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

**RADIOLOGIC PRESENTATION**  
**CLINICAL IMPRESSION**  
**SURGERY**  
**ADJUVANT TREATMENT**  
**FOLLOW-UP**

- **Maximal safe resection feasible**
  - Maximal excision → MRI
  - Age > 45 y → Observe or RT\(^a\),\(^f\)
  - Age ≤ 45 y → Observe\(^f\)

- **Maximal safe resection not feasible**
  - Stereotactic or open biopsy
  - Uncontrolled or progressive symptoms → RT\(^e\) or Chemotherapy (category 2B)
  - Stable/controlled symptoms → RT\(^e\) or Observe\(^f\) or Chemotherapy (category 2B)

- **MRI compatible with primary brain tumor\(^a\)**
  - Observation\(^b\)

- **MRI not compatible with primary brain tumor**

\(^a\) Biopsy first if MRI compatible with CNS lymphoma.
\(^b\) Surgery is generally recommended, but serial observations are appropriate for selected patients.
\(^c\) See Surgical Issues (BRAIN-1).
\(^d\) Post-op MRI should be done within 72 hours after surgery.
\(^e\) See Radiation Therapy Guidelines (BRAIN-2).
\(^f\) Regular follow-up is essential for patients receiving observation alone after resection.

**Note:** All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
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See Surgical Issues (BRAIN-1).
See Radiation Therapy Guidelines (BRAIN-2).
Oligodendrogliomas, particularly those that have chromosomal loss of 1p or combined 1p19q loss, have been reported to be sensitive to alkylator chemotherapy.
Adult Intracranial Ependymoma

**RADIOLOGIC PRESENTATION**
- Contrast enhanced MRI/CT compatible with primary brain tumor

**CLINICAL IMPRESSION**
- Bead enhancement

**SURGERY**
- Maximal resection feasible
- Maximal resection not feasible

**PATHOLOGY**
- See Adjuvant Treatment (EPEN-2)

**MAXIMAL RESECTION FEASIBLE**
- Maximal excision
- Ependymoma or Anaplastic ependymoma

**MAXIMAL RESECTION NOT FEASIBLE**
- Stereotactic or open biopsy
- Ependymoma or Anaplastic ependymoma

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*Biopsy first if MRI compatible with CNS lymphoma.*

See Surgical Issues (BRAIN-1).
Ependymoma, status post maximal resection

<table>
<thead>
<tr>
<th>PATHOLOGY</th>
<th>POSTOPERATIVE STAGING</th>
<th>ADJUVANT TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ependymoma, status post maximal resection</td>
<td>Contrast enhanced brain and spine MRI; Consider CSF analysis</td>
<td>Total resection, MRI ± CSF spine negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subtotal resection, MRI ± CSF spine negative</td>
</tr>
<tr>
<td></td>
<td>Total or subtotal resection, MRI ± CSF spine positive</td>
<td>Craniospinal RT</td>
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</table>

Anaplastic ependymoma, status post maximal resection

<table>
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<th>POSTOPERATIVE STAGING</th>
<th>ADJUVANT TREATMENT</th>
</tr>
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<tr>
<td>Anaplastic ependymoma, status post maximal resection</td>
<td>Contrast enhanced brain and spine MRI; Consider CSF analysis</td>
<td>Total or subtotal resection, MRI ± CSF spine negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total or subtotal resection, MRI ± CSF spine positive</td>
</tr>
</tbody>
</table>

Ependymoma or anaplastic ependymoma status post stereotactic or open biopsy

<table>
<thead>
<tr>
<th>PATHOLOGY</th>
<th>POSTOPERATIVE STAGING</th>
<th>ADJUVANT TREATMENT</th>
</tr>
</thead>
<tbody>
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<td>Contrast enhanced brain and spine MRI; Consider CSF analysis</td>
<td>MRI ± CSF spine negative</td>
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<tr>
<td></td>
<td></td>
<td>MRI ± CSF spine positive</td>
</tr>
</tbody>
</table>

See Follow-up and Recurrence (EPEN-3)

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Adult Intracranial Ependymoma

**FOLLOW-UP**

Brain and spine MRI (if initially positive) every 3–4 mo for 1 y, then every 4-6 mo for year 2, then every 6-12 mo

**RECURRENT**

Spine or brain recurrence

Resectable → Resection with RT, if no prior RT

Unresectable → RT, if no prior RT

**Consider chemotherapy**

**Consider RT** or

**Best supportive care**

---

*See Radiation Therapy Guidelines (BRAIN-2).*

*Consider SRS if geometrically favorable.*

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**GLIO-1**

**Anaplastic Astrocytoma/Anaplastic Oligodendroglioma/Glioblastoma Multiforme**

**RADIOLOGIC PRESENTATION**

- MRI suggestive of high-grade glioma

**CLINICAL IMPRESSION**

- Multidisciplinary input for treatment planning if feasible

**SURGERY**

- Maximal resection feasible
- Maximal excision ± BCNU wafer (category 2B)

**PATHOLOGY**

- MRI if frozen section diagnosis supports high-grade glioma
- Anaplastic astrocytoma (AA)
- Anaplastic oligodendroglioma (AO)
- Glioblastoma multiforme (GBM)

**Note:**

- Biopsy first if MRI compatible with CNS lymphoma.
- See Surgical Issues (BRAIN-1).
- If frozen section diagnosis supports high-grade glioma.
- Post-op MRI should be done within 72 hours after surgery.

---

**See Adjuvant Treatment (GLIO-2)**

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Anaplastic Astrocytoma/Anaplastic Oligodendroglioma/Glioblastoma Multiforme

**PATHOLOGY**

- Anaplastic astrocytoma (AA)
  - Treated with BCNU wafer: RT± chemotherapy
  - No BCNU wafer

- Anaplastic oligodendroglioma (AO)
  - Treated with BCNU wafer: RT± chemotherapy
  - No BCNU wafer

- Glioblastoma multiforme (GBM)
  - Treated with BCNU wafer: RT± chemotherapy
  - No BCNU wafer

**ADJUVANT TREATMENT**

- RT± chemotherapy

**FOLLOW-UP**

- Observe or Post RT chemotherapy
  - Age < 70 y
  - Good performance status
  - AO > AA

- MRI 2-6 wk after RT, then every 2-3 mo for 2-3 y

- See Recurrence (GLIO-3)

---

*See Radiation Therapy Guidelines (BRAIN-2).*


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Anaplastic Astrocytoma/Anaplastic Oligodendroglioma/Glioblastoma Multiforme

**RECURRENT**

- **Diffuse or multiple**
  - **Resectable**
    - Resection + BCNU polymer
  - **Unresectable**

- **Local**
  - Resection without BCNU polymer

**SALVAGE**

- Best supportive care if poor performance status or systemic chemotherapy
- Surgery for symptomatic, large lesion
- Consider highly conformal RT (category 2B)
- Systemic chemotherapy or reirradiation
- Highly conformal RT or systemic chemotherapy

~g,h~

- Anaplastic oligodendrogliomas have been reported to be especially sensitive to chemotherapy. Chemotherapy using temozolomide or nitrosourea-based regimens may be appropriate.
- A response after two consecutive failures is unlikely.

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~e~ See Radiation Therapy Guidelines (BRAIN-2).
Limited (1-3) Metastatic Lesions

CLINICAL PRESENTATION

1-3 metastatic lesions on MRI

- Known history of cancer

WORKUP

If concern exists regarding diagnosis of CNS lesions

Stereotactic or open biopsy/resection

Stereotactic or open biopsy/resection

See Clinical Presentation and Primary Treatment (LTD-2)

No known history of cancer

- Chest x-ray/CT
- Abdominal/pelvic CT
- Other tests as indicated

No other readily accessible tumor for biopsy

Stereotactic or open biopsy/resection

CLINICAL PRESENTATION

- No known history of cancer
CLINICAL PRESENTATION

Small cell lung cancer or Disseminated systemic disease with poor systemic treatment options

Limited systemic disease or Reasonable systemic treatment options

PRIMARY TREATMENT

Resectable

Whole-brain RT

Unresectable

Surgical resection, consider WBRT or Stereotactic radiosurgery (SRS), consider WBRT

Brain MRI

Observe or Whole-brain RT (WBRT)

Whole-brain RT and/or radiosurgery

See Follow-up and Recurrence (LTD-3)

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Notes:
- Consider surgery to relieve mass effect.
- Choice of therapy depends in part on size of lesion, e.g., small (<2cm), deep, non-symptomatic lesions may consider treatment with SRS versus larger, symptomatic lesions that may be more appropriate for surgery. Decisions also depend on institutional practice.
- See Surgical Issues (BRAIN-1).
- See Radiation Therapy Guidelines (BRAIN-2).
**FOLLOW-UP**

MRI every 3 mo for 1 y then as clinically indicated

**RECURRENT**

<table>
<thead>
<tr>
<th>Recurrent disease; local site</th>
<th>Previous surgery or WBRT</th>
<th>Surgery or Stereotactic radiosurgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior stereotactic radiosurgery ± WBRT</td>
<td>Surgery</td>
<td></td>
</tr>
</tbody>
</table>

**TREATMENT**

| 1-3 lesions | Surgery or Stereotactic radiosurgery or WBRT |
| > 3 lesions | WBRT; Consider chemotherapy |

If patient relapses, See LTD-4

---

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**Limited (1-3) Metastatic Lesions**

**RECURRENCE**

- No prior RT
  - Whole-brain RT

- Systemic disease progression, with limited systemic treatment options
  - Best supportive care or chemotherapy or reirradiation, if prior positive response to RT or highly conformal RT

- Prior RT
  - Consider surgery to relieve mass effect.

---

**TREATMENT**

- Chemotherapy selection consistent with sensitivity of primary site.

---

**Notes:**
- Consider surgery to relieve mass effect.
- See Radiation Therapy Guidelines (BRAIN-2).
- Chemotherapy selection consistent with sensitivity of primary site.

---

**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

**CLINICAL PRESENTATION**
- **Known history of cancer**
  - If concern exists regarding diagnosis of CNS lesions
  - Stereotactic or open biopsy/resection

- **No known history of cancer**
  - Whole-brain irradiation ± stereotactic radiosurgery

**WORKUP**
- Known history of cancer
  - CBC
  - Chest x-ray/CT
  - Abdominal/pelvic CT
  - Other tests as indicated

- No other readily accessible tumor for biopsy
  - Stereotactic or open biopsy/resection

**PRIMARY TREATMENT**
- Consider surgery to relieve mass effect.
- See Radiation Therapy Guidelines (BRAIN-2).
- SRS should only be considered in selected cases (e.g., limited number of lesions).

---

*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).

---

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Multiple (>3) Metastatic Lesions

FOLLOW-UP

MRI every 3 mo for 1 y

Recurrence

RECURRENT

Systemic disease progression, with limited systemic treatment options

Stable systemic disease or reasonable systemic treatment options

TREATMENT

Best supportive care or Chemotherapy or Reirradiation if prior positive response to RT

Surgery or Highly conformal RT or Reirradiation if prior positive response to RT or Chemotherapy or Stereotactic radiosurgery

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aConsider surgery to relieve mass effect.
Carcinomatous/Lymphomatous Meningitis

**WORKUP**

- Physical exam with careful neurologic evaluation
- Consider brain and spine MRI if patient is a candidate for treatment
- CSF exam (if safe)

**DIAGNOSIS**

- Positive CSF cytology
- Positive radiologic findings with supportive clinical or CSF findings in a patient known to have a malignancy

**RISK STATUS**

**Poor risk**:
- Low KPS
- Multiple, serious, major neurologic deficits
- Extensive systemic disease with few treatment options
- Bulky CNS disease
- Encephalopathy

**See Treatment (CLMEN-2)**

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

**See Treatment (CLMEN-2)**

---

\(^a\)Patients with exceptionally chemosensitive tumors, eg, SCLC, lymphoma; may be treated.

---

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## Carcinomatous/Lymphomatous Meningitis

### RISK STATUS

<table>
<thead>
<tr>
<th>Poor risk&lt;sup&gt;a&lt;/sup&gt;:</th>
<th>Consider RT to symptomatic sites and Supportive care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low KPS</td>
<td></td>
</tr>
<tr>
<td>Multiple, serious, major neurologic deficits</td>
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<tr>
<td>Extensive systemic disease with few treatment options</td>
<td></td>
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<tr>
<td>Bulky CNS disease</td>
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<tr>
<td>Encephalopathy</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Good risk:</th>
<th>Initial intrathecal or intraventricular chemotherapy&lt;sup&gt;b&lt;/sup&gt; + RT to bulky disease, symptomatic sites and Consider systemic chemotherapy</th>
<th>Strongly consider CSF flow scan via subcutaneous reservoir with ventricular catheter</th>
<th>See CSF flow scan results (CLMEN-3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High KPS</td>
<td></td>
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<td></td>
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<tr>
<td>No major neurologic deficits</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimal systemic disease</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Reasonable systemic treatment options, if needed</td>
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</tr>
</tbody>
</table>

<sup>a</sup>Patients with exceptionally chemosensitive tumors, eg, SCLC, lymphoma; may be treated.

<sup>b</sup>Initiation of chemotherapy should not be delayed for flow study.

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Carcinomatous/Lymphomatous Meningitis

**PRIMARY TREATMENT**

- **Normal flow**
  - Induction intrathecal chemotherapy for 4-6 wk, if otherwise stable disease
  - Reassess CSF from site where CSF cytology was originally positive; if CSF cytology was originally negative reassess from lumbar region

- **Flow abnormalities**
  - RT to sites of obstruction ± intrathecal chemotherapy
  - Repeat CSF flow scan

- See CSF cytology negative (CLMEN-4)
- See CSF cytology positive (CLMEN-4)

**CSF flow scan**

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See Treatment for poor risk (CLMEN-2)
Carcinomatous/Lymphomatous Meningitis

POSTINDUCTION THERAPY

CSF cytology negative → Continue induction intrathecal chemotherapy for 1 mo → Maintenance intrathecal chemotherapy and Monitor CSF cytology every month

CSF cytology positive

Patient clinically stable or improving and there is no evidence of clinical or radiologic progression of leptomeningeal disease → Continue induction intrathecal chemotherapy for 4 wk or Consider switching intrathecal drugs for 4 wk

Evidence of clinical or radiologic progression of leptomeningeal disease

Cytology continually positive and/or evidence of clinical or radiologic progression of leptomeningeal disease → Supportive care, which may include RT to symptom sites or Chemotherapy

CSF cytology negative

Maintenance intrathecal chemotherapy and Monitor CSF cytology every month

Negative cytology

Cytology continually positive and/or evidence of clinical or radiologic progression of leptomeningeal disease

Supportive care, which may include RT to symptom sites or Chemotherapy

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Diagnostic by Tissue Evaluation

CT/MRI suggestive of lymphoma → Hold steroids, if possible →

- CSF sample or Eye exam with biopsy for tissue or Brain biopsy with hematopathology review of all slides →
  - Positive diagnosis of primary CNS lymphoma → See Primary Treatment (PCNS-2)
  - Biopsy not diagnostic of primary CNS lymphoma → See Primary Treatment (PCNS-2)
  - Other CNS tumor → See NCCN CNS guidelines Table of Contents

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**STAGING EVALUATION/WORK-UP**

- **Positive diagnosis of primary CNS lymphoma**
  - Slit lamp eye exam
  - Lumbar puncture, (LP) if safe
  - MRI
  - HIV
  - Chest x-ray
  - CBC, platelets, liver function tests

- **Biopsy not diagnostic of primary CNS lymphoma**
  - Prior steroids
  - No prior steroids

- **KPS ≥ 40**
  - and creatinine clearance ≥ 50
  - High-dose (≥ 3g/m²) methotrexate-based regimen ± RT
  - If LP positive or spinal MRI positive, consider intrathecal chemotherapy

- **KPS < 40 or creatinine clearance < 50**
  - Discontinue steroids and rebiopsy when disease progresses
  - Work-up for other CNS diagnosis or rebiopsy

**PRIMARY TREATMENT**

- **KPS ≥ 40**
  - and creatinine clearance ≥ 50
  - High-dose (≥ 3g/m²) methotrexate-based regimen ± RT
  - If LP positive or spinal MRI positive, consider intrathecal chemotherapy

- **KPS < 40 or creatinine clearance < 50**
  - Discontinue steroids and rebiopsy when disease progresses
  - Work-up for other CNS diagnosis or rebiopsy

---

*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.

*f* If eye exam positive, monitor carefully for response to treatment. Consider RT to orbits or intraorbital chemotherapy.

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PROGRESSIVE DISEASE

Prior whole-brain RT

Progressive disease

Prior high-dose methotrexate-based regimen without prior RT

Previous response with long duration

Re-treat with high-dose methotrexate-based regimen

No response or short duration

Consider chemotherapy ± intrathecal chemotherapy ± spinal RT

Consider WBRT or involved field RT ± chemotherapy

Nonimmunosuppressed Primary CNS Lymphoma

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**Metastatic Spine Tumors**

**PRESENTATION**

- Patient diagnosed with cancer
  - Severe, rapidly increasing back pain
  - Neurologic symptoms

**WORKUP**

- Possible biopsy
- Neurologic exam
- Spinal MRI
- Abnormal
  - (Urgent) Spinal MRI
  - Steroids
  - See NCCN Pain Guidelines

**TREATMENT**

- Treatment (surgery or focal RT or chemotherapy) or Close observation (MRI follow-up in 2-3 months)
- Spinal cord compression
- Metastases to spine; no compression
- No tumor

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*a* If the patient is unable to have an MRI, then a CT myelogram is recommended.

*b* The recommended minimum dose of steroids is 4 mg of dexamethasone every 6 hours, although dose of steroids may vary (10-100 mg). Methylprednisolone can be used instead of dexamethasone. For rapid neurologic deterioration or significant myelopathy, a stat MRI is recommended. A randomized trial supported the use of high-dose steroids (Sorensen PS, Helweg-Larsen S, Mouridsen H, Hansen HH. Effect of high-dose dexamethasone in carcinomatous metastatic spinal cord compression treated with radiotherapy: A randomized trial. Eur J Cancer 1994;30A:22-27). Steroid use should be tapered within 3 days.
### Metastatic Spine Tumors

#### PRESENTATION

**No tumor**
- Evaluate for other causes of pain and/or neurologic symptoms
- Pain management ([See NCCN Pain GL](#))
- Consider physical therapy

**Spinal cord Compression**
- Strongly consider surgery if:
  - Spinal instability
  - Radioresistant
  - Rapid neurologic deterioration
  - Unknown primary
  - Previous RT

**Metastases to spine; no compression**
- Spinal instability
  - Surgery or vertebroplasty
- No spinal instability
  - RT

### TREATMENT

**Spinal cord Compression**
- All others
  - RT
  - Consider chemotherapy if chemosensitive tumor (e.g., lymphoma, breast)

**Metastases to spine; no compression**
- Spinal instability
  - Surgery or vertebroplasty
- No spinal instability
  - RT

---

- **Surgery could involve tumor resection with or without spinal stabilization.** Spinal instrumentation is recommended if there is preoperative spinal instability or if instability is expected to occur after tumor resection.
- **Spinal instability is grossly defined as the presence of significant kyphosis or subluxation (deformity), or of retropulsed bone fragment.**
- **Radioresistant tumors include renal carcinoma, melanoma or sarcoma.**
- **Short RT regimens given over 2 weeks or less.**
- **Intractable pain** can be treated by implantation of a subarachnoid pump, tumor resection/stabilization, or vertebroplasty/kyphoplasty depending on stability, extent of disease, and location in the spinal column.

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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
• Gross total resection where feasible
• Stereotactic biopsy
• Open biopsy/debulking

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: 30-44 Gy

HIGHLY CONFORMAL RADIATION THERAPY
- Brachytherapy
- Stereotactic fractionated radiotherapy
- Stereotactic radiosurgery
- IMRT
- Protons

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Summary of the Guidelines updates

Highlights of major changes in the 2.2006 version of the Central Nervous System Cancers guidelines from the 1.2006 version include:

Radiation Therapy: Dose for metastases changed from 30-40 Gy to 30-44 Gy (BRAIN-2).

Highlights of major changes in the 2006 version of the Central Nervous System Cancers guidelines from the 2.2005 version include:

- It was noted that brain MRI should be done within 24-72 hours and spine MRI should be delayed 2-3 weeks post-surgery (EPEN-2).
- Consideration of RT was added as an option for resectable recurrence of adult intracranial ependymoma (EPEN-3).
- A footnote was added to clarify the use of BCNU wafer if frozen section supports the diagnosis of high-grade glioma (GLIO-1).
- Footnote “g” regarding chemotherapy with anaplastic oligodendrogliomas was clarified (GLIO-3).
- Brain and spine MRI are a consideration if the patient is a candidate for treatment (CLMEN-1).
- Consideration of RT to symptomatic sites was added as a treatment option for poor risk patients (CLMEN-2).
- A reference was added to footnote “b” (SPINE-1).
- Footnote “f” was changed to define RT as short regimens given over 2 weeks or less (SPINE-2).
- Gross total resection where feasible replaced major tumor removal (BRAIN-1).
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 2006, an estimated 18,820 new cases of primary brain and other nervous system neoplasms will be diagnosed in the United States. These tumors will be responsible for approximately 12,820 deaths. The incidence of primary malignant brain tumors has been increasing over the last 25 years, especially in elderly persons (rates are increasing at about 1.2% each year). 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 highly responsive or, alternatively, highly resistant to radiation or chemotherapy. Because of this marked heterogeneity, the prognostic features and treatment options for brain tumors must be carefully reviewed for each patient. The involvement of an interdisciplinary team (including neurosurgeons, radiation therapists, oncologists, neurologists, or neuroradiologists) is a key factor in the appropriate management of these patients. These NCCN CNS Cancers guidelines focus on management of adults with CNS cancers.

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 (1) age and performance status (PS) of the patient; (2) proximity to “eloquent” areas of the brain; (3) feasibility of decreasing the mass effect with aggressive surgery; (4) resectability of the tumor (including the number and location of lesions); and (5) in patients with recurrent disease, the time since the last surgery.

The surgical options include stereotactic biopsy, open biopsy or debulking procedure, or gross total tumor resection where feasible, which is usually characterized as removal of more than 90% 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 RT, and stereotactic radiosurgery. Three-dimensional conformal external-beam radiation is the most common approach, but intensity-modulated radiation therapy (IMRT) may also be administered to selected patients. RT 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 can be administered to patients with poor PS to accelerate completion of therapy and to minimize the number of hospital visits.

Tumor Types
The NCCN CNS Cancer Guidelines focus on high-grade invasive astrocytomas, low-grade invasive astrocytomas, oligodendrogliomas, ependymomas, brain metastases, carcinomatous/lymphomatous meningitis, primary CNS lymphoma (non-AIDS), and metastatic spinal tumors. 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 8000 to 10,000 new cases are diagnosed per year in North America; peak incidence occurs from ages 45 to 55 years.
high-grade astrocytomas diffusely infiltrate surrounding tissues and frequently cross the midline to involve the contralateral brain. Patients with these neoplasms often present with symptoms of increased intracranial pressure, seizures, or focal neurologic findings related to the size and location of the tumor and to associated peritumoral edema. These tumors usually do not have associated hemorrhage or calcification but produce considerable edema and mass effect in image study as well as enhance after the administration of intravenous contrast. Tumor cells have been found in the peritumoral edema, which corresponds to the T2-weighted MRI abnormalities. As a result, this volume is frequently used to define radiation treatment portals.

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

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 when compared with biopsy alone as a strong prognostic factor. 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 (KPS) 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. Surgery also improves the outcome for patients with recurrent high-grade astrocytomas.

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. Survival at 1 year was 3% with surgery alone, 12% with postoperative BCNU, and 24% with postoperative radiation. Currently, 59.4-60 Gy (divided into 30 to 33 fractions) is administered to the involved field. A shorter course of radiation, such as 40 Gy in 15 fractions over 3 weeks, can be used in elderly patients with equivalent results. Alternative doses, fractions, and schedules have been
explored without significant improvements in adult patients with malignant gliomas. The role of focal radiation techniques in this diffusely infiltrative disease remains undefined. The Radiation Therapy Oncology Group (RTOG) conducted a randomized trial of conventional radiotherapy to 60 Gy and BCNU alone or preceded by a radiosurgery boost (to 15-24 Gy) in patients with glioblastoma multiforme of 4 cm or less. However, the results were disappointing with no improvement in local control or survival with stereotactic radiosurgery boost. Similarly, a trial done at Princess Margaret Hospital randomly assigned patients to 50 Gy external-beam radiation with or without temporary I-125 seed implant to 60 Gy; however, this trial did not show any survival benefit. The Gliasite balloon has been 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.

Traditionally, chemotherapy was felt to be of marginal value in the treatment of newly diagnosed patients with high-grade gliomas. Walker and colleagues did a randomized study of (1) a nitrosourea alone, versus (2) radiation alone, versus (3) radiation plus a nitrosourea. Although a slight improvement in survival was noted at 18 months in the group of patients who were treated with radiation plus BCNU compared with those who had received radiation alone, the difference in survival curves between the two groups was not statistically significant. More than 20 years later (2001), the Medical Research Council reported results from the largest randomized trial of adjuvant chemotherapy in high-grade gliomas. In this study, 674 patients were randomly assigned to either radiation alone or radiation plus PCV (procarbazine, lomustine [CCNU], and vincristine). No survival benefit was seen with the addition of PCV, even in patients with anaplastic astrocytomas.

In contrast, two meta-analyses reviewed data from randomized trials of high-grade glioma patients, and both found a modest survival benefit when chemotherapy was added to postoperative radiation. Specifically, in the most recently published meta-analysis (GMT Group, 2002) of 12 studies involving approximately 3000 patients with high-grade gliomas who were treated either with postoperative radiation alone or with radiation plus chemotherapy, there was an absolute increase in 1-year survival from 40% to 46% and a 2-month increase in median survival when chemotherapy was added to postoperative radiation.

Most of these trials studied nitrosourea-based chemotherapy regimens. Temozolomide, a newer drug that is classified as an atypical alkylating agent, received U.S. Food and Drug Administration (FDA) approval for the treatment of patients newly diagnosed with glioblastoma multiforme in March 2005. Temozolomide received accelerated FDA approval for recurrent anaplastic astrocytomas in 1999; however, the accelerated approval requirements no longer apply. In Europe, temozolomide’s approved indication is for the treatment of both recurrent anaplastic astrocytoma and recurrent glioblastoma multiforme. A recent phase III, randomized study assessed temozolomide in 573 patients with glioblastoma multiforme
who received either (1) daily temozolomide (75 mg/m²) administered with postoperative RT followed by 6 cycles of adjuvant temozolomide (150-200 mg/m²/day given 5 days during each 28-day cycle); or (2) radiotherapy alone. Temozolomide resulted in a statistically better median survival (14.6 versus 12.1 months) and 2-year survival (26.5% versus 10.4%) when compared with RT. However, the design of this study does not shed light on what is responsible for the improvements in survival: the temozolomide administered with radiation, following radiation, or both. Subsequent analyses suggest that MGMT (O-6-methylguanine-DNA methyltransferase) status may determine which patients obtain benefit from adjuvant temozolomide therapy. MGMT (a DNA repair enzyme) may cause resistance to DNA-alkylating drugs commonly used in the treatment of anaplastic oligodendrogliomas and other malignant gliomas. Note that side effects for temozolomide include nausea, vomiting, headaches, fatigue, and anorexia. Preventive treatment for Pneumocystis carinii pneumonia (PCP) is required when temozolomide is administered with radiotherapy (FDA Talk Paper, March 16, 2005). In elderly patients with glioblastoma multiforme, temozolomide alone may be useful to avoid side effects with RT (eg, excessive fatigue and frequent worsening of neurologic deficits). However, in elderly patients with good performance status, adjuvant chemotherapy and RT may be useful.

In terms of adjuvant treatment for anaplastic astrocytomas, the PCV regimen has commonly been used, in large part, based on the results of a phase III trial that compared BCNU to PCV following RT in patients with high-grade gliomas. This study found a survival benefit for patients with anaplastic astrocytomas who received PCV. However, a subsequent retrospective analysis determined that there is little difference between PCV and BCNU. Additionally, the Medical Research Council study (2001) previously discussed found no improvement in survival when patients with anaplastic astrocytomas were treated with PCV. There are no published data directly comparing the benefit of postoperative chemotherapy with temozolomide to a nitrosourea in patients with newly diagnosed anaplastic astrocytomas. This study is currently underway through the RTOG; however, no results have been reported yet. Given the better side-effect profile of temozolomide and the recent positive results of the phase III trial reported by Stupp and colleagues, temozolomide is recommended (category 1) for postoperative chemotherapy in patients with glioblastoma multiforme.

Unfortunately, currently available chemotherapy does not provide cures in any of these patients. In addition to temozolomide and the nitrosoureas, agents that also have some activity against gliomas and are commonly used as second-line chemotherapy include procarbazine, irinotecan, cisplatin, and carboplatin. Many other agents are currently being studied. For chemotherapy-naïve patients with glioblastoma multiforme who experience recurrence or progression, temozolomide and cisplatin may be useful.

Other routes of drug delivery have been evaluated. Local administration of BCNU using a biodegradable polymer (Gliadel wafer) placed intraoperatively in the surgical cavity has demonstrated a statistically significant, improvement in survival for patients with recurrent high-grade gliomas. As a result, the FDA approved the Gliadel wafer for...
this indication. A study in 32 patients with malignant glioma showed a statistically significant prolongation of survival when BCNU polymer was used as initial therapy in combination with RT. A phase III trial of the Gliadel wafer compared to placebo in newly diagnosed patients (240) with malignant glioma also found a statistically significant improvement in median survival from 11.6 months in the placebo group to 13.9 months in the BCNU-wafer treated group. This benefit was maintained 2 and 3 years after implantation. On the basis of these studies, the FDA extended the approval of BCNU polymer wafers for use in malignant gliomas as initial therapy (February 2003). The European regulatory agencies similarly extended their approval to its initial use in October 2004.

Patients with primary brain tumors or brain metastases frequently take medications to control seizures. Some of the more commonly used anticonvulsants, such as phenytoin and carbamazepine, are known to induce the hepatic cytochrome P450 isoenzyme system. Induction of these hepatic enzymes can enhance clearance of concurrently administered drugs that are eliminated by hepatic oxidative metabolism, resulting in lower blood levels of a drug and decreased efficacy. Hepatic enzyme-inducing anticonvulsants (HEIAs) have been shown to dramatically affect the pharmacology of some chemotherapy agents, such as irinotecan and paclitaxel. As a result, a patient who is taking an HEIA will require a higher than standard dose of these particular chemotherapy agents in order to obtain therapeutic plasma levels. One way to avoid this problem is to switch the patient to a non-HEIA, such as gabapentin, lamotrigine, or levetiracetam.

**Treatment Algorithm**

The NCCN Panel wrote a treatment algorithm for patients with newly diagnosed and recurrent high-grade astrocytomas using the previous information. When a patient presents with a clinical and radiologic picture suggestive of a high-grade astrocytoma, neurosurgical input is needed regarding the maximal feasible tumor resection. The patient should receive a biopsy first if the MRI is suggestive of CNS lymphoma. Whenever possible, major tumor removal should be performed. If high-grade glioma is supported by frozen section diagnosis, BCNU wafer is also recommended (category 2B). The extent of tumor debulking should be documented with an immediate 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 should be performed to establish the diagnosis.

After surgical intervention, patients can be treated with or without BCNU wafer followed by RT with or without chemotherapy (see GLIO-2). For patients (younger than 70 years of age with good performance status) with glioblastoma multiforme, a high level of evidence supports the use of daily temozolomide (75 mg/m²) administered with postoperative RT followed by 6 months of temozolomide (150-200 mg/m²/day times 5 days each month). If there is a prolonged delay in tumor recurrence and a second-stage surgery is required, then the BCNU wafers can be re-inserted because they are biologically active for only 3 weeks, although remnants can be visualized on MRI for up to 1 year. The BCNU wafers can be used as local chemotherapy to avoid systemic toxicity of oral or parental chemotherapy, because there is no detectable blood level of BCNU...
when the wafer is applied. Alternatively, the wafer can be used to help prevent local tumor recurrence (which occurs in approximately 90% of patients with glioblastoma) in combination with systemic chemotherapy.

Currently, temozolomide is often administered to patients with glioblastoma multiforme and anaplastic astrocytoma, although BCNU, CCNU, or PCV can be used to treat anaplastic astrocytoma.\textsuperscript{37} Young patients with good PS and lower-grade tumors probably benefit more from chemotherapy than do poorer prognostic groups. Oligodendrogliomas, particularly those that have chromosomal loss of 1p or combined 1p19q loss, have been reported to be especially sensitive to alkylator chemotherapy.\textsuperscript{38} Temozolomide or nitrosourea based chemotherapy regimens may be appropriate. Thus, testing for 1p19q markers can be considered. Patients should be followed closely with serial MRI scans (at 2-6 weeks and then every 2-3 months for 2-3 years) after the completion of RT. Because RT can produce additional blood-brain barrier dysfunction, corticosteroid requirements may actually increase; therefore, scans may appear worse during the first 3 months after completion of RT, even though there is no actual tumor progression. Early MRI scans allow for appropriate titration of corticosteroid doses, depending on the extent of mass effect and brain edema. Later scans are used to identify tumor recurrence. Early detection of recurrence is warranted, because local and systemic treatment options are available for patients with recurrent disease.

When recurrent disease is detected, management depends on the patient’s age, PS, 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, repeat resection can be done, with or without a BCNU-impregnated wafer placed locally in the surgical bed; further options depend on whether BCNU was used (see GLIO-3). If the local recurrence is unresectable or surgery is deemed too risky, options include highly conformal RT or systemic chemotherapy (using temozolomide or nitrosourea-based regimens). For diffuse or multiple recurrent disease, systemic chemotherapy is recommended. Best supportive care should also be strongly considered, especially if the patient has a poor PS. Surgery can be an option for a symptomatic large lesion. A response to further chemotherapy is unlikely after two consecutive agents have failed to produce a response.

### 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; however, the NCCN algorithm does not encompass pilocytic astrocytomas because these tumors are curable by surgery.
alone. 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 anaplastic astrocytoma.

**Treatment Overview**

Although low-grade astrocytomas are commonly thought to be benign, most of these tumors behave aggressively despite surgery and RT. A low-grade astrocytoma can transform into a glioblastoma during a period of 5 to 10 years. The best management strategy for a patient with seizures and a probable low-grade astrocytoma has yet to be defined. Whenever possible, total removal should be attempted, because survival and recurrence-free intervals are superior when the tumors can be safely removed. Furthermore, a gross total removal could potentially delay or prevent malignant progression. 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 neurologic 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 reviewed 126 patients with astrocytomas and mixed
After gross total removal, patient survival rates 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 RT, 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 have suggested prolonged survival in patients who underwent gross total resection, compared with those patients who underwent less radical excision. Berger and colleagues have shown an inverse correlation between the postsurgical 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. Third, a large tumor burden is removed, which also may enhance the effect of RT. As a result of these considerations, the general recommendation for treating an astrocytoma is to first attempt 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. However, others have reported no prolongation of survival in irradiated patients. A randomized trial of early versus delayed radiotherapy in adult patients was conducted by the European Organization for Research and Treatment of Cancer (EORTC). In this trial, patients with low-grade gliomas were randomly assigned to either (1) 54 Gy postoperative radiation; or (2) no immediate therapy. With a median follow-up of 5 years, the 5-year disease-free survival was better with immediate postoperative radiation (44% versus 37%; P = 0.02). However, the 5-year overall survival was the same (63% versus 66%) indicating that deferring the postoperative therapy can be an option for a selected group of patients. Further analysis of mature data is necessary before firm recommendations can be made based on this study. Although delaying radiation in young healthy patients without progressive neurologic decline can be controversial, there is a consensus to proceed with immediate postoperative radiation in older patients after a less-than-total resection, because their survival is as poor as patients with anaplastic astrocytoma.

When radiation is given to patients with low-grade astrocytomas, it is administered with restricted margins. Whole-brain RT (WBRT) 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 RT 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 on the lack of evidence for increased efficacy with higher doses. In a randomized trial conducted by the EORTC in patients with low-grade astrocytomas, no survival difference was observed when 45 Gy was compared with 59.4 Gy. With a median follow-up of 6 years, the 5-year disease-free survival and the 5-year overall survival were the same. Patients were randomly assigned to receive either (1) 50.4 Gy in 28 fractions, or (2) 64.8 Gy in 36 fractions in another combined NCCTG (North Central Cancer Treatment Group), RTOG, and ECOG (Eastern Cooperative Oncology Group) study. With a median follow-up of 6.3 years, the 5-year disease-free survival and the 5-year overall survival were again the same indicating that lower doses of RT are probably as effective as higher doses of radiation for low-grade gliomas. Enthusiasm for interstitial radiation or stereotactic radiosurgery in recurrent low-grade astrocytomas has decreased due to lack of evidence for efficacy.

Currently, chemotherapy is not used in the treatment of low-grade astrocytomas in which a maximal safe resection is feasible, but chemotherapy may be considered at recurrence. The RTOG recently conducted a clinical trial that allowed observation alone for completely resected low-grade gliomas in patients younger than 40 years and randomly assigned younger patients who were sub-totally resected and older patients who received any kind of resection to postoperative radiation to 54 Gy with or without PCV chemotherapy for 6 cycles. This study has completed the accrual, and the results are awaiting publication.

**Treatment Algorithm**

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 within 72 hours after surgery. 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 RT may also be considered for patients in this age group who have had complete excision (see ASTR-1). Regular follow-up is essential for patients receiving observation alone after resection. Although surgery is generally recommended, serial observations are appropriate for selected patients.
Patients who only had a diagnostic biopsy or subtotal excision are more likely to be treated with immediate RT, especially if their symptoms are uncontrolled or progressive; chemotherapy (category 2B) is also an option. Because of concerns about the neurotoxicity of RT, patients with residual asymptomatic low-grade astrocytoma may be followed until their disease progresses. Observation 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. Chemotherapy (category 2B) and irradiation are other options.

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, especially if progression-free survival is more than 2 years after prior RT, the new lesion is outside the target of previous RT, or the recurrence is small and geometrically favorable. 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. 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. On histopathologic assessment, these tumors can be confused with glioblastoma multiforme; however, 50% to 70% of low-grade oligodendrogliomas and anaplastic oligodendrogliomas have specific molecular genetic alterations (allelic losses of chromosomes 1p and 19q) that can help distinguish them from other types of gliomas.

The median survival for patients with low-grade oligodendrogliomas is about 10 years; for anaplastic oligodendrogliomas, survival is about 3 to 5 years. Patients with mixed oligoastrocytomas tend to have the same outcome as patients with pure oligodendrogliomas.

Treatment Overview

Maximal feasible resection is preferred, as previously noted for patients with low-grade astrocytomas. Gross total removal of these tumors is often possible, because most occur in the frontal lobes and because the tumors are frequently well demarcated. Retrospective data have suggested that RT improves local control and survival. Low-grade oligodendrogliomas and anaplastic oligodendrogliomas are chemosensitive tumors, however, the optimal timing of chemotherapy in the treatment of these tumors needs to be defined. Tumors with mixed oligoastrocytoma histology have a better prognosis than pure astrocytomas but not as good as pure oligodendrogliomas.
Treatment Algorithm

The treatment algorithm for patients with low-grade oligodendrogliomas is identical to the treatment algorithm for low-grade astrocytomas. Evidence is strong that gross total removal of the tumor leads to longer survival.\textsuperscript{55,56,62} 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 oligodendrogliomas registered by the Cancer Registry of Norway during a 25-year period.\textsuperscript{53} In this study involving 170 patients, survival was significantly longer in patients who received RT. 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 oligodendrogliomas included 82 patients.\textsuperscript{55} The survival of the 63 patients who received RT 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 RT. 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-1); this is especially true for patients younger than 45 years. For patients with subtotally excised low-grade oligodendrogliomas, the considerations are the same as for patients with low-grade astrocytomas.

Three multicenter trials compared the results of RT for low-grade gliomas, including oligodendrogliomas, with either delaying the radiation until time of recurrence\textsuperscript{46} or using high-dose versus low-dose radiation.\textsuperscript{47,48} In these trials, 25% of the patients had oligodendrogliomas. Although time to progression was longer in the immediate therapy group in the EORTC study, progressing patients whose RT had been delayed could be successfully salvaged, and survival was identical in both arms.\textsuperscript{46} In both the EORTC trial\textsuperscript{47} and the intergroup randomized study,\textsuperscript{48} no benefit of the high-dose RT compared to the low-dose RT delivered in identical fractionation was noted. However, more toxicity in the higher dose arm was documented. Therefore, the current recommendation for low-grade oligodendrogliomas is that lower RT doses in the range of 45 to 50.4 Gy are superior to higher doses.\textsuperscript{63} Delay of radiation for tumors in noneloquent regions and for small asymptomatic tumors in eloquent regions is a viable option based on current information.\textsuperscript{63} Because of the improved outcomes with the availability of improved mapping and surgical navigation techniques,\textsuperscript{62} an interdisciplinary approach\textsuperscript{63} based on institutional experience, expertise, and outcomes should be discussed frankly with each patient.

The radiation technique used for oligodendrogliomas is similar to the technique used for astrocytic gliomas. The occasional tendency of oligodendrogliomas to spread via the cerebrospinal fluid (CSF) does not justify the need for craniospinal radiation. Low-grade oligodendrogliomas and anaplastic oligodendrogliomas are considered to be chemosensitive brain tumors. Moreover, patients with these types of brain tumors who also have chromosomal loss of 1p or combined 1p19q loss in their tumors are more likely to respond to chemotherapy and have a better survival compared to other patients with oligodendrogliomas or anaplastic oligodendrogliomas who do not have...
these genetic alterations in their tumors. However, it is unclear at this time how to incorporate this molecular genetic information into treatment decisions for these patients.

In the treatment algorithm for newly diagnosed low-grade oligodendrogliomas (see ASTR-1), recommendations include postoperative radiation, chemotherapy (category 2B), or observation (depending on age, extent of surgical resection, and symptoms). Surgery is generally recommended, but serial observations are appropriate for selected patients. Although chemotherapy is traditionally reserved for tumor recurrence, chemotherapy (category 2B) may be an appropriate adjuvant therapy. However, there is a lack of prospective studies that define the role of chemotherapy in the treatment of oligodendrogliomas. There are no data, for example, showing that chemotherapy given up front along with radiation improves survival as opposed to reserving its use for when the tumor recurs. There are also no data to show that in these chemosensitive tumors it is reasonable to use chemotherapy alone postoperatively and to defer radiation until time of recurrence.

As with low-grade oligodendrogliomas, it is unclear how to best incorporate chemotherapy into the treatment strategy for anaplastic oligodendrogliomas and mixed anaplastic oligoastrocytomas. Results from an intergroup phase III randomized trial of PCV plus radiation versus radiation alone in anaplastic oligodendrogliomas and mixed anaplastic oligoastrocytomas were presented at the 2004 ASCO annual meeting. There was no difference in median survival between patients who received PCV before radiation and those who received radiation alone. Patients with tumors demonstrating the 1p19q deletions lived longer, but treatment-specific outcomes for these patients were not reported (longer follow-up time is needed). The RTOG recently conducted a phase II study of preradiation chemotherapy in patients with newly diagnosed anaplastic oligodendrogliomas and mixed anaplastic oligoastrocytomas. If a complete response was achieved after 6 cycles of temozolomide, then the patient was followed without radiation. If there was no complete response, then the patient was treated with radiation and concurrent temozolomide. No results from this study have been reported yet. In summary, there are now specific chromosomal alterations that are powerful prognostic variables for patients with oligodendrogliomas and anaplastic oligodendrogliomas. Patients whose tumors exhibit allelic loss of 1p and 19q have a better survival than patients whose tumors do not have these specific chromosomal alterations. However, it is too early to tell if this molecular genetic information can be used to guide therapeutic decisions regarding the timing of chemotherapy. Data are needed from prospective clinical trials.

In terms of chemotherapy for newly diagnosed or recurrent oligodendrogliomas and anaplastic oligodendrogliomas, PCV has been most extensively studied; approximately 66% patients show responses to this chemotherapy regimen. However, because of PCV’s toxicity, temozolomide may be a reasonable alternative. Temozolomide has been shown to produce a response rate (complete response and partial response) of 44% in patients with recurrent oligodendrogliomas and anaplastic oligodendrogliomas who had previously been treated with PCV. A recent study found that temozolomide was effective in patients with progressive low-grade oligodendrogliomas; 51% of patients improved, especially those with uncontrolled epilepsy.
Ependymomas and Anaplastic Ependymomas

Ependymomas occur in both adults and children. In adults, approximately 33% of ependymomas arise infratentorially and 66% arise supratentorially; the opposite is true in children. 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.\(^{69,70}\)

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. RT 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 because 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.\(^{71}\) The uncertain implication of high histologic grade (or anaplastic ependymoma) similarly favors the use of local fields.\(^{72}\) Based on dose-response analyses for ependymomas, the typical radiation dose is between 50 and 55 Gy locally using 1.8-2.0 Gy per fraction.\(^{71}\) The high rate of local failure after incomplete resection has stimulated ongoing investigations of high-dose, hyperfractionated irradiation and of precision-volume stereotactic radiosurgical “boosts” to residual disease sites. Doses of 59.4-60 Gy in 30-33 fractions using a conformal technique are generally used.

For anaplastic ependymomas, researchers have recommended irradiating the entire craniospinal axis\(^{73,74}\) or administering whole-brain irradiation, with an additional boost for high-grade supratentorial lesions located away from the CSF pathways, if leptomeningeal spread is not evident. 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;\(^{71,72}\) and (4) spinal metastases may not be prevented by prophylactic treatment.\(^{71,74}\) As a result, the routine use of “prophylactic” craniospinal or whole-brain irradiation does not appear to lead to improvement in survival.\(^{71,72,74}\)

The role of chemotherapy in the treatment of ependymomas is poorly defined. Although many drugs have been tried, ependymomas do not appear particularly responsive to chemotherapy. In children or adults with newly diagnosed ependymomas, no studies have demonstrated a survival advantage with chemotherapy plus irradiation, when compared with irradiation alone. However, chemotherapy is 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 contrast-enhanced spinal MRI scan reveals disease, 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. CSF analysis should also be considered.

Follow-up of ependymoma depends on the extent and location of the disease. For localized disease, contrast-enhanced MRI of the involved site should be done 2 to 3 weeks postoperatively and then every 3 to 4 months for 1 year. The interval can then be extended to every 4-6 months for year 2 and then every 6 to 12 months, depending on the physician’s concern regarding the extent of disease, histology, and other relevant factors. If tumor recurrence in the brain or spine is noted on one of these scans, resection should be considered. Surgery should be followed with RT if radiation was not given originally. If the recurrence is unresectable, radiation is a possible option if radiation was not given originally; consider stereotactic radiosurgery if geometrically favorable. Chemotherapy or best supportive care should also be considered, depending on the histologic type, extent of disease, age of the patient, and PS. Radiation is considered another option for respectable recurrence.

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 (see NCCN Guidelines for Treatment of Cancer by Site). For example, because therapy for metastatic breast cancer is improving, CNS involvement is becoming more common. 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. 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 WBRT compared with WBRT alone and found a dramatic difference in survival in patients with surgically accessible, single brain metastases. However, nearly 50% of these patients were 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 either stereotactic radiosurgery or WBRT. After complete resection of a single metastatic lesion, WBRT decreases recurrences in the brain but does not improve survival. Stereotactic radiosurgery can be used in the initial treatment of patients with only one or two appropriate brain metastases (ie, small, deep) or in those who relapse after whole-brain irradiation. The survival results can be comparable to those for surgical resection. There has never been a randomized trial comparing stereotactic radiosurgery with surgical resection. A multi-institutional retrospective analysis of stereotactic radiosurgery for solitary metastasis, which comes closest to addressing this issue, showed median overall and functionally independent survival rates were 56 and 44 weeks respectively, indicating that the stereotactic radiosurgery is at least equivalent, if not superior to surgical resection. 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 already heavily pretreated with potentially effective agents. However, temozolomide may be useful in patients with previously untreated brain metastases from metastatic melanoma. Temozolomide given on a prolonged schedule plus thalidomide is being investigated by the Cancer and Leukemia Group B in patients with brain metastases.

**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 with chest x-ray or CT, abdominal or pelvic CT, or other tests as indicated. 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, if concerns regarding the diagnosis of CNS lesions exist, a stereotactic or open biopsy or resection is also needed. 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 WBRT rather than surgery.

For patients with limited systemic disease or for whom reasonable systemic treatment options exist, aggressive management should be strongly considered. For resectable lesions, options include surgery or stereotactic radiosurgery; WBRT can be considered (see LTD-2). For unresectable disease, WBRT and/or radiosurgery can be used. The choice of therapy partly depends on the size of the lesion,
whether the patient has symptoms, and institutional practice. The extent of surgery depends on the lesion’s accessibility and the overall condition of the patient. For example, stereotactic radiosurgery may be used for a limited number of small (< 2 cm), deep, nonsymptomatic lesions; however, surgery may be more appropriate for larger, symptomatic lesions. Macroscopic total removal is the objective of surgery, given the studies demonstrating a survival benefit.86

Although previously controversial, WBRT after a surgical resection of a single brain metastasis was shown to be useful by Patchell and colleagues (1998).77 Their study randomly assigned patients to surgical resection alone compared with surgical resection and WBRT (50.4 Gy given in 28 fractions). Although the addition of WBRT to surgery decreased the incidence of CNS recurrence anywhere in the brain from 70% to 18% ($P < .001$), survival did not differ between the two treatment arms.77 The use of WBRT after surgical or stereotactic 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 (see NCCN Guidelines for Treatment of Cancer by Site). Patients with progressive extracranial disease, with expected survival less than 3 months, should be treated with WBRT alone. A randomized study showed that surgical resection of a single lesion, followed by WBRT in patients with active systemic disease, did not improve survival compared with WBRT alone.83

Patients should be followed with MRI every 3 months for 1 year and then as clinically indicated. For patients with recurrent disease, prior therapy clearly influences the choice of further therapies. Patients with recurrent CNS disease should be assessed for local versus systemic disease, because therapy will differ (see LTD-3). For local recurrences, if patients were previously treated with surgery or WBRT, surgery or stereotactic radiosurgery is considered; however, surgery alone is recommended in patients with prior stereotactic radiosurgery with or without WBRT. The algorithm for distant brain recurrences branches depending on whether patients have either 1-3 lesions or more than 3 lesions, although these are still considered to be limited lesions. WBRT 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 patients87 with more than 3 lesions, if the multiple lesions cannot be controlled by a combination of surgery and radiosurgery.88

If systemic CNS disease progression occurs in the setting of limited systemic treatment options, WBRT (30-40 Gy, given in 10-20 fractions) should be administered, if the patients have not been previously irradiated (see LTD-4). Surgery should be considered to relieve mass effect.88 For patients who have received prior WBRT, reirradiation may be considered only if they had a positive response to the first course of RT treatment. This further radiation may include WBRT (20-30 Gy, given in 10-15 fractions)89 or fractionated, limited-field conformal therapy. Chemotherapy consistent with sensitivity of primary site or best supportive care may also be considered.
Treatment Algorithm for Multiple Metastatic Lesions

Patients diagnosed with multiple (ie, > 3) metastatic lesions should be treated with WBRT (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 RT can be considered (20 Gy, delivered in 5 fractions). Palliative surgery should be considered if one lesion is causing a life-threatening mass effect, hemorrhage, or hydrocephalus. Occasionally, surgery has a role if one lesion is “dominant” and the patient is steroid dependent because of peritumoral edema and/or radiation necrosis.

After WBRT, patients should have a repeat contrast-enhanced MRI scan every 3 months for 1 year. 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 if they had a prior positive response to RT. For patients with stable systemic disease, options include surgery, highly conformal RT, reirradiation if they had a positive response to prior RT, chemotherapy, or stereotactic radiosurgery.

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. Tumor cells gain access to the leptomeninges by hematogenous dissemination or by 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 neurologic symptoms or signs and if the patient is considered a candidate for treatment. A definitive diagnosis is most commonly made by lumbar puncture if it is safe to the patient. The CSF protein is typically increased, and there may be a pleocytosis or decreased glucose levels. The CSF cytology is positive approximately 50% of the time with the first lumbar puncture, and 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 KPS; multiple, serious, major neurologic deficits; extensive systemic disease with few treatment options; bulky CNS disease; and neoplastic meningitis related to encephalopathy. The good-risk group includes patients with a high KPS, no major neurologic deficits, minimal systemic disease, and reasonable systemic treatment options. Many patients fall in between these two groups, 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. RT 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 (e.g., small cell lung cancer, lymphoma) may be treated.

Good-risk patients can receive radiation to symptomatic sites and to areas of bulky disease identified on neuroimaging studies. In addition, intrathecal or intraventricular (using a surgically implanted subcutaneous reservoir and ventricular catheter [SRVC]) chemotherapy can be administered; systemic chemotherapy can be considered. 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.

When dosing intrathecal chemotherapy for adults, no adjustment is made based on weight or body surface area. With methotrexate, thiotepa, and cytarabine, a typical dosing schedule is initially twice a week for 4 weeks; if the CSF cytology becomes negative, then continue with once-a-week administration of intrathecal chemotherapy for another 4 weeks, followed by once-a-month maintenance doses. Methotrexate (10-12 mg) is the drug most frequently used for intrathecal administration. Oral leucovorin (folinic acid) can be given (10 mg twice a day for 3 days starting the day of treatment) to reduce possible systemic toxicity without interfering with the efficacy of methotrexate in the CSF. Intrathecal thiotepa (10 mg) can also be used in solid tumors, and cytarabine (50 mg) 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 initially (rather than twice per week) followed by once-a-month maintenance treatment. In a randomized controlled trial, depot cytarabine was found to increase the time to neurologic progression, with a response rate comparable to methotrexate, while offering the benefit of a less demanding schedule of injection. One study suggests that high-dose systemic methotrexate might be better than intrathecal therapy.

If an SRVC is placed, a CSF flow scan should be strongly considered. CSF flow abnormalities are common in patients with neoplastic meningitis and often lead to increased intracranial pressure. Administering chemotherapy into the ventricle of a patient with a ventricular outlet obstruction increases the patient’s risk for leukoencephalopathy. In addition, the agent administered will not reach the lumbar subarachnoid space where the original CSF cytology was positive. CSF flow scans are easily performed in most nuclear medicine departments. Indium 111-DTPA is administered into the SRVC, and imaging of the brain and spine is performed immediately after injection and then imaging is done again at 4 and 24 hours. If significant flow abnormalities are seen, 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 (i.e., with supportive measures).
For patients with a normal CSF flow scan and otherwise stable disease, induction intrathecal chemotherapy should be given for 4 to 6 weeks (see CLMEN-3) and then the patient should be reassessed clinically and with a repeat CSF cytology. Because the cytology is much less likely to be positive from the SRVC than from the lumbar subarachnoid space, it is critical that it be sampled from the site where the cytology was originally positive. If the CSF cytology was originally negative, then reassess from the lumbar region. If the patient is clinically stable or improving and there is no clinical or radiologic evidence of progressive leptomeningeal disease, the patient should receive another month of “induction” intrathecal chemotherapy or should consider switching intrathecal drugs for 4 weeks. This regimen should be followed by 1 week per month of maintenance therapy if the cytology has converted to negative. The CSF cytology status should be followed every month.

**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 if the cytology is persistently positive, the clinician has two options: (1) chemotherapy; (2) supportive care, which may include RT to symptom sites.

**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. 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. 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). These NCCN guidelines have 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. 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.

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. 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. 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. In some patients, however, the tumor does not enhance by CT or MRI scans, thus confusing and delaying the diagnosis. 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 or uveal evaluation, the intracranial lesion often requires a biopsy for a definitive diagnosis (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 cytotoxic 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. 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. 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 when compared with 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 3000 to 5000 cGy. However, the responses were brief, and patients often developed recurrent disease within a matter of months. These findings 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.
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 RT have been noted by DeAngelis (1995), as well as by other investigators. 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. However, high-dose methotrexate may also be effective (see “High-Dose Methotrexate”).

**Chemotherapy** In general, methotrexate-based chemotherapy regimens are more effective against primary CNS lymphoma than non-methotrexate regimens. 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. Compared with methotrexate-based regimens, the progression-free and overall survival rates are lower in these non-methotrexate 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 RT 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. A multicenter RTOG study demonstrated improved survival with the combination of chemotherapy, using high-dose methotrexate plus RT when compared with previous reports of RT alone; delayed neurotoxicity remains a risk of this approach. Neuwelt and colleagues (1991) suggest withholding RT 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 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. In many of these investigations, chemotherapy was administered before RT 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.\textsuperscript{112} They noted complete responses in 9 patients and partial responses in 4 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.\textsuperscript{101,108} The overall median survival for the cohort was 42.5 months, with partial responses in 17 patients and stable disease in 5 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.\textsuperscript{107} 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 3 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 workup involves 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, 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. Preradiation chemotherapy, as opposed to postradiation chemotherapy, has been emphasized 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.
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 (≥ 3 g/m²) is the single most active agent against primary CNS lymphoma and should be a part of any chemotherapy regimen chosen to treat this disease. 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.¹¹５ 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; a high-dose methotrexate-based regimen is most commonly used (see PCNS-2). Whether one performs whole-brain irradiation after systemic chemotherapy depends on the responsiveness of the disease to chemotherapy (ie, whether a complete response occurs) 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.

If a patient is found to have malignant uveitis, orbital radiation has been the standard recommendation because of poor penetration of systemic chemotherapy into the uveal fluid. However, there are reports of clearance of ocular lymphoma in patients who were treated with systemic high-dose methotrexate.¹¹⁶ Therefore, with a primary CNS lymphoma patient who has asymptomatic ocular involvement, a reasonable strategy is to delay radiation to the orbits in order to see if high-dose methotrexate is effective. Intraocular injection of chemotherapy remains investigational. 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.

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 PS; 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 (see NCCN Palliative Care Guidelines).
**Progressive Disease**  For younger patients with good PS who are treated with pre-radiation chemotherapy and ultimately relapse, treatment is usually 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, “local” radiation may have a role, particularly in the spinal axis, for those patients with neurologic morbidity from a focal lesion.

For patients who were initially treated with high-dose methotrexate based 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 several factors, including the duration of response to initial chemotherapy, which is possibly the most important (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, for patients who relapse within a very short time after systemic chemotherapy, consider using WBRT or involved-field RT, with or without chemotherapy. Alternative chemotherapeutic regimens should be considered for patients not suited for WBRT. Rituximab (anti-CD20 monoclonal antibody) and temozolomide are active in relapsed primary CNS lymphoma; these agents may be especially useful in older patients. 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.

**Metastatic Spinal Tumors**

Metastatic spinal cord compression affects 5% to 14% of all patients with cancer (> 20,000 cases are diagnosed each year in the United States). The primary cancers causing spinal metastases are breast, lung, and prostate cancers; the thoracic spine is the most common site. Metastatic spinal tumors also include carcinomas of unknown origin that metastasize to the spine. However, Pancoast (superior sulcus) tumors and primary sarcomas arising from the spine are excluded, because they are not considered to be metastatic spinal tumors. Spinal lesions are divided into three main categories based on the type of symptoms associated with the lesions (see SPINE-1). The first category comprises patients with an incidental, asymptomatic metastatic lesion that can be observed with MRI follow-up in 2 to 3 months. However, biopsy and further treatment (ie, surgery, focal RT, or chemotherapy) of an incidental lesion are indicated if treatment of the patient as a whole is altered as a result of treatment of the incidental lesion. In the absence of symptoms, it is not mandatory to obtain a spinal MRI for every incidental metastatic lesion seen on surveillance bone scans. The second category involves severe, rapidly increasing back pain (including pain involving the cervical, thoracic, lumbar spine, or sacrum) attributable to the tumor. It can include mechanical or radicular types of pain. Increasing intensity, duration, and changes in the character of pain should trigger an evaluation with an MRI study, even in patients with pre-existing degenerative spine conditions. On the other hand, not every patient with minor, transient back pain and history of cancer needs an MRI.
The third category involves neurologic symptoms including weakness, paresthesias, and bladder or bowel incontinence (constipation and diarrhea are not included).123,124

A normal neurologic examination implies that there is no radiculopathy or myelopathy correlating with the patient’s symptoms. An abnormal neurologic examination includes motor abnormalities, sphincter abnormalities, and/or sensory deficits attributable to a dysfunction of nerve root(s) and/or the spinal cord. Therefore, presence of radiculopathy, myelopathy, or cauda equina syndrome is indicative of an abnormal examination. However, reflex asymmetry and/or presence of pathologic reflexes (Babinsky, Hoffman), as well as sensory deficits of a stocking/glove distribution are excluded as indicators of an abnormal examination. Patients with an abnormal neurologic examination should receive steroids. The dose of steroids may vary (10-100 mg) with a recommended minimum dose of 4 mg of dexamethasone every 6 hours.125 Methylprednisolone can be used instead of dexamethasone. A randomized trial supported the use of high-dose steroids, but it should be tapered within 3 days.126 For patients with rapid neurologic deterioration or patients with significant myelopathy, an urgent noncontrast spinal MRI is recommended. 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.

Radiographic spinal cord compression implies deformation of the spinal cord because of epidural tumor, retropulsed bone fragment, or both.125 It should be noted that epidural tumor may occupy part of the spinal canal with or without partial obliteration of CSF around the spinal cord. Those cases do not qualify as radiographic spinal cord compression, because there is no cord deformation. For tumors occurring below L1, any canal compression of 50% or more should be considered of equal importance as spinal cord compression.

Metastases to the spine without cord compression include the presence of tumor in the vertebral body, pedicle(s), lamina, transverse, or spinous process. It can also include epidural disease (without cord deformation).

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 (see SPINE-2). In the event that no tumor is found on MRI, additional tests can be performed (eg, lumbar puncture if there is suspicion of neoplastic meningitis, electromyelogram/nerve conduction [EMG/NC] studies for paraneoplastic conditions, or appropriate imaging to exclude a plexus tumor).

Because uniform criteria for spinal instability secondary to tumor do not currently exist, a consultation by a surgeon is recommended.127 Spinal instability is grossly defined as the presence of significant kyphosis or subluxation (deformity) or of retropulsed bone fragment. Not every pathologic fracture implies spinal instability. The degree of
Kyphosis or subluxation compatible with instability depends on the location of the tumor in the spine and cannot be defined in absolute terms. The cross-sectional area of the vertebral body unaffected by the tumor and the patient’s bone mineral density are additional factors affecting stability. In addition, vertebral body involvement is more important than dorsal element involvement with regard to stability. Circumferential disease as well as junctional and contiguous tumor location should be taken into account when assessing spinal stability.\textsuperscript{128}

Rapid neurologic deterioration is considered when the patient’s neurologic examination is becoming worse on a daily basis and the patient’s ambulatory status is threatened. This deterioration is particularly important if it occurs when the patient is already on a steroid regimen. Significant myelopathy implies presence of either a sensory level (ie, to pinprick) or loss of ambulatory status or bladder/bowel incontinence. Unknown primary tumor implies a negative workup by the patient’s oncologist. Alternatively, a CT-guided biopsy of the spinal lesion can be performed for diagnostic purposes; however, in the presence of spinal cord compression, decompressive surgery should be considered as the best option for a patient with an unknown primary tumor.

For patients with spinal cord compression, strongly consider surgery if patients have spinal instability, radioresistant tumors (eg, renal carcinoma, melanoma, sarcoma, colon carcinoma), rapid neurologic deterioration, unknown primary, and/or previous RT.\textsuperscript{123,129,130} Category 1 evidence supports the role of surgery for those willing to undergo operation.\textsuperscript{131} Surgery can involve tumor resection with or without spinal stabilization; surgery can be through an anterior, posterior, or a circumferential approach.\textsuperscript{131} Spinal instrumentation is recommended if there is preoperative spinal instability or if instability is expected to occur after tumor resection.\textsuperscript{126} Surgery also includes vertebroplasty/kyphoplasty, especially for patients with multiple myeloma.\textsuperscript{132} It also includes implantation of a subarachnoid pump (morphine pump) for patients with intractable pain who are not candidates for tumor resection or vertebroplasty/kyphoplasty. The “all others” category (see SPINE-2) includes patients with compression but without evidence of spinal instability who have a radiation-sensitive tumor and a stable neurologic examination with a previously established histological diagnosis.\textsuperscript{133} Short RT regimen over 2 weeks or less is given to these patients. Many fractionation schemes have been reported; the most common is a total of 30 Gy in 3-Gy daily fractions for 10 days.\textsuperscript{134} Note that nonambulatory patients with spinal cord compression who receive radiation alone have less chance of regaining their ability to walk than nonambulatory patients who receive surgery and radiation; however, many patients with spinal cord compression are not candidates for surgery.\textsuperscript{135} It is currently unclear whether surgery plus RT is better for selected patients or whether RT for patients with spinal instability produces worse outcomes.\textsuperscript{135}

For patients with multiple myeloma or lymphoma without evidence of spinal cord compression, chemotherapy can be considered in lieu of RT. Patients with slow-growing, symptomatic malignancies (eg,
breast/renal carcinoma) or with solitary spinal metastases (especially if the original tumor has been resected) can alternatively be treated with surgery before RT. The role of newer forms of RT (eg, IMRT, radiosurgery) in the treatment of metastatic spinal tumors needs to be defined, yet they should be considered for patients with recurrent tumors who have undergone prior surgery and conventional RT.

Intractable pain means either that pain is not controlled with oral analgesics or that the patient cannot tolerate the medication because of side effects (see SPINE-2). Intractable pain because of metastatic spinal tumor(s) can be treated by implantation of a subarachnoid pump, tumor resection/stabilization, or vertebroplasty/kyphoplasty depending on stability, extent of disease, and location in the spinal column (see NCCN Cancer Pain Guidelines).126

Disclosures for the NCCN Central Nervous System Guidelines Panel

At the beginning of each panel meeting to develop NCCN guidelines, panel members disclosed the names of companies, foundations, and/or funding agencies from which they received research support; for which they participate in speakers’ bureau, advisory boards; and/or in which they have equity interest or patents. Members of the panel indicated that they have received support from the following: Enzon Pharmaceuticals, MGI Pharma and Schering-Plough. Some panel members do not accept any support from industry. The panel did not regard any potential conflicts of interest as sufficient reason to disallow participation in panel deliberations by any member.
References


73. Wällner KE, Wara WM, Sheline GE, et al. Intracranial ependymomas: Results of treatment with partial or whole brain


133. Siegal T, Siegal T. Surgical management of malignant epidural tumors compressing the spinal cord. In: Schmidek HH. Operative
