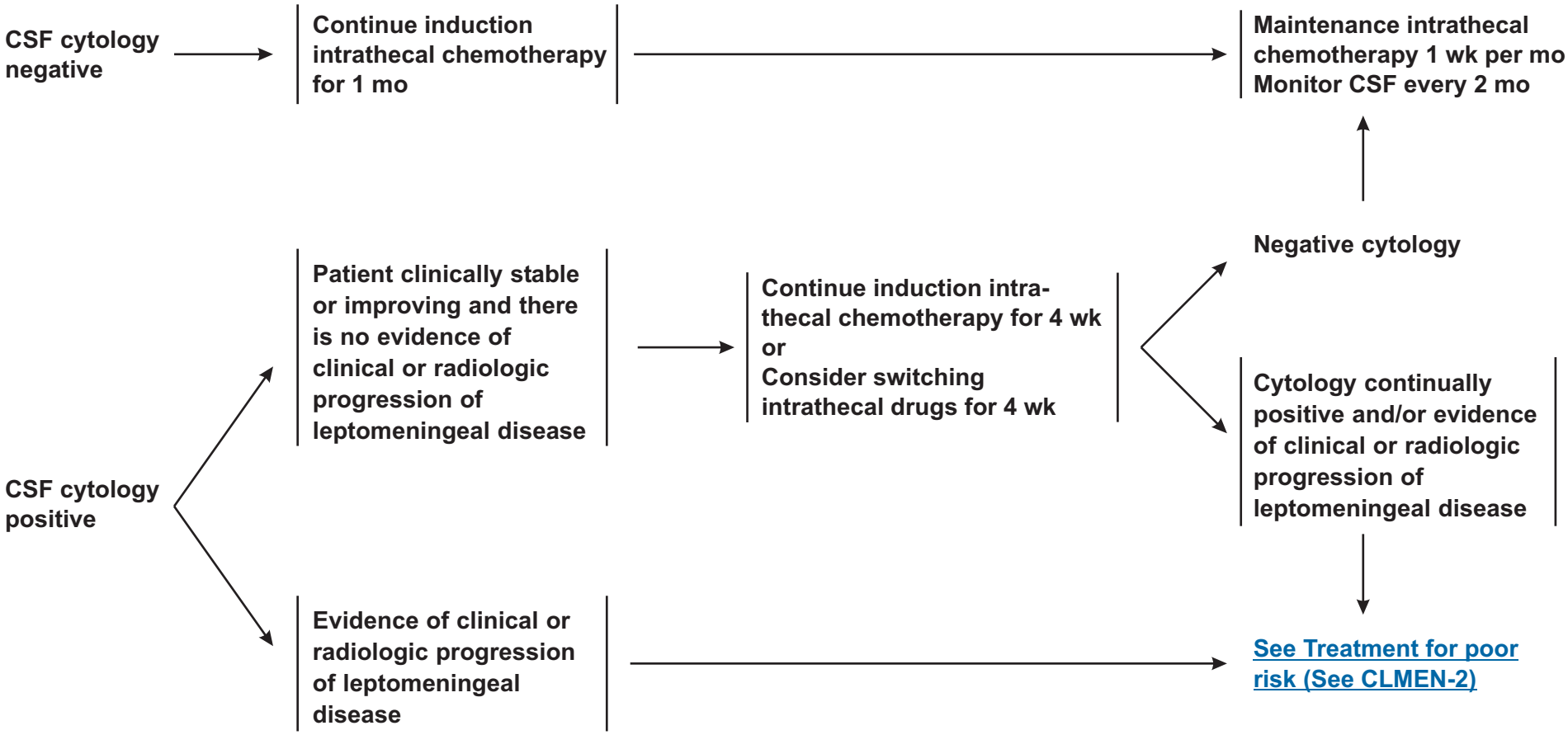
Carcinomatous/Lymphomatous Meningitis

POSTINDUCTION THERAPY



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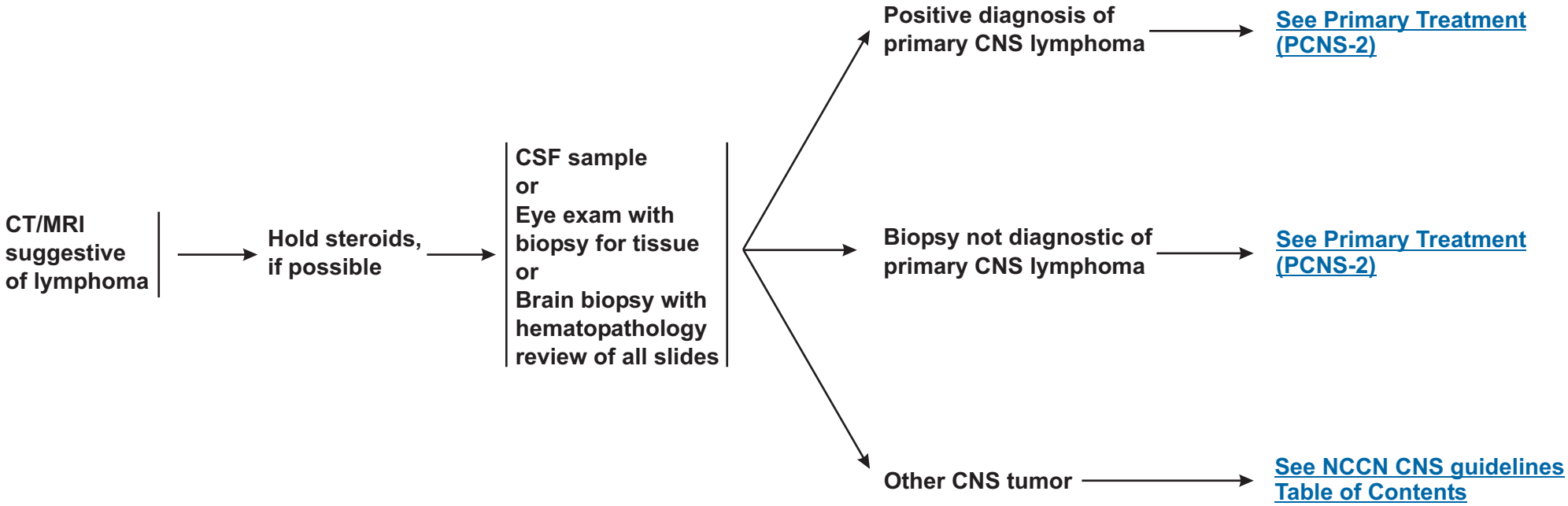
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Nonimmunosuppressed Primary CNS Lymphoma

DIAGNOSIS BY TISSUE EVALUATION



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Nonimmunosuppressed Primary CNS Lymphoma

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STAGING EVALUATION/WORK-UP

PRIMARY TREATMENT

Positive diagnosis of primary CNS lymphoma

- Slit lamp eye exam
- Lumbar puncture, (LP) if safe
- Spinal MRI
- HIV
- Chest x-ray
- CBC, platelets, liver function tests

KPS ≥ 40[a,b] and creatinine clearance ≥ 50

→ **High-dose (≥ 3g/m^2) methotrexate-based regimen[c] ± RT[e]**
- If eye exam positive, RT to orbits
- If LP positive or spinal MRI positive, consider intrathecal chemotherapy

KPS < 40[a,b] or creatinine clearance < 50

→ **Whole-brain RT (45 Gy)**
- If eye exam positive, RT to orbits
- If LP positive or spinal MRI positive, consider intrathecal chemotherapy + focal spinal RT

or Chemotherapy[d]

Biopsy not diagnostic of primary CNS lymphoma

- **Prior steroids** → **Discontinue steroids and rebiopsy when disease progresses**
- **No prior steroids** → **Work-up for other CNS diagnosis or rebiopsy**

See Progressive Disease (PCNS-3)

[a] KPS may improve dramatically with steroids.
[b] Age and performance status guidelines have not been firmly established and consultation between physician and patient regarding risks and benefits of aggressive therapy is mandatory.
[c] Participation in clinical trials is highly recommended.
[d] Consider alternate chemotherapy regimens for patients who cannot tolerate methotrexate.
[e] Avoid RT in patients over 60 years of age when possible.

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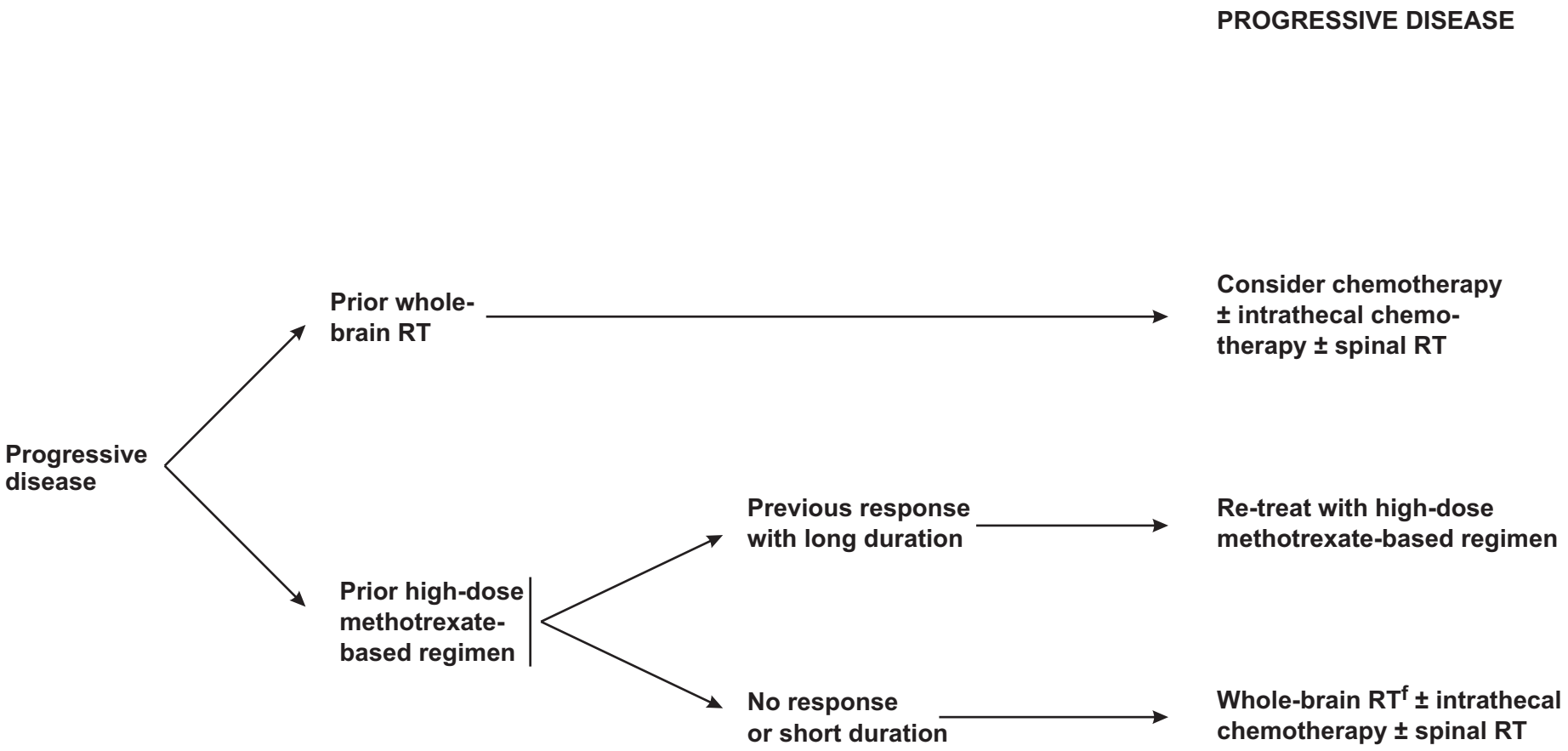

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[f]Consider alternate chemotherapy regimens for patients not appropriate for WBRT.

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SURGICAL ISSUES

GUIDING PRINCIPLES
- Maximal tumor removal
- Minimal surgical morbidity
- Accurate diagnosis

FACTORS
- Age
- PS
- Feasibility of decreasing the mass effect with surgery
- Resectability, including number of lesions, location of lesions, time since last surgery (recurrent patients)
- New versus recurrent tumor

OPTIONS
- Stereotactic biopsy
- Open biopsy/debulking
- Major tumor removal (> 80%)

TISSUE
- Maximum to pathologist
- Review by experienced neuropathologist

Postoperative MRI should be performed within 24-72 hours to determine the extent of resection

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RADIATION THERAPY GUIDELINES

RADIATION THERAPY (fractionated external beam)

- Field to include tumor volume and margins
  Dose to brain tumor: 1.8-2.0 Gy/day to a total dose of 45-60 Gy
- Hypofractionation in patients with poor performance status
- Prophylactic dose to spine (if indicated): 24-36 Gy
- Dose for metastases: 30-40 Gy

HIGHLY CONFORMAL RADIATION THERAPY

- Brachytherapy
- Stereotactic fractionated radiotherapy
- Stereotactic radiosurgery

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Manuscript

NCCN Categories of Consensus

Category 1: There is uniform NCCN consensus, based on high-level evidence, that the recommendation is appropriate.

Category 2A: There is uniform NCCN consensus, based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 2B: There is nonuniform NCCN consensus (but no major disagreement), based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 3: There is major NCCN disagreement that the recommendation is appropriate.

All recommendations are category 2A unless otherwise noted.

Overview

In the year 2003, an estimated 18,300 new cases of primary brain and nervous system neoplasms will be diagnosed in the United States (Jemal et al, 2003). These tumors will be responsible for approximately 13,100 deaths (Jemal et al, 2003). Metastatic disease to the central nervous system (CNS) occurs much more frequently, with an incidence about 10 times that of primary brain tumors. It is estimated between 20% and 40% of patients with systemic cancer will develop brain metastases.

Primary and metastatic brain tumors are a heterogeneous group of neoplasms with varied outcomes and management strategies. Primary brain tumors range from the very uncommon, noninvasive, surgically curable, pilocytic astrocytomas to glioblastoma multiforme, the most common intraparenchymal brain tumor in adults, which is highly invasive and virtually incurable. Likewise, patients with metastatic brain disease may have rapidly progressive systemic disease or no systemic cancer at all. These patients may have one or dozens of brain metastases, and they may have a malignancy that is very responsive or very resistant to radiation or chemotherapy. As a result of this marked heterogeneity, the prognostic features and treatment options must be carefully reviewed for each patient. The involvement of neurosurgeons, radiation therapists, oncologists, neurologists, and neuroradiologists is a key factor in the appropriate management of these patients.

Treatment Principles

Several important principles guide surgical and radiation therapy (RT) for adults with primary 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. (see BRAIN-1). Decisions regarding aggressiveness of surgery for a primary brain tumor are complex and depend on the age and performance status of the patient; the proximity to “eloquent” areas of the brain; the feasibility of decreasing the mass effect with aggressive surgery; the resectability of the tumor (including the number and location of lesions); and, in patients with recurrent disease, the time since the last surgery (Sawaya et al, 1998).

The surgical options include stereotactic biopsy, open biopsy or debulking procedure, or major tumor resection, which is usually characterized by removing more than 80% of a tumor. The pathologic diagnosis is critical and often difficult to determine accurately; therefore, as much tissue as possible should be

delivered to the pathologist. Review by an experienced neuropathologist is highly recommended. In addition, a postoperative magnetic resonance imaging (MRI) scan, with and without contrast, should be obtained 24 to 72 hours after surgery to document the extent of disease after surgical intervention.

Radiation therapists use several different treatment approaches in patients with primary brain tumors, including brachytherapy, stereotactic fractionated radiotherapy, and stereotactic radiosurgery. Conformal external-beam radiation is the most common approach, but local RT techniques (including external focal, brachytherapy, and stereotactic radiosurgery) may also be administered to selected patients. Radiation therapy for patients with primary brain tumors usually involves only the tumor volume and margins (see BRAIN-2). Tumor volume is commonly defined as the region showing T2-weighted abnormalities on an MRI scan plus a 1- to 2-cm margin. Although the dose of radiation administered can vary, the total dose prescribed to most primary brain tumors is 45 to 60 Gy using 1.8 to 2.0 Gy/day. If the spine is also treated, it should receive a prophylactic dose of 24 to 36 Gy. The dose for metastases is 30 to 40 Gy. Hypofractionation is often administered to patients with poor performance status to minimize the number of visits to the radiation department.

Tumor Types

The NCCN Central Nervous System Cancer Guidelines focus on high-grade invasive astrocytomas, low-grade invasive astrocytomas, oligodendrogliomas, ependymomas, brain metastases, carcinomatous meningitis, and CNS lymphoma (non-AIDS). These guidelines are updated annually to include new information or treatment philosophies as they become available. However, because this field changes continually, practitioners should use all of the available information to determine the best clinical options for their patients with primary or metastatic brain tumors.

High-Grade Invasive Astrocytomas

Grade III (anaplastic astrocytoma) and grade IV (glioblastoma multiforme) astrocytomas are the most common primary brain tumors in adults and account for 2.3% of all cancer-related deaths. Glioblastoma multiforme tumors account for more than 50% of all gliomas, and peak incidence occurs from ages 45 to 55 years. The high-grade astrocytomas diffusely infiltrate surrounding tissues and frequently cross the midline to involve the contralateral brain. Patients with these neoplasms often present with symptoms of increased intracranial pressure, seizures, or focal neurologic findings related to the size and location of the tumor and associated peritumoral edema. These tumors usually do not have associated hemorrhage or calcification but produce considerable edema and mass effect, 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.

It is difficult to assess the results of therapy using computerized tomographic (CT) scan or MRI scans because the extent and distribution of contrast enhancement, edema, and mass effect are more a function of blood-brain barrier integrity than of changes in the size of the tumor. Thus, other factors that exacerbate blood-brain barrier dysfunction (such as surgery, radiation, and tapering of corticosteroids) can mimic tumor progression by increasing contrast enhancement, T2-weighted abnormalities, and mass effect. The most important prognostic factors in patients with high-grade astrocytomas are histologic diagnosis, age, performance status,

type and duration of symptoms, and extent of surgical resection (Curran et al, 1993).

Treatment Overview

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. The median survival with surgery alone is approximately 4 months. A prospective study in patients with malignant glioma showed that extensive surgery was valuable compared to biopsy alone as a strong prognostic factor (Laws et al, 2003). Most studies suggest that the extent of resection lengthens survival and is especially effective in patients older than 50 years with glioblastoma multiforme and a Karnofsky performance score more than 70. Using current microneurosurgical techniques, it is possible to resect malignant gliomas in gross total fashion. An aggressive approach in which 98% or more of the tumor mass is resected results in a statistically significant survival advantage (Hentschel and Sawaya, 2003). Surgery also improves the outcome for patients with recurrent high-grade astrocytomas (Harsh et al, 1987).

Radiation is standard therapy for patients with high grade astrocytomas after either maximal excision or biopsy, based on a randomized trial conducted in the 1970s comparing postoperative supportive care, carmustine (BCNU), radiation, and radiation plus BCNU (Walker et al, 1978). Survival at 1 year was 3% with surgery alone, 12% with postoperative BCNU, and 24% with postoperative radiation. Currently, 60 Gy, divided into 30 to 36 fractions, is administered to the involved field. Alternative doses, fractions, and schedules have been explored without significant improvements. The role of focal radiation techniques in this diffusely infiltrative disease remains undefined.

Chemotherapy is of marginal value in patients with glioblastoma multiforme, but it may be more beneficial in younger patients and those with anaplastic astrocytomas. Randomized studies using intravenous BCNU demonstrated a slight improvement in survival at 18 months but no benefit at 12 or 24 months (Walker et al, 1980). A meta-analysis also demonstrated a modest survival benefit afforded by postoperative adjuvant chemotherapy (Fine et al, 1993). A recently completed randomized Medical Research Council study (2001) of adjuvant chemotherapy, which included nearly 700 patients, failed to show a benefit for procarbazine, CCNU, and vincristine (PCV) in patients with malignant gliomas. Furthermore, this study failed to demonstrate a survival benefit for PCV chemotherapy in patients with anaplastic astrocytoma. Unfortunately, currently available chemotherapy does not provide cures in even a few of these patients. Other nitrosoureas have been no more effective than BCNU (Lesser and Grossman, 1994). Temozolomide, which is approved by the U.S. Food and Drug Administration (FDA) for use in patients with recurrent anaplastic astrocytoma, is being studied in the adjuvant setting and in patients with glioblastoma multiforme. Procarbazine, CPT-11, and cisplatin also have modest activity in these tumors. Many other agents are currently being studied. Multiagent chemotherapy regimens have not been shown to be superior to BCNU alone in patients with glioblastoma multiforme. Although, one study suggested the combination of procarbazine, lomustine (CCNU), and vincristine (PCV) might be superior to BCNU in patients with anaplastic astrocytoma, subsequent analyses suggest that there is little difference between this regimen and BCNU (Prados et al, 1999). Neoadjuvant approaches also have yet to demonstrate a survival advantage in this disease.

Recent studies have convincingly demonstrated that P450-inducing anticonvulsants (such as phenytoin, phenobarbital, and carbamazepine [Tegretol]) can dramatically affect the pharmacology of many chemotherapeutic agents (Fetell et al, 1997; Grossman et al, 1998; Kuhn, 2002; Crews et al, 2002). Other routes of delivery have been tried, but these have been associated with additional cost, toxicity, and no clear evidence of improved survival. Local administration of BCNU chemotherapy using a biodegradable polymer (Gliadel wafer) placed intraoperatively in the surgical cavity has demonstrated a modest, but statistically significant, improvement in survival in patients with recurrent high-grade astrocytomas (Brem et al, 1995). As a result, the FDA has approved the Gliadel wafer for this indication. Recent studies show that BNCU polymer slightly prolongs survival in newly diagnosed patients with glioblastoma multiforme that is amenable to optimal resection (Westphal et al, 2003). The Gliasite balloon (Tatter et al, 2003) was recently approved by the FDA as a novel device to provide local postoperative irradiation to high-grade gliomas, but no efficacy trials have been conducted to date.

Treatment Algorithm

The previous information was used to construct a treatment algorithm for patients with newly diagnosed and recurrent high-grade astrocytomas. When a patient presents with a clinical and radiologic picture compatible with a high-grade astrocytoma, neurosurgical input is needed regarding the maximal feasible tumor resection. Whenever possible, major tumor removal should be performed. The extent of tumor debulking should be documented with an immediate postoperative MRI scan performed with and without contrast. If major tumor removal is deemed too risky, a stereotactic or open biopsy should be performed to establish the diagnosis.

After surgical intervention, RT should be administered as previously described (see BRAIN-2). Because chemotherapy is of marginal benefit and is not curative, it may be administered as adjuvant therapy or withheld until the time of tumor recurrence. In general, BCNU is administered to patients with glioblastoma multiforme, and temozolomide or PCV is given to patients with anaplastic astrocytoma (Yung et al, 1999). Young patients with good performance status and lower grade tumors probably benefit more from chemotherapy than poorer prognostic groups. Patients should be followed closely with serial MRI scans (at 2-6 weeks and then every 2-3 months) after the completion of RT. Because RT can produce additional blood-brain barrier dysfunction, corticosteroid requirements may actually increase; therefore, scans may look worse during the first 3 months after completion of radiotherapy, even though there is no actual tumor progression. Early MRI scans allow for appropriate titration of corticosteroid doses, depending on the extent of mass effect and brain edema. Later scans are used to identify tumor recurrence. Early detection of recurrence is warranted because local and systemic treatment options are available for patients with recurrent disease.

When recurrent disease is detected, management depends on the patient's age, performance status, histology, response to initial therapy, time since original diagnosis, and whether the recurrence is local or more diffuse. If the tumor appears to be local, the options include (1) repeat resection, with or without a BCNU-impregnated wafer placed locally in the surgical bed; (2) highly conformal RT approaches; or (3) the administration of systemic chemotherapy (including nitrosoureas, temozolomide, procarbazine). If the tumor is unresectable or surgery is deemed to be too risky, highly conformal RT or systemic chemotherapy can be considered. Systemic chemotherapy (including nitrosoureas, temozolomide, procarbazine)

may be the best option if the tumor recurrence is diffuse, bilateral, or multifocal. Surgery can be considered for a symptomatic large lesion. Best supportive care should also be strongly considered, especially if the patient has a poor performance status. Salvage therapy for patients with recurrent disease can include best supportive care and systemic chemotherapy; however, a response after two consecutive failures is unlikely.

Low-Grade Invasive Astrocytomas

Low-grade astrocytomas are a diverse group of relatively uncommon malignancies, and outcomes depend on many factors. Of these malignancies, 70% are diffuse astrocytomas (fibrillary, protoplasmic, and gemistocytic types), which are poorly circumscribed, invasive, and gradually evolve into higher-grade astrocytomas. Gliomatosis cerebri is characterized by widespread dissemination of neoplastic astrocytes, often involving an entire cerebral hemisphere. The most common noninfiltrative astrocytomas are the pilocytic astrocytomas, which are circumscribed, often surgically resectable, and rarely transform. These are more common in the cerebellum of children but also occur in the cerebral cortex of adults. Many other rare low-grade astrocytomas also exist, such as the pleomorphic xanthoastrocytoma, subependymal giant cell astrocytoma, and subependymoma.

Patients with infiltrative low-grade tumors usually present with seizures (66%), headache, and/or weakness. The median duration from onset of symptoms to diagnosis ranges from 6 to 17 months. The mean age at presentation for these tumors is 37 years. The most powerful predictor of survival is age. The average 10-year survival rate for children is 83%, whereas the median survival is only 5 years for those older than 40 years. Other important prognostic factors for survival include long duration of symptoms, excellent postoperative neurologic status, and diploid tumors with a low labeling index. These tumors typically are nonenhancing, low-attenuation lesions on CT scans and MRI scans. However, the imaging “diagnosis” of low-grade astrocytoma is incorrect about 25% of the time; the most common alternate diagnosis is high-grade astrocytoma.

Treatment Overview

Despite the common notion that low-grade astrocytomas are benign, most of these tumors behave aggressively despite surgery and RT (Shaw et al, 1989). The best management strategy for a patient with seizures and a probable low-grade astrocytoma has yet to be defined (Keles et al, 2001). Whenever possible, total removal should be attempted because survival and recurrence-free intervals are superior when the tumors can be safely removed (Soffietti et al, 1989; Phillipon et al, 1993; Lo et al, 2001). Furthermore, a gross total removal could potentially delay or prevent malignant progression (Kilic et al, 2002). Of course, for tumors that are infiltrative and involve eloquent areas, a total removal may not be feasible and an aggressive approach could result in neurological deficits.

Surgery remains an important diagnostic and therapeutic modality for patients with low-grade astrocytomas. The primary surgical goal is to provide adequate tissue for a pathologic diagnosis and grading. Needle biopsies are often performed when lesions are in deep or critical regions of the brain. Biopsy results can be misleading because gliomas often have varying degrees of cellularity, mitoses, or necrosis from one region to another. Thus, small samples can provide a lower histologic grade.

The role of gross total surgical tumor excision in low-grade astrocytomas remains unresolved, although most of the available retrospective biomedical literature suggests a survival benefit from aggressive surgical resection. Because these tumors are relatively uncommon, published series generally include patients treated for decades, which introduces additional variables. In the past, for example, the completeness of surgical excision was based on the surgeon's report. This approach is relatively unreliable when compared with assessment by modern postoperative imaging studies. Furthermore, most patients also received RT, and thus the net effect of the surgical procedure on outcome is difficult to evaluate. Shaw and colleagues (1989) reviewed 126 patients with astrocytomas and mixed oligoastrocytomas. Patient survival rates after gross total removal were 52% at 5 years and 23% at 10 years. These survival rates were identical to those after subtotal removal or biopsy only. Most patients received postoperative radiotherapy, but a higher proportion in the subtotal removal group received this treatment. This experience suggests that if RT is applied, the degree of surgical removal may be less important. Other studies (Soffietti et al, 1989; Philippon et al, 1993) have suggested prolonged survival in patients who underwent gross total resection, compared with those patients who underwent less radical excision. Berger and colleagues (1994) have shown an inverse correlation between the post-surgical residual tumor volume and the length of survival in patients with low-grade astrocytomas.

Biological considerations also favor an attempt at a complete excision of an astrocytoma. First, the tumor may contain higher-grade foci, which may not be reflected in a small specimen. Second, complete excision may decrease the risk of future dedifferentiation to a more malignant astrocytoma (Kilic et al, 2002). Third, a large tumor burden is removed, which also may enhance the effect of radiotherapy. As a result of these considerations, the general recommendation for treating an astrocytoma is to first attempt as complete an excision of tumor as possible without compromising function.

No consensus exists regarding the proper timing of postoperative radiation in low-grade astrocytomas. Some oncologists advocate immediate RT, whereas others delay radiation until tumor progression is evident. In Shaw's study (1989), immediate RT did prolong survival in patients with these tumors. Also, higher doses seemed to be more effective; 5-year survival rates were 68%, 47%, and 21% for patients receiving a total dose of 53 Gy or higher, less than 53 Gy, and no radiation, respectively (Shaw et al, 1989). However, others have reported no prolongation of survival in irradiated patients (Philippon et al, 1993). A randomized trial conducted by the European Organization for Research and Treatment of Cancer (EORTC) showed no difference in overall survival between delayed and immediate radiation, but an improved time to recurrence was noted with immediate radiotherapy (Karim et al, 1996). Further analysis of mature data is necessary before firm recommendations can be made based on this study. A similar study by the Brain Tumor Cooperative Group (BTCG) has not yet been reported. Although delaying radiation in young healthy patients without progressive neurologic decline is controversial, there is a consensus to proceed with immediate postoperative radiation in older patients after a less-than-total resection because their survival is as poor as patients with anaplastic astrocytoma.

When radiation is given to patients with low-grade astrocytomas, it is administered with restricted margins. Whole-brain RT results in more treatment-related neurotoxicity than does localized RT in these patients, who are often young and may survive for years. A T2-weighted MRI scan is the best means for evaluating tumor extent. In

general, contrast administration is not helpful because these tumors enhance weakly or not at all. The target volume is defined by the tumor with a 2-cm margin. Every attempt should be made to decrease the radiation dose outside the target volume. Therefore, the use of only two parallel opposed portals is not recommended. A wedged pair beam is adequate for many lateral tumors. The dose outside the target can be further decreased by the use of multiple beams and three-dimensional planning, and their use is encouraged. Stereotactic radiotherapy and intensity-modulated beams are being studied at a few institutions, but their value is not known at present. The standard radiation dose for low-grade astrocytomas is 54 Gy, given at a rate of 1.8 Gy per day. The selection of 54 Gy as the standard dose is based on its relative safety when applied to a limited volume of the brain and the lack of evidence for increased efficacy with higher doses. It should be noted, however, the EORTC completed a study comparing total radiation doses of 45 Gy and 59.4 Gy (both given at a rate of 1.8 Gy daily) in patients with low-grade astrocytomas (Karim et al, 1996). Overall survival and disease-free survival were identical in the two treatment groups. Enthusiasm for interstitial radiation in recurrent low-grade astrocytomas has decreased with the wider availability of stereotactic radiosurgery.

Currently, chemotherapy has no role in the standard treatment of low-grade astrocytomas except possibly at recurrence (Quinn et al, 2003). The Radiation Therapy Oncology Group (RTOG) will soon initiate studies to evaluate preliminary data suggesting chemotherapy might be efficacious in low-grade astrocytomas.

Treatment Algorithm

The initial portion of this treatment algorithm for patients with low-grade astrocytomas is identical to the treatment algorithm for high-grade astrocytomas. When possible, maximal resection is recommended for low-grade astrocytomas and the actual extent of resection should be documented with an immediate postoperative MRI scan. For patients undergoing complete excision, observation alone is reasonable after the surgical intervention. These tumors tend to behave more aggressively in patients older than 45 years; therefore, immediate radiotherapy may also be considered for patients in this age group who have undergone complete excision (see ASTR-2).

Patients who only had a diagnostic biopsy or subtotal excision are more likely to be treated with immediate radiotherapy, especially if they are symptomatic or have signs of progressive disease. Because of concerns about the neurotoxicity of radiotherapy (Lo et al, 2003), patients with residual asymptomatic low-grade astrocytoma may be treated with irradiation at the time of diagnosis or followed until their disease progresses. This approach is also reasonable in patients with diffuse low-grade astrocytoma because neurotoxicity increases with the size of the RT port required to encompass the entire lesion.

Patients should be followed using MRI every 3 to 6 months for 5 years and then less frequently. At the time of recurrence, surgery is considered for resectable lesions. This can be followed by radiation, if it was not previously administered, or by reirradiation, if the patient had a positive response to prior radiation. Local recurrence can also be treated with local RT and/or chemotherapy.

Oligodendrogliomas and Anaplastic Oligodendrogliomas

Oligodendrogliomas are thought to arise from oligodendrocytes, whereas mixed oligoastrocytomas probably develop from a common

glial stem cell. Together, they account for less than 15% of all primary brain tumors (Nijjar et al, 1993). Radiographically, the low-grade oligodendrogliomas appear well demarcated, occasionally contain calcifications, and do not enhance with contrast. The typical "fried egg" appearance of these tumors is evident in paraffin but not in frozen sections. Anaplastic oligodendrogliomas are characterized by high cellularity, nuclear pleomorphism, frequent mitosis, endothelial proliferation, and necrosis. These tumors can be pathologically confused with glioblastoma multiforme but have a better prognosis and are more responsive to therapy.

The median survival for patients with low-grade oligodendrogliomas is about 10 years and for anaplastic oligodendrogliomas, survival is about 3 to 5 years (Lindegaard et al, 1987). Patients with mixed oligoastrocytomas tend to have the same outcome as patients with pure oligodendrogliomas (Shaw et al, 1994).

Treatment Overview

Maximal feasible resection is preferred (Shaw et al, 1992), as previously noted for patients with low-grade astrocytomas. Gross total removal of these tumors is often possible because the majority occur in the frontal lobes and the tumors are frequently well-demarcated (Mork et al, 1985). Retrospective data have suggested that RT improves local control and survival (Yeh et al, 2002). Anaplastic oligodendrogliomas are chemosensitive (Cairncross et al, 1994; van den Bent et al, 2003a).

Treatment Algorithm

The treatment algorithm for patients with low-grade oligodendrogliomas is similar to the treatment algorithm for low-grade astrocytomas. Evidence is strong that gross total removal of the tumor leads to longer survival (Mork et al, 1985; Shaw et al, 1992; Berger and Rostomily, 1997). The value of immediate postoperative radiation is still debated because no randomized study has addressed this question. The largest retrospective study was conducted using patients with oligodendroglioma registered by the Cancer Registry of Norway during a 25-year period (Lindegaard et al, 1987). In this study involving 170 patients, survival was significantly longer in patients who received radiation therapy. However, the survival benefit was apparent only in the first 6 years of follow-up and only among patients who had less than a total surgical resection. The Mayo Clinic experience with oligodendroglioma included 82 patients (Shaw et al, 1992). The survival of the 63 patients who received radiotherapy was comparable to the survival of the smaller group of 19 who underwent surgery only. However, the two patient groups were quite different because the patients with poorer prognosis were referred for radiotherapy. When only patients who underwent a subtotal resection were compared, survival was prolonged with radiation.

For completely resected low-grade oligodendrogliomas, the consensus is postoperative radiation may be withheld if the patient is carefully followed (see ASTR-2); this is especially true for young patients. For patients with subtotally excised low-grade oligodendrogliomas, the considerations are the same as for patients with low-grade astrocytomas.

Two multicenter trials compared the results of radiotherapy for low-grade glioma, including oligodendroglioma, when either delaying the radiation until time of recurrence (Karim et al, 2002) or using high-dose versus low-dose radiation (Shaw et al, 2002). Although time to progression was longer in the immediate therapy group in the EORTC study, progressing patients whose radiotherapy had been delayed could be successfully salvaged, and survival was identical in both

arms (Karim et al, 2002; Stupp and Baumert, 2003). Of the progressing patients, 66% subsequently received radiation accounting for only 38% of the patients in the observation group. Thus, radiotherapy could be withheld in almost 66% of patients for more than 5 years (Karim et al, 2002; Stupp and Baumert, 2003). The intergroup randomized study by Shaw and colleagues (Shaw et al, 2002) found no benefit of the high-dose (64.8 Gy) RT versus the low-dose (50.4 Gy) RT delivered in identical fractionation; more toxicity in the higher dose arm is documented. Therefore, the current recommendation for low-grade gliomas is that lower doses in the range of 45 to 50.4 Gy are superior to higher doses (Buatti et al, 2002). Delay of radiation for tumors in noneloquent regions and small asymptomatic tumors in eloquent regions are viable options based on current information (Buatti et al, 2002). Because of the improved outcomes with the availability of improved mapping and surgical navigation techniques (Berger and Rostomily, 1997), an interdisciplinary approach (Buatti et al, 2002) based on institutional experience, expertise, and outcomes should be discussed frankly with each patient.

The radiation technique used in oligodendrogliomas is similar to the technique used in astrocytic gliomas. The occasional tendency of oligodendrogliomas to spread via the cerebrospinal fluid (CSF) does not justify the need for craniospinal radiation. Oligodendrogliomas have been reported to be sensitive to chemotherapy (van den Bent, 2003b). Chemotherapy using PCV (Buckner et al, 2003) or temozolomide (Brada et al, 2003; van den Bent et al, 2003b) may be appropriate adjuvant treatment for progressive or refractory low-grade oligodendroglioma or low-grade astrocytoma (Quinn et al, 2003) (see ASTR-2). The treatment algorithm for patients with anaplastic oligodendrogliomas is similar to the algorithm for high-grade astrocytomas. The value of neoadjuvant PCV is currently under study in an RTOG protocol.

Ependymomas and Anaplastic Ependymomas

Ependymomas occur in both children and adults. In children, approximately 66% of ependymomas arise infratentorially and 33% arise supratentorially. The opposite is true in adults. These tumors can cause hydrocephalus and increased intracranial pressure, mimic brainstem lesions, cause multiple cranial nerve palsies, produce localizing cerebellar deficits, and cause neck stiffness and head tilt if they infiltrate the upper portion of the cervical cord (Levin et al, 1993; Packer et al, 1996).

Treatment Overview

Outcome is closely related to the extent of surgical resection. Patients with totally resected tumors tend to have the best prognosis. Even benign or low-grade ependymomas, if incompletely resected, have poor outcomes.

Radiation therapy significantly improves tumor control and survival. Survival at 5 years ranges from 33% to 80% in irradiated patients. Supratentorial ependymomas generally have a poorer prognosis than their infratentorial counterparts because a greater proportion of supratentorial lesions are of high grade, and larger volumes of residual disease tend to be present after surgical resection at this location.

The relatively low rate of neuraxis involvement and the equivalent outcome in series comparing local versus full craniospinal irradiation argue strongly for restricting the radiation volume to the posterior fossa in children with ependymomas (Vanuytsel et al, 1992). The uncertain implication of high histologic grade (or anaplastic ependymoma) similarly favors the use of local fields (Goldwein et al, 1991). Based on dose-response analyses for ependymomas, the typical radiation dose is between 50 and 55 Gy locally (Vanuytsel et

al, 1992). The high rate of local failure after incomplete resection has stimulated ongoing investigations of high-dose, hyperfractionated irradiation and precision-volume stereotactic radiosurgical "boosts" to residual disease sites.

For anaplastic ependymomas, researchers have recommended irradiating the entire craniospinal axis (Wallner et al, 1986; Vanuytsel and Brada, 1991) or administering whole-brain irradiation, with an additional boost for high-grade supratentorial lesions located away from the CSF pathways, if there is no evidence of leptomeningeal spread. However, studies have demonstrated that (1) local recurrence is the primary pattern of failure, (2) spinal seeding is uncommon in the absence of local failure, (3) the patterns of failure are similar in patients with high-grade tumors who are treated with local fields or craniospinal axis irradiation (Goldwein et al, 1991; Vanuytsel et al, 1992), and (4) spinal metastases may not be prevented by prophylactic treatment (Vanuytsel and Brada, 1991; Vanuytsel et al, 1992). As a result, the routine use of "prophylactic" craniospinal or whole-brain irradiation does not appear to lead to improvement in survival (Goldwein et al, 1991; Vanuytsel and Brada, 1991; Vanuytsel et al, 1992).

The role of chemotherapy in the treatment of ependymomas is poorly defined. Although many drugs have been tried, ependymomas do not appear to be particularly responsive to this treatment modality. Moreover, to date, no studies have demonstrated a survival advantage with chemotherapy in addition to irradiation, when compared with irradiation alone, in children or adults with newly diagnosed ependymomas. However, chemotherapy is nevertheless sometimes considered as a salvage option to best supportive care.

Treatment Algorithm

The treatment algorithm for adult ependymomas revolves around histology, extent of surgical resection, and extent of disease in the craniospinal axis. For patients with a well-differentiated ependymoma who have undergone a gross total resection and have a negative screening spinal MRI scan, either limited-field radiation or observation (category 2B) is acceptable (see EPEN-2). However, if a spinal MRI scan reveals disease in the spine, craniospinal irradiation should be administered. Patients with anaplastic ependymoma should also have a spinal MRI scan after a biopsy or subtotal resection. If the MRI scan is negative, limited-field RT is normally given. However, if the spinal MRI scan is positive, craniospinal irradiation is indicated.

Follow-up of ependymoma depends on the extent and location of the disease. For localized disease, MRI of the involved site should be done 1 to 2 months postoperatively and then every 3 to 4 months for 1 year. The interval can then be extended to every 6 months for year 2, depending on the physician's concern regarding the extent of disease, histology, and other relevant factors. If tumor recurrence in the brain or spine is noted on one of these scans, surgery for symptomatic relief should be considered. Surgery should be followed with RT if radiation was not given originally. If surgical intervention is unlikely to provide relief, radiation is a possible option. Chemotherapy or best supportive care should also be considered, depending on the histologic type, extent of disease, age of the patient, and performance status.

Intraparenchymal Brain Metastases

Metastases to the brain are the most common intracranial tumors in adults and occur ten times more frequently than do primary brain

tumors. As a result of advances in the diagnosis and treatment of metastatic brain lesions, most patients are helped by treatment and do not die of brain metastases. Brain metastases occur in 20% to 40% of adults with cancer and are most common in patients with cancers of the lung, breast, an unknown primary, and melanoma. These lesions result from hematogenous metastases and are most common at the junction of the gray and white matter where the relatively narrow caliber of the blood vessels tends to trap tumor emboli. More than 60% of patients with brain metastases also have lung lesions.

Most (80%) brain metastases occur in the cerebral hemispheres, an additional 15% occur in the cerebellum, and 5% occur in the brainstem. Approximately 80% of patients with brain metastases have a history of a systemic cancer, and 70% have multiple brain metastases evident on MRI scans (DeVita et al, 2000). The presenting signs and symptoms of metastatic brain lesions are similar to those of other mass lesions in the brain. The best diagnostic test is a contrast-enhanced MRI scan; however, not all brain lesions in patients with cancer are metastases.

Treatment Overview

Two randomized prospective studies assessed surgery plus radiation compared with radiation alone in patients with relatively radioresistant tumors and found a dramatic difference in survival in patients with surgically accessible, single brain metastases. However, nearly 50% of these patients are not candidates for surgery because of the inaccessibility of the tumor, extensive systemic disease, or other factors. These patients and others with multiple brain metastases should receive whole-brain radiotherapy. After complete resection of a single metastatic lesion, whole-brain radiotherapy decreases recurrences in the brain (Patchell et al, 1998). Focal RT (ie, radiosurgery) may be useful in managing unresectable lesions. Chemotherapy is rarely used as primary therapy for brain metastases. Many tumors that metastasize to the brain are not very chemosensitive (eg, non-small cell lung cancer, unknown primaries, melanoma) or have been heavily pretreated with potentially effective agents.

Treatment Algorithm for Limited Metastatic Lesions

Patients who present with a single mass or multiple lesions suggestive of metastatic cancer to the brain, and do not have a known primary, require a careful systemic workup (Weinberg et al, 2001). If no other readily accessible tumor is available for biopsy, a craniotomy or stereotactic biopsy is indicated to establish a diagnosis. Among patients with a known history of cancer, surgical resection is limited to those with accessible tumors and limited systemic disease. Exquisitely radiosensitive tumors, such as small cell lung cancer and lymphoma, should be treated with whole-brain radiation rather than surgery.

For patients with limited systemic disease or for whom reasonable systemic treatment options exist, aggressive management of 1-3 lesions should be strongly considered (see LTD-2). For resectable lesions, surgery should be considered (Patchell et al, 1990; Noordijk et al, 1994), whereas for unresectable disease, radiosurgery (Auchter et al, 1996; Bindal et al, 1996) or other forms of high-dose localized conformal therapy should be used. The extent of surgery depends on the lesion's accessibility and the overall condition of the patient. Total removal is preferred, given the studies demonstrating a survival benefit with this treatment approach (Lang et al, 1998).

Whether to add whole-brain radiotherapy after a surgical resection of a single brain metastasis remained controversial until the recent

study by Patchell and colleagues (1998). This study randomly assigned patients to surgical resection alone compared with surgical resection and whole-brain radiotherapy (50.4 Gy given in 28 fractions). Although the addition of whole-brain radiotherapy to surgery decreased the incidence of CNS recurrence anywhere in the brain from 70% to 18% ($P < .001$), there was no difference in survival between the two treatment arms (Patchell et al, 1998). The use of whole-brain radiotherapy after surgical or radiosurgical treatment of single or multiple tumors appears to be less effective in preventing the development of new lesions in patients with radioresistant histologies (eg, melanoma, renal cell carcinoma, sarcoma) than in those patients with lung or breast adenocarcinoma. Patients with progressive extracranial disease should be treated with whole-brain radiotherapy alone. A randomized study showed that surgical resection of a single lesion, followed by whole-brain radiotherapy in patients with progressive systemic disease, did not improve survival compared with whole-brain radiotherapy alone (Noordijk et al, 1994).

Patients should be followed with MRI every 3 months for 1 year and then as clinically indicated (see LTD-3). For patients with recurrent disease, prior therapy clearly influences the choice of further therapies. Patients with recurrent CNS disease should be evaluated for the status of systemic disease. If progressive CNS disease occurs in the setting of systemic progression, whole-brain radiotherapy (30-40 Gy, given in 10-20 fractions) should be administered, if the patients have not been previously irradiated (see LTD-4). For patients who have received prior whole-brain radiotherapy, reirradiation may be considered only if they had a positive response to the first course of treatment. This further radiation may include whole-brain radiotherapy (20-30 Gy, given in 10-15 fractions) (Coia, 1992) or fractionated, limited-field conformal therapy. Chemotherapy or best supportive care may also be considered.

Surgery, radiosurgery, whole-brain RT, or high-dose fractionated conformal therapy may be considered for patients with recurrent CNS disease but stable or responding systemic disease (see LTD-5). For patients who have received prior whole-brain radiotherapy, reirradiation may be considered only if they had a positive response to the first course of treatment. The algorithm branches depending on whether patients have 1-3 lesions or more than 3 lesions, although these are still considered to be limited lesions. Surgery should be considered to relieve mass effect in patients with more than 3 lesions (Lang et al, 2004). The algorithm branches again depending on whether patients have previously had RT. Whole-brain RT should be used (30-40 Gy, given in 10-20 fractions) if this modality was not used for initial therapy. Chemotherapy may be considered for select patients (van den Bent, 2003c) with more than 3 lesions, if the multiple lesions can not be controlled by a combination of surgery and radiosurgery (Lang et al, 2004).

Treatment Algorithm for Multiple Metastatic Lesions

Patients diagnosed with multiple (ie, > 3) metastatic lesions should be treated with whole-brain radiotherapy (30-40 Gy, given in 10-20 fractions) with or without stereotactic radiosurgery in selected cases (ie, limited number of lesions). For patients with poor neurologic performance, a more rapid course of radiotherapy can be considered (20 Gy, delivered in 5 fractions) (Borgelt et al, 1980). Surgery should be considered as palliative if one lesion is causing a life-threatening mass effect, hemorrhage, or hydrocephalus. Occasionally, there will be a role for surgery if one lesion is “dominant” and the patient is steroid dependent because of peritumoral edema and/or radiation necrosis (Lang et al, 2004).

Every 3 months after whole-brain radiotherapy for 1 year, patients should have a repeat contrast-enhanced MRI scan. If a recurrence is found (see MU-2), the algorithm branches depending on whether patients have (1) systemic disease progression with limited systemic treatment options, or (2) stable systemic disease or reasonable systemic treatment options. For patients with systemic disease progression, options include best supportive care, chemotherapy, or reirradiation. For stable systemic disease, the algorithm branches again depending on whether the patient has (1) 1-3 lesions, or (2) more than 3 lesions. Patients with stable systemic disease and more than 3 lesions may be offered further whole-brain radiotherapy, if they had a positive response to the first course of therapy; chemotherapy or highly conformal RT are other options. If the repeat scan shows 1-3 recurrent lesions and the patient has stable systemic disease, possible options include surgery or highly conformal radiotherapy (Alexander et al, 1995).

Neoplastic Meningitis

Neoplastic meningitis and leptomeningeal carcinomatosis refer to the multifocal seeding of the leptomeninges by malignant cells. Carcinomatous meningitis occurs when these cells originate from a solid tumor. When this is related to a systemic lymphoma, it is called lymphomatous meningitis (Jayson and Howell, 1996; Chamberlain, 1997; Grossman and Krabak, 1999). Tumor cells gain access to the leptomeninges by hematogenous dissemination or direct extension. Once these cells reach the CSF, they are disseminated throughout the neuraxis by the constant flow of CSF. The CSF travels from the ventricles through the foramen of Magendie and Luschka to the spinal canal and over the cortical convexities to the arachnoid granulations. Infiltration of the leptomeninges by any malignancy is a serious complication that results in substantial morbidity and mortality. Neoplastic meningitis occurs in approximately 5% of patients with cancer. This disorder is being diagnosed with increasing frequency as patients live longer and as neuroimaging studies improve. The most common cancers to involve the leptomeninges are breast cancer, lung cancer, and melanoma. Without treatment, the median survival of patients diagnosed with this disorder is 4 to 6 weeks, with death resulting from progressive neurologic dysfunction.

The goals of treatment in patients with leptomeningeal metastases are to improve or stabilize the neurologic status of the patient and to prolong survival. Standard therapy involves RT to symptomatic sites of the neuraxis and to disease visible on neuroimaging studies, in addition to intrathecal chemotherapy. These therapies increase the median survival to 3 to 6 months and often provide effective local control, allowing patients to die from systemic rather than neurologic complications of their neoplasm. Early diagnosis and therapy are critical to preserving neurologic function.

Patient Evaluation

Patients present with signs and symptoms ranging from injury to nerves that traverse the subarachnoid space, direct tumor invasion of the brain or spinal cord, alteration in the local blood supply, obstruction of normal CSF flow pathways leading to increased intracranial pressure, or interference with normal brain function. Patients should have a physical examination with a careful neurologic evaluation; MRI of the brain and spine should also be done, if the patient has appropriate neurological symptoms or signs. A definitive diagnosis is most commonly made by lumbar puncture. The CSF protein is typically increased, and there may be a pleocytosis or decreased glucose levels. The CSF cytology is positive approximately 50% of the time with the first lumbar

puncture, and 85% of the time after three CSF examinations in patients who are ultimately proven to have neoplastic meningitis.

However, the CSF cytology is persistently negative in 10% to 15% of patients with leptomeningeal carcinomatosis. In these cases, (1) a suspicious CSF examination (eg, increased protein, low glucose, and/or a pleocytosis) combined with suggestive clinical findings (eg, multifocal neuraxis involvement, such as cranial nerve palsies and a lumbar radiculopathy that cannot be explained otherwise), and/or (2) suggestive radiologic features (eg, subarachnoid masses, diffuse contrast enhancement of the meninges, or hydrocephalus without a mass lesion) can be sufficient to treat when the patient is known to have a systemic malignancy. Although a positive CSF cytology in patients with solid tumors is virtually always diagnostic, reactive lymphocytes from infections (eg, herpes zoster infection) can often be mistaken for malignant lymphocytes.

Patient Stratification for Treatment

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

Treatment Algorithm for Neoplastic Meningitis

Patients in the poor-risk group are usually offered supportive care measures. These measures can include analgesics (for neuropathic pain, increased intracranial pressure, or leptomeningeal irritation) and anticonvulsants, if needed. Radiation therapy is commonly administered to symptomatic sites (eg, to the whole brain for increased intracranial pressure or to the lumbosacral spine for a developing cauda equina syndrome). If the patient stabilizes or improves, a more aggressive treatment approach may be considered. Patients with exceptionally chemosensitive tumors (eg, small cell lung cancer, lymphoma) may be treated. Good-risk patients should also receive appropriate supportive care measures as previously described, along with radiation to symptomatic sites and to areas of bulk disease identified on neuroimaging studies. In addition, intrathecal or intraventricular (using a surgically implanted subcutaneous reservoir and ventricular catheter [SRVC]) chemotherapy is administered. Initially, intrathecal chemotherapy is usually given by lumbar puncture, and the SRVC is placed later to administer the drugs more conveniently. Initiation of chemotherapy should not be delayed for flow study.

Methotrexate, the drug most frequently used (Glantz et al, 1998), is administered initially in an “induction” mode twice each week at a dose of 10 to 12 mg (ie, it is not dosed per square meter). Intrathecal thiotepa can also be used in solid tumors, and cytarabine is often administered for lymphomatous meningitis. A depot form of cytarabine is now available that allows patients with lymphomatous meningitis to be treated every 2 weeks rather than twice per week

(Glantz et al, 1999a). In a randomized controlled trial, depot cytarabine was found to increase the time to neurological progression, with a response rate comparable to methotrexate, while offering the benefit of a less demanding schedule of injection (Glantz et al, 1999b). One study suggests that high-dose systemic methotrexate might be better than intrathecal therapy (Glantz et al, 1998).

If an SRVC is placed, a CSF flow scan is strongly recommended (Glantz et al, 1995; Chamberlain and Kormanik, 1997). Cerebrospinal fluid flow abnormalities are common in patients with neoplastic meningitis and often lead to increased intracranial pressure. Administering chemotherapy into the ventricle of a patient with a ventricular outlet obstruction increases the patient's risk for leukoencephalopathy. In addition, the agent administered will not reach the lumbar subarachnoid space where the original CSF cytology was positive. Cerebrospinal fluid flow scans are easily performed in most nuclear medicine departments. Indium 111-DTPA is administered into the SRVC, and imaging of the brain and spine is performed immediately after injection and then again at 4 and 24 hours. If significant flow abnormalities are seen, RT is administered to the sites of obstruction and a CSF flow scan is repeated. If CSF flow normalizes, which occurs most commonly in radiosensitive neoplasms, intrathecal chemotherapy commences. If significant flow abnormalities remain, then the patient should be treated as a poor-risk patient (ie, with supportive measures).

For patients with a normal CSF flow scan, intrathecal chemotherapy should be administered aggressively (“induction” chemotherapy) for 4 weeks (see CLMEN-4). The patient should then be reassessed clinically and with a repeat CSF cytology. Because the cytology is much less likely to be positive from the SRVC than from the lumbar subarachnoid space, it is critical that it be sampled from the site where the cytology was originally positive. If the patient is clinically stable or improving and the cytology has converted to negative, the patient should receive another month of “induction” intrathecal chemotherapy or should consider switching intrathecal drugs for 4 weeks. This should be followed by 1 week per month of maintenance therapy.

Progressive Disease

The patient's clinical and CSF status should be followed every 2 months. However, if the patient's clinical status is deteriorating from progressive leptomeningeal disease or the cytology is persistently positive, the clinician has three options. The patient can be treated for another 4 weeks with the same chemotherapy and reassessed, another intrathecal agent can be tried, or purely supportive care measures can be used.

Primary CNS Lymphoma

Primary CNS lymphoma is an aggressive form of non-Hodgkin's lymphoma that develops within the brain, spinal cord, eye, or leptomeninges without evidence of systemic involvement (Fine and Mayer, 1993; DeAngelis, 1995). Overall, primary CNS lymphoma accounts for 0.5% to 2% of all primary brain tumors. However, its incidence has increased dramatically during the past 20 years in immunocompetent and immunocompromised patients (Coté et al, 1996). In immunocompetent primary CNS lymphoma patients, the mean age at diagnosis is 55 years; in immunocompromised patients, it is often younger (eg, 31 years in AIDS patients). This algorithm has been written for nonimmunosuppressed patients with primary CNS lymphoma.

Pathology

Pathologically, primary CNS lymphoma is a vasocentric neoplasm composed of a dense, monoclonal proliferation of lymphocytes that are usually classified as large-cell or immunoblastic type and most often derive immunophenotypically from B cells (Fine and Mayer, 1993; Traweek, 1998). The tumor is infiltrative and typically extends beyond the primary lesion, as shown by CT or MRI scans, into regions of the brain with an intact blood-brain barrier. The brain parenchyma is involved in more than 90% of all primary CNS lymphoma patients, and the condition can be multifocal in more than 50% of cases (Fine and Mayer, 1993; DeAngelis, 1995; Johnson et al, 1997; Traweek, 1998).

Tumors are often periventricular and may involve ependymal lining cells or, if more peripherally located, may extend to the leptomeninges. Leptomeningeal involvement may remain localized to adjacent parenchymal sites or can be more diffuse (ie, positive cytology) in up to 30% of patients. Ocular involvement may develop independently in 10% to 20% of primary CNS lymphoma patients with primary brain disease. Less often, the tumor arises within the eye as the initial manifestation of primary CNS lymphoma. In rare cases, the spinal-cord parenchyma may be an initial or secondary site of primary CNS lymphoma.

Symptomatic Presentation

Patients with primary CNS lymphoma may present with various symptoms because of the multifocal nature of the disease. The most common complaint at diagnosis is a focal neurologic deficit (eg, hemiparesis, dysphasia), which occurs in more than 50% of all patients (Fine and Mayer, 1993; DeAngelis, 1995). Alterations of mental status (eg, loss of memory or confusion) and symptoms of increased intracranial pressure (eg, headache, nausea) are each noted in approximately 33% of patients. Seizure activity is less common and develops in 10% of patients. With ocular involvement, symptoms (blurred vision or floaters) develop in about 50% of patients. When the spinal cord is affected, patients complain of neck or back pain or they develop myelopathy.

Neuroradiologic evaluation is important to assist in the diagnosis of primary CNS lymphoma and to evaluate the effectiveness of subsequent therapy (Fine and Mayer, 1993; Johnson et al, 1997). On a CT scan, primary CNS lymphoma is usually isodense or hyperdense compared to the brain and enhances in most cases. With MRI, the tumor is often isointense or hypointense on T1- and T2-weighted images and enhances frequently. However, there are cases in which the tumor does not enhance by CT or MRI scans, thus confusing and delaying the diagnosis (DeAngelis, 1993). It is also important to note that the imaging features of primary CNS lymphoma may be profoundly affected by prior use of steroids (eg, dexamethasone). Enhancement may be decreased or eliminated, and tumor volume may shrink dramatically.

Initial Evaluation

As previously mentioned, patients with primary CNS lymphoma can present with various symptoms and signs, including those associated with increased intracranial pressure, focal deficits, encephalopathy, and psychiatric alterations. Although primary CNS lymphoma often appears radiographically similar to other types of intracranial mass lesions, several CT and MRI features should raise the suspicion of lymphoma. These features include a periventricular distribution, ring enhancement, multiple lesions, and a smaller amount of edema than might otherwise be expected from a similar-sized metastatic tumor or glioma.

If, based on the MRI scan, there is a reasonably high suspicion of primary CNS lymphoma, it is preferable not to start therapy empirically with steroids unless medically indicated. In addition, a lumbar puncture with evaluation of CSF is recommended, if it can be done safely and without concern for herniation from increased intracranial pressure. Although the CSF from these patients often contains a lymphocytosis, it is uncommon for the cytologist to see malignant lymphoid cells. Nevertheless, the yield for a positive diagnostic test can be increased by the use of molecular markers of monoclonality, such as an immunoglobulin gene rearrangement. It is also recommended that patients undergo an ophthalmologic evaluation including a slit-lamp examination, to exclude an obvious malignant uveitis.

Despite CSF and uveal evaluation, the intracranial lesion ultimately needs to be biopsied to make a definitive diagnosis in most cases (see PCNS-1). Here again, use of immunohistochemistry to assess for monoclonality with gamma or kappa light chains and/or the use of molecular markers can be valuable in differentiating an inflammatory lesion from a malignant lymphoma. Even with these markers, however, a biopsy may occasionally be falsely negative, particularly if the patient had been treated previously with steroids. Thus, if a biopsy is nondiagnostic, we recommend that the steroids be tapered and the patient followed closely, both clinically and radiographically. If and when the lesion recurs, the lesion should be quickly re-biopsied before the initiation of steroids. If, on the other hand, a lesion is biopsied and no definitive diagnosis of lymphoma is made, and the patient does not have a history of steroid therapy, other diagnoses (eg, inflammatory processes) should be considered.

Treatment Considerations

Steroid Administration. Steroids are cytolytic for primary CNS lymphomas and can significantly alter the appearance of these tumors on CT scans and MRI. It is recommended that steroids be withheld or used judiciously until diagnostic tissue can be obtained in patients suspected of having primary CNS lymphoma. Not only can steroids alter the CT scan or MRI target used by the surgeon, decreasing enhancement and lesion size, they may also affect the histologic appearance of tissue samples, preventing a definitive pathologic diagnosis (Traweek, 1998). The KPS can improve dramatically with steroids. Administration of steroids is appropriate if the patient has severely increased intracranial pressure and is in danger of herniation.

Stereotactic Biopsy. In contrast to the principles previously outlined for invasive astrocytomas and other gliomas, the surgical goals for primary CNS lymphoma are more modest and involve obtaining diagnostic tissue with minimal risk of morbidity and without a formal attempt at surgical resection (DeAngelis et al, 1990; Neuwalt et al, 1991; DeAngelis et al, 1992; Fine and Mayer, 1993; DeAngelis, 1995). Currently, most authors recommend stereotactic biopsy as the surgical method of choice. This approach stems from the fact that data demonstrate a survival advantage for patients who have had a complete resection or extensive subtotal resection versus those who have had only a stereotactic biopsy. In addition, aggressive resection has been associated with considerable risk for postoperative neurologic deficits.

Radiation Therapy. The role of RT for patients with primary CNS lymphoma continues to evolve. Early studies demonstrated that these tumors were radiosensitive and that complete and partial responses could be obtained using doses ranging from 2000 to 5000

cGy. However, the responses were brief, and patients often developed recurrent disease within a matter of months. This prompted the RTOG to design a dose-intensification study in which 41 patients with non-AIDS-related primary CNS lymphoma received 4000 cGy of whole-brain irradiation plus a 2000-cGy boost to involved regions (Nelson et al, 1992). The median survival for the cohort was only 12.2 months, and tumors recurred frequently in the boosted field.

Similar limitations of efficacy for high-dose radiotherapy have been noted by DeAngelis (1995), as well as by other investigators (Chamberlain and Corey-Bloom, 1991; Grossman and Moynihan, 1991; Jayson and Howell, 1996). Therefore, the currently recommended dose of RT for cerebral primary CNS lymphoma is between 4000 and 5000 cGy (whole brain), without a boost. However, RT should be avoided in patients older than 60 years. For patients with ocular lymphoma, irradiation is the treatment of choice; 3600 cGy should be administered to both eyes.

In general, non-methotrexate-based chemotherapy regimens have not been as effective against primary CNS lymphoma as regimens that do include methotrexate (Fine and Mayer, 1993; DeAngelis, 1995). Most of these non-methotrexate protocols are based on the CHOP model and feature cyclophosphamide in combination with other drugs, usually doxorubicin, vincristine, and prednisone. The progression-free and overall survival rates are lower in these non-methotrexate regimens than those achieved with methotrexate-based regimens, and they are often associated with an increased incidence of neurologic toxicity. The major reason cited for the decreased efficacy of CHOP and similar protocols is the poor penetration of the intact blood-brain barrier by cyclophosphamide and doxorubicin.

Timing of Radiotherapy and Chemotherapy

The major controversy regarding radiotherapy for primary CNS lymphoma involves the timing of treatment. Should it always be used as part of first-line therapy, in combination with chemotherapy, or should it be withheld in selected patients and not used until the time of recurrence? Although this issue has not been resolved, most authors recommend irradiation after some form of initial chemotherapy (Fine and Mayer, 1993; DeAngelis, 1995; DeAngelis et al, 1990; Neuwelt et al, 1991; DeAngelis et al, 1992; Gabbai et al, 1989; Hiraga et al, 1999; DeAngelis, 2001). A multicenter RTOG study demonstrates improved survival with the combination of chemotherapy, using high-dose methotrexate, plus radiation therapy compared with previous reports of RT alone (DeAngelis et al, 2002); delayed neurotoxicity remains a risk of this approach (DeAngelis et al, 2002).

Neuwelt and colleagues (1991) suggest withholding radiotherapy until recurrence or progression in all patients to decrease the risk of radiation-related neuropsychological sequelae. Others have similar recommendations but only for primary CNS lymphoma patients older than 50 years (DeAngelis, 1995; Freilich et al, 1996). DeAngelis and associates found that it was very uncommon for patients younger than 50 years to develop radiation-induced neurotoxicity.

The addition of chemotherapy has significantly improved disease-free and overall survival in patients with primary CNS lymphoma. With RT alone, median survival is approximately 12 months. When some form of chemotherapy has been added to the treatment regimen, median survival is extended; it ranges from 30 to 41 months (Fine and Mayer, 1993; DeAngelis, 1995; DeAngelis et al, 1990; DeAngelis et al, 1992; Hiraga et al, 1999; DeAngelis et al, 2002). In many of these investigations, chemotherapy was

administered before radiotherapy and often resulted in complete or partial responses.

Methotrexate appears to be the most effective drug and can be administered via the intravenous or intra-arterial route. Gabbai and associates (1989) reported a series of 13 patients given high-dose intravenous methotrexate before radiation. They noted complete responses in nine patients and partial responses in four patients, with an overall median survival of greater than 9 months. DeAngelis and colleagues also used preradiation methotrexate (intravenous and intrathecal) plus cytarabine in 31 patients with primary CNS lymphoma (DeAngelis, 1995; DeAngelis et al, 1992).The overall median survival for the cohort was 42.5 months, with partial responses in 17 patients and stable disease in five patients. Neuwelt and associates (1991) administered methotrexate via the intra-arterial route, in combination with osmotic blood-brain barrier disruption, cyclophosphamide, and procarbazine, to a series of 16 patients. In all of these patients, irradiation was withheld until the time of disease progression (and was eventually administered to 9 of 16 patients). Chemotherapy induced complete responses in 13 patients and partial responses in three patients, with an over-all median survival of 44.5 months. Neuropsychological follow-up of the responding patients who did not undergo irradiation demonstrated stable cognitive function.

Treatment Algorithm for CNS Lymphoma

Staging Workup. Once the diagnosis of primary CNS lymphoma is established, the patient should undergo a thorough staging workup. This includes a complete CNS evaluation including (if these tests had not previously been done) a slit-lamp eye examination, a lumbar puncture if possible, and a spinal MRI scan, particularly if the CSF is positive and/or the patient has symptoms referable to the spinal cord. An HIV blood test should also be performed because both prognosis and treatment of patients with HIV-related primary CNS lymphoma might be different than that of patients who are otherwise immunocompetent. Relative to the staging workup for systemic disease, it is generally felt that a chest x-ray, a good physical examination, and complete blood work (including a complete blood count, platelets, liver function tests) are sufficient to rule out systemic involvement. It is very uncommon or rare for a patient to present with neurologic symptoms and to have a CNS lymphoma on biopsy and then ultimately be found to have an occult systemic lymphoma after more sensitive testing such as CT scans, gallium scans, or bone marrow biopsies. Thus, these more elaborate tests are not necessary unless clinically indicated.

Preradiation versus Postradiation Chemotherapy. Once the diagnosis of primary CNS lymphoma has been established and the extent of disease determined, treatment should be initiated as soon as possible. There has been an emphasis on preradiation chemotherapy, as opposed to postradiation chemotherapy, for several theoretical reasons. At least for agents such as methotrexate and cisplatin, some data (albeit in the pediatric literature) indicate that pre-radiation chemotherapy is less neurotoxic than postradiation chemotherapy. Additionally, drug delivery to a primary CNS lymphoma may be increased before radiation, when the blood-brain barrier is maximally disrupted by the tumor, than after RT, which results in tumor regression as well as partial repair and closure of the blood-brain barrier behind the regressing tumor. Finally, preradiation chemotherapy allows one to assess the efficacy of chemotherapy without the confounding variable of irradiation.

High-Dose Methotrexate. Several different chemotherapy regimens and agents have been used with no current consensus on the optimal regimen. High-dose methotrexate is the one agent for which there clearly appears to be a consistently high response rate; therefore, high-dose methotrexate (≥ 3 g/m^2) is currently the "standard regimen." A series of phase I and phase II studies in the biomedical literature suggest that preradiation chemotherapy can prolong time to tumor progression and prolong median survival in patients treated with these agents, compared with radiation alone (DeAngelis et al, 2002). Most of the trials using preradiation chemotherapy, however, have demonstrated that elderly patients and/or patients who have an exceedingly poor KPS do not do well on chemotherapy.

Demographic Considerations. For healthier patients (ie, those 60 years or younger with a KPS ≥ 40 and a creatinine clearance ≥ 50; those older than 60 years with a KPS > 50), some type of preradiation chemotherapy is generally recommended, with high-dose methotrexate currently being the most common regimen (see PCNS-2). Whether one performs whole-brain irradiation after systemic chemotherapy depends on the responsiveness of the disease to chemotherapy (ie, whether there is a complete response) and on the clinical judgment of the medical and radiation oncologists. The panel recommends avoiding the addition of RT to methotrexate in patients older than 60 years, if possible (see PCNS-2).

If the patient is found to have a malignant uveitis, however, orbital radiation is required because the penetration of methotrexate and other drugs into the uveal fluid is poor. Additionally, if the patient is found to have a malignant pleocytosis in the CSF, direct intrathecal chemotherapy (either via a SRVC or by lumbar puncture) should be considered (see the NCCN Practice Guidelines for Carcinomatous/Lymphomatous Meningitis).

For patients with extremely poor KPS (< 40) or creatinine clearance less than 50, it is recommended that treatment consist of whole-brain irradiation (45 Gy) in order to rapidly induce a response, diminish neurologic morbidity, and optimize quality of life. Chemotherapy is also an option. If the lumbar puncture or spinal MRI is positive, consider intrathecal chemotherapy plus focal spinal RT for the few patients in this group who have an excellent response to whole-brain irradiation and who achieve a reasonable quality of life with improved performance status, systemic chemotherapy could be considered when their disease recurs. For patients in this group who do not achieve a significant benefit from RT and whose disease progresses, palliative care is suggested.

Progressive Disease. For younger patients with good performance status who are treated with pre-radiation chemotherapy and ultimately relapse, the treatment decision is usually between further chemotherapy and/or external-beam RT. Certainly, for those who have already had prior RT, the only option available is further systemic and/or intra-CSF chemotherapy. However, there may be a role for "local" radiation, particularly in the spinal axis, for those patients with neurologic morbidity from a focal lesion.

For patients who were initially treated with chemotherapy but did not receive external-beam RT, the decision about whether to use more chemotherapy or proceed to radiation at the time of relapse depends on a number of factors, possibly the most important of which is the duration of response to initial chemotherapy (see PCNS-3). If a patient had experienced a relatively long-term response (ie, > 1 year) with the first treatment regimen, then treating either with the same or another high-dose methotrexate-based regimen is

reasonable. However, patients who relapse within a very short time after systemic chemotherapy should receive whole-brain RT, with or without intrathecal chemotherapy, with or without spinal RT. Alternative chemotherapeutic regimens should be considered for patients not suited for whole-brain RT. Ultimately, the elucidation of the optimal chemotherapeutic regimen and the use of RT will depend on the results of clinical trials. Thus, all patients are encouraged to participate in clinical trials assessing improved treatments for this disease.

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