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**NCCN Guidelines Panel Disclosures**

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- NCCN Board of Directors
- NCCN Central Nervous System Cancer Sub-Committee Members

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- [List of members]

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## Clinical Trials

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

To find clinical trials online at NCCN member institutions, [click here](nccn.org/clinical_trials/physician.html).

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## Principles of Brain Tumor Therapy

- **Imaging (BRAIN-A)**
- **Surgery (BRAIN-B)**
- **Radiation (BRAIN-C)**
- **Systemic Therapy (BRAIN-D)**
- **Brain and Spinal Cord Tumor Management (BRAIN-E)**

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Updates in Version 1.2011 of the NCCN Guidelines from Version 1.2010 include:

**Global Changes:**
- A new algorithm was developed that provides recommendations for the treatment of Adult Medulloblastoma and Supratentorial PNET. (AMED-1 through AMED-3)
- A new algorithm was developed that provides recommendations for the treatment of Primary Spinal Cord Tumors. (PSCT-1 through PSCT-4)

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

- **ASTR-1**
  - Adjuvant Treatment for “High risk” and “Uncontrolled or progressive symptoms”: “Fractionated external beam RT ± Chemotherapy” changed to “Fractionated external beam RT or Chemotherapy”.

- **ASTR-2**
  - “Prior fractionated external beam RT” pathway; Last column: “Consider changing chemotherapy regimen” was added.
  - Footnote “m” was revised for clarity.

**Anaplastic Gliomas/Glioblastoma**

- **GLIO-2**
  - For anaplastic gliomas: New pathways were added for “Good performance status” and “Poor performance status.”

- **GLIO-3**
  - Under “Adjuvant Treatment” for poor performance status patients:
    - “Fractionated external beam RT” was clarified as “standard or hypofractionated”.
    - “Best supportive care” was listed as an option.
    - Footnote I: Changed to read “Treatment with carmustine wafer, reirradiation, or multiple prior systemic therapies, may impact enrollment in some adjuvant clinical trials.”

**Multiple (>3) Metastatic Lesions**

- **MU-1**
  - The “Known history of cancer” pathway was revised for clarity.
  - Footnote “c” that states, “As part of diagnostic evaluation, neuroimaging modalities such as MRI, DW-MRI, MRI-SPECT, or PET scan may be considered” is new to the algorithm.

**Metastatic Spine Tumors**

- **SPINE-3**
  - Third column was revised for clarity.

**BRAIN-C---Principles of Brain Tumor Radiation Therapy**
- These pages were revised extensively and now includes recommendations and dosing for the new Adult Medulloblastoma/Supratentorial PNET and Primary Spinal Cord Tumors algorithms.

**BRAIN-D---Principles of Brain Tumor Systemic Therapy**
- **Adult Low-Grade Infiltrative Supratentorial Astrocytoma/Oligodendroglioma:**
  - Recurrence, progressive or low grade disease: Footnote for “nitrosourea” that states “Addition of CCNU and procarbazine” was removed.

- **Glioblastoma**
  - Adjuvant Treatment “Concurrent temozolomide” was clarified as “Concurrent (with RT) temozolomide”.
  - Adjuvant temozolomide was clarified as “post RT temozolomide”

- **Primary CNS Lymphoma**
  - Primary Treatment: Single agent high-dose methotrexate or higher in combination with...” was clarified as “High-dose methotrexate or higher as single agent or in combination with...”

- Recurrence or progressive disease: “Consider HDT with stem cell rescue” was clarified as “Consider high-dose chemotherapy with autologous stem cell reinfusion in patients who achieve a complete response with conventional doses of salvage chemotherapy or have no residual disease after re-resection”.

- **Adult Medulloblastoma and Supratentorial PNET--New Section**
  - This is a new section that lists systemic therapy agents and regimens for Adjuvant treatment, Recurrence/Salvage therapy, or patients who have received prior chemotherapy.
Adult Low-Grade Infiltrative Supratentorial Astrocytoma/Oligodendroglioma (Excluding Pilocytic Astrocytoma)

**Radiologic Presentation**
- MRI compatible with primary brain tumor
  - Maximal safe resection feasible
    - Maximal safe resection
    - Fractionated external beam RT or Observe or Chemotherapy
  - Maximal safe resection not feasible
    - Subtotal resection or open biopsy or stereotactic biopsy
    - Fractionated external beam RT or Observe or Chemotherapy
- MRI compatible with primary brain tumor
  - Observation

**Clinical Impression**
- Observation

**Surgery**
- Age > 40 y
  - Low risk
    - Maximal safe resection
    - Fractionated external beam RT or Observe or Chemotherapy
  - High risk
    - Maximal safe resection
    - Fractionated external beam RT or Observe or Chemotherapy

**Adjunctive Treatment**
- Fractionated external beam RT or Observe or Chemotherapy

**Follow-Up**
- MRI every 3-6 mo for 5 y then at least annually
  - See Recurrence (ASTR-2)

- Adjuvant Treatment
  - Fractionated external beam RT or Observe or Chemotherapy

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

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

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

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

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

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

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

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

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

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

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

See Principles of Brain Tumor Systemic Therapy (BRAIN-D).
NCCN Guidelines™ Version 1.2011
Adult Low-Grade Infiltrative Supratentorial Astrocytoma/Oligodendroglioma (Excluding Pilocytic Astrocytoma)

RECURRENT

Prior fractionated external beam RT

Resectable → Surgery → Chemotherapy → Progression

Unresectable → Chemotherapy → Progression

No prior fractionated external beam RT

Resectable → Surgery → Chemotherapy → Progression

Unresectable

Consider changing chemotherapy regimen or reirradiation with conformal RT in select cases, especially if progression free survival is greater than 2 y after prior RT or if new lesion outside target of prior RT or the recurrence is small and geometrically favorable or Best supportive care

Fractionated external beam RT or chemotherapy (category 2B for chemotherapy)

Recurrence or progressive, low-grade disease

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

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

At recurrence, there is a high propensity for these tumors to undergo malignant transformation. Sixty percent or more of astrocytomas and 40%-50% of oligodendrogliomas will eventually undergo transformation to a higher grade.

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

- **MRI suggestive of high-grade glioma**

  - Multidisciplinary input for treatment planning if feasible

  - Maximal safe resection feasible with goal for image-verified complete resection

  - Maximal safe resection 
    ± carmustine (BCNU) wafer (category 2B)

  - MRI

  - Maximal safe resection not feasible

- **Pathology**

  - Anaplastic gliomas

  - Glioblastoma

  

  See Adjuvant Treatment (GLIO-2)

  See Adjuvant Treatment (GLIO-3)

- **Clinical Impression**

  - Multidisciplinary input for treatment planning if feasible

  - Maximal safe resection feasible with goal for image-verified complete resection

  - Maximal safe resection 
    ± carmustine (BCNU) wafer (category 2B)

  - MRI

  - Maximal safe resection not feasible

  - Stereotactic biopsy
  - Open biopsy
  - Subtotal resection
  - MRI after resection

- **Surgery**

  - Anaplastic gliomas

  - Glioblastoma

  

  See Adjuvant Treatment (GLIO-2)

  See Adjuvant Treatment (GLIO-3)

- **Radiologic Presentation**

  - MRI suggestive of high-grade glioma

  - Multidisciplinary input for treatment planning if feasible

  - Maximal safe resection feasible with goal for image-verified complete resection

  - Maximal safe resection 
    ± carmustine (BCNU) wafer (category 2B)

  - MRI

  - Maximal safe resection not feasible

  - Stereotactic biopsy
  - Open biopsy
  - Subtotal resection
  - MRI after resection

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

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**NCCN Guidelines™ Version 1.2011**

**Anaplastic Gliomas/Glioblastoma**

### PATHOLOGY

- **Anaplastic gliomas**  
  Consider 1p19q analysis (category 1 for prognostic marker)

### ADJUVANT TREATMENT

- Good performance status (KPS ≥ 70)
  - Fractionated external beam RT, or chemotherapy, or combined chemoradiation (category 3 off clinical trial, category 2A on trial)

- Poor Performance status (KPS < 70)
  - Fractionated external beam RT (standard or hypofractionated), or chemotherapy, or best supportive care

### FOLLOW-UP

- MRI 2-6 wk after RT, then every 2-4 mo for 2-3 y, then less frequently

---

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

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

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

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

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Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
This pathway includes the classification of mixed anaplastic oligoastrocytoma (AOA), anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), and other rare anaplastic gliomas.

This pathway also includes gliosarcoma.

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

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


Duration of treatment for glioblastomas beyond 6 months is unknown. Duration of therapy for anaplastic astrocytoma is unknown.
This pathway includes the classification of mixed anaplastic oligoastrocytoma (AOA), anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), and other rare anaplastic gliomas.

- **Resection with carmustine wafer, reirradiation, or multiple prior systemic therapies, may impact enrollment in some adjuvant clinical trials.**
- **Consider MR spectroscopy, MR perfusion, or brain PET to rule out radiation necrosis.**
- **Within the first 3 months after completion of RT and concomitant temozolomide, diagnosis of recurrence can be indistinguishable from pseudoprogression on neuroimaging. With pseudoprogression, stabilization or improvement should be expected within 3 mo of the end of radiotherapy.**
- **Anaplastic oligodendroglialomas have been reported to be especially sensitive to chemotherapy. Chemotherapy using temozolomide or nitrosourea-based regimens may be appropriate.**
- **Especially if long interval since prior RT and/or good response to prior RT.**

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**NCCN Guidelines™ Version 1.2011**

**Adult Intracranial Ependymoma** (Excluding Subependymoma and Myxopapillary)

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<th>CLINICAL IMPRESSION</th>
<th>SURGERY^d</th>
<th>PATHOLOGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximal resection feasible^c</td>
<td>Maximal safe resection</td>
<td>Ependymoma or Anaplastic ependymoma</td>
<td>See Adjuvant Treatment (EPEN-2)</td>
</tr>
<tr>
<td>Maximal resection not feasible</td>
<td>Stereotactic biopsy or Open biopsy or Subtotal resection</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

---

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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RADIOLOGIC PRESENTATION^a

- Contrast enhanced MRI/CT compatible with primary brain tumor^b
  - Maximal resection feasible^c
  - Maximal resection not feasible

CLINICAL IMPRESSION

- Maximal safe resection

SURGERY^d

- Stereotactic biopsy or Open biopsy or Subtotal resection

PATHOLOGY

- Ependymoma or Anaplastic ependymoma

---

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PATHOLOGY

Ependymoma, status post maximal safe resection

- Contrast enhanced brain and spine MRI, consider CSF analysis

- Total resection, MRI spine negative, CSF negative

- Subtotal resection, MRI spine negative, CSF negative

- Total or subtotal resection, MRI spine positive or CSF positive

- Limited-field fractionated external beam RT or Observe (if supratentorial)

- Limited-field fractionated external beam RT

- Craniospinal RT

Anaplastic ependymoma, status post maximal resection

- Contrast enhanced brain and spine MRI, CSF analysis

- Total or subtotal resection, MRI spine negative, CSF negative

- Total or subtotal resection, MRI spine negative, CSF positive

- Limited-field fractionated external beam RT

- Craniospinal RT

Ependymoma or Anaplastic ependymoma status post stereotactic or open biopsy or subtotal resection

- Contrast enhanced brain and spine MRI, CSF analysis

- MRI spine negative, CSF negative

- MRI spine positive or CSF positive

- Limited-field fractionated external beam RT

- Craniospinal RT

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

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

See Follow-up and Recurrence (EPEN-3)

Within 24-72 hours:
- Spine MRI should be delayed by at least 2-3 weeks post surgery to avoid post surgical artifacts.
- If MRI spine negative, then lumbar puncture should be done after MRI. Lumbar puncture for CSF should be delayed at least 2 weeks after surgery to avoid possible false positive cytology. Lumbar puncture may be contraindicated (eg, posterior fossa mass).

See Principles of Brain Tumor Radiation Therapy (BRAIN-C).
### NCCN Guidelines™ Version 1.2011

**Adult Intracranial Ependymoma (Excluding Subependymoma and Myxopapillary)**

#### FOLLOW-UP\(^a\)

<table>
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<tr>
<th>Brain and spine MRI (if initially positive) every 3-4 mo for 1 y, then every 6-12 mo</th>
<th>Spine or brain recurrence</th>
<th>MRI of brain and spine and CSF analysis</th>
<th>Progression</th>
</tr>
</thead>
</table>

#### RECURRENCE

- Resection with limited field external beam RT\(^h, i\), if no prior RT\(^h\)
- If unresectable, RT\(^h, i\) if no prior RT\(^h\)

#### CLINICAL STAGING

- MRI of brain and spine and CSF analysis

#### TREATMENT FOR PROGRESSION

- RT\(^h, i\) or Consider re-irradiation or Consider chemotherapy\(^i, k\) or Best supportive care

---

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

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

\(i\) Consider stereotactic radiosurgery (SRS) if geometrically favorable.

\(j\) Chemotherapy should be reserved for patients who are refractory to surgery or radiation.

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

---

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Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
**NCCN Guidelines™ Version 1.2011**
Adult Medulloblastoma and Supratentorial PNET\(^a\)

**RADIOLOGIC PRESENTATION**
- Contrast-enhanced MRI compatible with primary brain tumor\(^c\)

**CLINICAL IMPRESSION**
- Maximal safe resection possible\(^d\)
- Maximal safe resection not possible\(^d\)

**SURGERY**
- Maximal safe resection
- Stereotactic biopsy\(^f\)
or
- Open biopsy or
- Partial resection

---

\(^a\) Excluding pineoblastomas and esthesioneuroblastoma.

\(^b\) See Principles of Brain Tumor Imaging (BRAIN-A).

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

\(^d\) Placement of ventriculoperitoneal (VP) shunt for management of hydrocephalus is acceptable if needed.

\(^e\) See Principles of Brain Tumor Surgery (BRAIN-B).

\(^f\) Strongly recommend referring patient to a brain tumor center to be evaluated for possible further, more complete surgical resection.

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

<table>
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<th>Standard risk for recurrence:</th>
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<td>- Localized brain tumor &lt; 1.5 cm² residual tumor</td>
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<tr>
<td>- No spine metastases and negative CSF</td>
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<tr>
<td>- No disseminated disease</td>
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<table>
<thead>
<tr>
<th>High risk for recurrence:</th>
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<tbody>
<tr>
<td>- Unresectable tumor or residual tumor &gt; 1.5 cm²</td>
</tr>
<tr>
<td>- Disseminated disease within or outside of the neuroaxis</td>
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<tr>
<td>- Large cell/anaplastic medulloblastoma</td>
</tr>
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<td>- Supratentorial PNET</td>
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ADJUVANT TREATMENT

- Craniospinal radiation
- Concurrent chemoRT followed by post-radiation chemotherapy

See Follow-up (AMED-3)

- Craniopinal radiation and post-radiation chemotherapy

---

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

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Excluding pineoblastomas and esthesioneuroblastoma.

Within 24-72 hours.

Spine MRI should be delayed by at least 3 weeks post surgery to avoid post surgical artifacts.

Contrast-enhanced brain and spine MRI CSF analysis


If only biopsy is possible, consider pre-irradiation chemotherapy followed by an attempt at resection.

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

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

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

Recommend a platinum-based chemotherapy regimen such as either of the treatment arms used in the Children’s Oncology Group study referenced in footnote o.
**NCCN Guidelines™ Version 1.2011**
**Adult Medulloblastoma and Supratentorial PNET**

### FOLLOW-UP

<table>
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<th>RECURRENT</th>
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<th>SURGERY</th>
<th>TREATMENT FOR PROGRESSION</th>
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<tbody>
<tr>
<td>Brain MRI every 3 mos and spine MRI every 6 mos for 2 y; then brain MRI every 6 months and spine MRI every year for 3 y; then brain MRI yearly</td>
<td>Recurrent disease</td>
<td>Localized brain recurrence</td>
<td>Chemotherapy and/or Additional radiation, such as stereotactic radiosurgery, after resection or High-dose chemotherapy with autologous stem cell reinfusion</td>
</tr>
<tr>
<td>MRI of brain and spine</td>
<td>CSF analysis</td>
<td>Maximum safe resection</td>
<td></td>
</tr>
<tr>
<td>Bone scan</td>
<td>CT scans of chest, abdomen and pelvis, bone marrow biopsy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disseminated disease</td>
<td>Chemotherapy or Best supportive care, including focal radiation, if indicated</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**Excluding pineoblastomas and esthesioneuroblastoma.**

**See Principles of Brain Tumor Imaging (BRAIN-A).**

**See Principles of Brain Tumor Systemic Therapy (BRAIN-D).**

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

**Consider resection for palliation of symptoms where indicated.**


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

---

**Note:** All recommendations are category 2A unless otherwise indicated.

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

- **MRI** suggestive of lymphoma
  - Biopsy with least invasive approach
    - Hold initiation of steroids, if possible prior to diagnostic procedure
  - Consider CSF sampling, if safe and
    - Consider eye exam; biopsy if exam suggests lymphoma and
    - Brain biopsy if neither CSF nor eye yields diagnosis

- Biopsy not diagnostic of primary CNS lymphoma

- Positive diagnosis of primary CNS lymphoma
  - See Primary Treatment (PCNS-2)

- Other CNS tumor
  - See NCCN Central Nervous System Cancers guidelines
  - Table of Contents

---

*a* If patient is HIV positive, consider highly active cardiac retroviral therapy.

*b* Contrast CT, if patient cannot have MRI.

*c* If stereotatic biopsy is not available refer to a specialized center.

*d* Tissue sampling and CSF should include flow cytometry, CSF cytology, and may consider gene rearrangements.

---

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

**Positive diagnosis of primary CNS lymphoma**
- Initiate steroids
  - Slit lamp eye exam
  - Lumbar puncture (LP) if safe
  - Spine MRI, if symptomatic or positive CSF
  - HIV
  - Platelets, liver function tests
  - CT chest/abdomen/pelvis
  - Bone marrow biopsy (category 2B)
  - Consider testicular ultrasound for men > 60 y (category 2B)
  - Consider body FDG-PET scan if intracranial mass.

**Biopsy not diagnostic of primary CNS lymphoma**
- Prior steroids
  - Discontinue steroids and rebiopsy when disease progresses
- No prior steroids
  - Work-up for other CNS diagnosis or rebiopsy

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

**KPS**
- KPS ≥ 40
- KPS < 40 despite treatment with corticosteroids

**PRIMARY TREATMENT**
- High-dose methotrexate-based regimen ± WBRT after completion of chemotherapy
  - If CSF positive or spinal MRI positive, consider intra-CSF chemotherapy (category 2B)
  - If eye exam positive, intraocular chemotherapy (category 2B) or RT to globe

- WBRT
  - If eye exam positive, RT to globe
  - If LP positive or spinal MRI positive, consider intrathecal chemotherapy + focal spinal RT or Chemotherapy.

**WBRT**
- May increase toxicity, especially in patients > 60 y and may be withheld in the primary setting.

**See Principles of Brain Tumor Systemic Therapy (BRAIN-D).**

**See Principles of Brain Tumor Radiation Therapy (BRAIN-C).**

**Alternative chemotherapy regimens for patients who cannot tolerate methotrexate.**

**KPS may improve dramatically with steroids. Reassess KPS after initial course of steroids for potential change in therapy.**

**Dose adjusted for GFR.**

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

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PROGRESSIVE DISEASE

Prior WBRT

Progressive disease

Prior high-dose methotrexate-based regimen without prior RT

Previous response with long duration (≥ 12 mo)

No response or short duration (< 12 mo)

Reirradiation

Consider high-dose therapy with stem cell rescue (category 2B)

Best supportive care

Re-treat with high-dose methotrexate

Systemic chemotherapy

Consider high-dose therapy with stem cell rescue (category 2B)

Best supportive care

WBRT or involved field RT ± chemotherapy

Consider high-dose therapy with stem cell rescue (category 2B)

Best supportive care

1 See Principles of Brain Tumor Systemic Therapy (BRAIN-D).

0 See Principles of Brain Tumor Radiation Therapy (BRAIN-C).

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
NCCN Guidelines™ Version 1.2011
Primary Spinal Cord Tumors

RADIOLOGIC PRESENTATION

Intradural mass by spine MRI

Intradural intramedullary

MRI well defined/circumscribed

Intradural extramedullary

MRI poorly defined/infiltrative

CLINICAL PRESENTATION

Asymptomatic

Symptomatic

SURGERY

Observation or Maximum safe resection

Maximum safe resection

Observation or Biopsy

Biopsy

See PSCT-3

See PSCT-2

See PSCT-2

Follow-up

Follow-up

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

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

bConsider a multidisciplinary review in treatment planning, before surgery and once pathology is available (See Principles of Brain Tumor Management [BRAIN-E]).

cSee Principles of Brain Tumor Surgery (BRAIN-B).
# Primary Spinal Cord Tumors

## Radiologic Presentation

<table>
<thead>
<tr>
<th>Intradural Intramedullary tumor</th>
<th>MR well defined/circumscribed</th>
<th>Intradural Intramedullary tumor</th>
<th>MRI poorly defined/infiltrative</th>
</tr>
</thead>
</table>

## Pathology

<table>
<thead>
<tr>
<th>Ependymoma</th>
<th>Infiltrative glioma</th>
</tr>
</thead>
</table>

### Ependymoma

See Adult Intracranial Ependymoma (EPEN-1) and (EPEN-2)

### Infiltrative glioma

See Adult Low-Grade Infiltrative Supratentorial Astrocytoma/Oligodendroglioma (ASTRO-1) and Anaplastic gliomas/Glioblastoma (GLIO-1)

## Clinical Presentation

<table>
<thead>
<tr>
<th>Symptomatic</th>
<th>Asymptomatic</th>
</tr>
</thead>
</table>

### Partial resection or biopsy

- Symptomatic: Observation or RT
- Asymptomatic: Observation or RT

### Image verified complete resection

- Symptomatic: Observation
- Asymptomatic: Observation

## Adjuvant Treatment

- Observation
- Observation or RT

## Follow-Up

Follow-up See (PSCT-4)

---

### Low grade glioma

- Symptomatic: Adult Low-Grade Infiltrative Supratentorial Astrocytoma/Oligodendroglioma (ASTRO-1)
- Asymptomatic: See Anaplastic gliomas/Glioblastoma (GLIO-1)

---

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.

---

PSCT-2
Intradural extramedullary

Solitary

or

Multiple
Consider:
- Neurofibromatosis
- Schwannomatosis
- Leptomeningeal metastases
  (See LEPT-1)

Asymptomatic

Symptomatic

Maximum safe resection

- Meningioma
  (See MENI-1)

Other subtypes:
- Peripheral nerve sheath tumor
- Myxopapillary ependymoma

Follow-up
  See (PSCT-4)

RADIOLOGIC PRESENTATION

CLINICAL PRESENTATION

SURGERY

PATHOLOGY

FOLLOW-UP

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.
### Patients managed by:
- Observation
- Maximum safe resection for intradural intramedullary tumor
- Intradural extramedullary tumor

<table>
<thead>
<tr>
<th>FOLLOW-UP&lt;sup&gt;a&lt;/sup&gt;</th>
<th>RECURRENCE</th>
<th>TREATMENT FOR RECURRENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients managed by:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observation</td>
<td></td>
<td>Re-resection</td>
</tr>
<tr>
<td>or</td>
<td></td>
<td>or</td>
</tr>
<tr>
<td>Maximum safe</td>
<td></td>
<td>RT&lt;sup&gt;d&lt;/sup&gt; or re-irradiation (include stereotactic radiotherapy), if surgery not possible or Chemotherapy if further surgery or RT not possible</td>
</tr>
<tr>
<td>resection for</td>
<td></td>
<td></td>
</tr>
<tr>
<td>intradural</td>
<td></td>
<td></td>
</tr>
<tr>
<td>intramedullary tumor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intradural</td>
<td></td>
<td></td>
</tr>
<tr>
<td>extramedullary tumor</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>See Principles of Brain Tumor Imaging (BRAIN-A).
<sup>d</sup>See Principles of Brain Tumor Radiation Therapy (BRAIN-C).
<sup>e</sup>New or worsening symptoms or radiographic progression.
NCCN Guidelines™ Version 1.2011
Meningiomas

PRESENTATION

Radiographic diagnosis:
- Dural-based mass
- Homogenously contrast-enhancing
- Dura-tail
- CSF cleft

Meningioma by radiographic criteria
- or
Possible meningioma
- Consider biopsy/resection
- Consider octreotide scan if diagnostic doubt exists

TREATMENT

Asymptomatic

Small (< 30 mm)
- Observe (preferred)
- or
- Surgery if potential neurologic consequences and if accessible, followed by RT if WHO Grade 3 and consider sub-totally resected WHO Grade 2
- or
- RT if potential neurologic consequences

Large (≥ 30 mm)
- Surgery if accessible, followed by RT if WHO Grade 3; consider RT if incomplete resection and WHO Grade 1/2
- or
- Observe

Symptomatic

Small (< 30 mm)
- Surgery if accessible, followed by RT if WHO Grade 3 or RT

Large (≥ 30 mm)
- Surgery if accessible, followed by RT if WHO Grade 3; consider RT if incomplete resection and WHO Grade 1/2
- or
- RT

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.

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

### Recurrence/Progression

<table>
<thead>
<tr>
<th>Follow-Up</th>
<th>Recurrence/Progression</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO Grade 1 and 2, or unresected meningiomas: MRI at 3, 6, and 12 mo, then every 6-12 mo for 5 y, then every 1-3 y</td>
<td>Recurrent disease</td>
<td>Surgery if accessible</td>
</tr>
<tr>
<td></td>
<td>Not surgically accessible</td>
<td>Further RT possible</td>
</tr>
<tr>
<td></td>
<td>Not surgically accessible</td>
<td>Further RT not possible</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RT primary or Re-irradiation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chemotherapy</td>
</tr>
</tbody>
</table>

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**Notes:**
- WHO Grade 1 = Benign meningioma, WHO Grade 2 = Atypical meningioma, WHO Grade 3 = Malignant (anaplastic) meningioma
- See Principles of Brain Tumor Radiation Therapy (BRAIN-C).
- See Principles of Brain Tumor Systemic Therapy (BRAIN-D).

**Clinical Trials:** NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
**NCCN Guidelines™ Version 1.2011**

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

### CLINICAL PRESENTATION

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

- **Suspected tumor found outside CNS**
  - Biopsy or resection of tumor outside CNS

- **No known history of cancer**
  - **No other readily accessible tumor for biopsy**
  - **Stereotactic or open biopsy/resection**

### WORKUP

- **Known history of cancer**
  - **Chest x-ray/CT**
  - **Abdominal/pelvic CT**
  - **Consider body FDG-PET if 2-3 lesions and no primary found**
  - **Other tests as indicated**

- **No known history of cancer**
  - **If 2-3 lesions and no primary found**

### Notes

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

**Note:** All recommendations are category 2A unless otherwise indicated.

**Clinical Trials:** NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
**NCCN Guidelines™ Version 1.2011**

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

---

**CLINICAL PRESENTATION**

<table>
<thead>
<tr>
<th>Disseminated systemic disease with poor systemic treatment options&lt;sup&gt;c,d&lt;/sup&gt;</th>
<th>WBRT&lt;sup&gt;g&lt;/sup&gt; Consider chemotherapy&lt;sup&gt;h&lt;/sup&gt; (category 2B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newly diagnosed or stable systemic disease or Reasonable systemic treatment options&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Surgical resection, followed by WBRT&lt;sup&gt;f&lt;/sup&gt; (category 1) or stereotactic radiosurgery (SRS) or SRS&lt;sup&gt;g&lt;/sup&gt; + WBRT (category 1 for 1 metastasis) or SRS&lt;sup&gt;f&lt;/sup&gt; alone (category 2A)</td>
</tr>
<tr>
<td>Unresectable</td>
<td>WBRT&lt;sup&gt;g&lt;/sup&gt; and/or SRS</td>
</tr>
</tbody>
</table>

---

<sup>c</sup>Consider surgery to relieve mass effect.

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

<sup>e</sup>The decision to resect a tumor may depend upon the need to establish histologic diagnosis, the size of the lesion, its location, and institutional expertise. For example, smaller (< 2cm), deep, asymptomatic lesions may be considered for treatment with SRS versus larger (> 2 cm), symptomatic lesions that may be more appropriate for surgery. (Ewend MG, Morris DE, Carey LA, Ladha AM, Brem S: Guidelines for the initial management of metastatic brain tumors: role of surgery, radiosurgery, and radiation therapy. J Natl Compr Cancer Netw 2008; 6:505-513.)

<sup>f</sup>See Principles of Brain Tumor Surgery (BRAIN-B).

<sup>g</sup>See Principles of Brain Tumor Radiation Therapy (BRAIN-C).

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

**Note:** All recommendations are category 2A unless otherwise indicated.

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

---

**FOLLOW-UP**a

**RECURRENT**

- **Previous surgery**
  - **Previous WBRT** or **Prior SRS**
  - **1-3 lesions**
    - **Recurrent disease; local site**i
    - **MRI every 3 mo for 1 y then as clinically indicated**
    - **> 3 lesions**
      - **WBRT**g or **Consider chemotherapy**j,k
    - **Recurrent disease; distant brain ± local recurrence**
  - **Surgery or Single dose or fractionated stereotactic RT**g or **WBRT**g or **Consider chemotherapy**j,k
- **Surgery or Single dose or fractionated stereotactic RT**g,l or **Consider chemotherapy**j,k
- **Surgery or Single dose or fractionated stereotactic RT**g or **WBRT**f or **Consider chemotherapy**j,k
- **WBRT**g or **Consider chemotherapy**j,k

**TREATMENT**

- Surgery or Single dose or fractionated stereotactic RT or WBRT or Consider chemotherapy

---

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

---

See Principles of Brain Tumor Imaging (BRAIN-A).
See Principles of Brain Tumor Radiation Therapy (BRAIN-C).
Recurrence on radiograph can be confounded by treatment effects. Strongly consider tumor tissue sampling if there is a high index of suspicion of recurrence.
See Principles of Brain Tumor Systemic Therapy (BRAIN-D).
Local or systemic chemotherapy.
If patient had previous SRS with a good response > 6 mo, then reconsider SRS if imaging supports active tumor and not necrosis.
### Limited (1-3) Metastatic Lesions

**TREATMENT**

<table>
<thead>
<tr>
<th>RECURRENCE</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>No prior WBRT</td>
<td>WBRT(^g) or Best supportive care</td>
</tr>
<tr>
<td>Prior WBRT</td>
<td>Best supportive care or Reirradiation, if prior positive response to RT(^g)</td>
</tr>
</tbody>
</table>

**Systemic disease progression, with limited systemic treatment options**

\(^g\)See Principles of Brain Tumor Radiation Therapy (BRAIN-C).

**Note:** All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
## NCCN Guidelines™ Version 1.2011
### Multiple (>3) Metastatic Lesions

#### CLINICAL PRESENTATION

<table>
<thead>
<tr>
<th>Known history of cancer</th>
<th>No known history of cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple (&gt;3) metastatic lesions on CT or MRI</td>
<td>Chest x-ray/CT, Abdominal/pelvic CT, Consider body FDG-PET if no primary found, Other tests as indicated</td>
</tr>
</tbody>
</table>

#### WORKUP

<table>
<thead>
<tr>
<th>If concern exists regarding diagnosis of CNS lesions</th>
<th>No other readily accessible tumor for biopsy</th>
<th>Stereotactic or open biopsy/resection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stereotactic or open biopsy/resection</td>
<td>Stereotactic or open biopsy/resection</td>
<td>WBRT</td>
</tr>
</tbody>
</table>

#### PRIMARY TREATMENT

- WBRT

---

**Note:** All recommendations are category 2A unless otherwise indicated.

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

---

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

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

*c As part of diagnostic evaluation, neuroimaging modalities such as MRI, DW-MRI, MRI-SPECT, or PET scan may be considered.

*d Consider surgery to relieve mass effect.

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

*f SRS should only be considered in selected cases (eg, limited number of lesions).
**NCCN Guidelines™ Version 1.2011**

**Multiple (>3) Metastatic Lesions**

---

**FOLLOW-UP**

MRI every 3 mo for 1 y, then as clinically indicated  →  Recurrent disease

**RECURRENCE**

Systemic disease progression, with limited systemic treatment options  →  Best supportive care or Reirradiation

Stable systemic disease or reasonable systemic treatment options  →  Surgery or Reirradiation or Chemotherapy

---

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

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

*g See Principles of Brain Tumor Systemic Therapy (BRAIN-D).

**Note:** All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
**NCCN Guidelines™ Version 1.2011**  
Leptomeningeal Metastases

<table>
<thead>
<tr>
<th>WORKUP</th>
<th>DIAGNOSIS</th>
<th>RISK STATUS</th>
</tr>
</thead>
</table>
| • Physical exam with careful neurologic evaluation  
• Brain and spine MRI if patient is a candidate for radiotherapy and/or intra-CSF chemotherapy  
• CSF exam | CSF positive for tumor cells or Positive radiologic findings with supportive clinical findings  
or Signs and symptoms with suggestive CSF in a patient known to have a malignancy | Poor risk:
• Low Karnofsky performance status (KPS)  
• Multiple, serious, major neurologic deficits  
• Extensive systemic disease with few treatment options  
• Bulky CNS disease  
• Encephalopathy |
| | | Good risk:
• High KPS  
• No major neurologic deficits  
• Minimal systemic disease  
• Reasonable systemic treatment options, if needed |

**Discussion**

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.

---

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

*b* Intra-CSF chemotherapy includes intrathecal (intralumbar) and intraventricular (intra-Ommaya).

*c* Caution is indicated in patients who are anticoagulated, thrombocytopenic, or who have a bulky intra-cranial mass.

*d* With all malignancies, send for a cell count, differential (including hematopathology review), glucose, and protein. With lymphoma, add flow cytometry. With malignancies other than lymphoma, add cytopathology.

*e* For solid malignancies, CSF analysis utilizes cytopathology. For hematologic malignancies, use flow cytometry.

*f* Suggestive CSF includes high WBC, low glucose, and high protein. If CSF is not positive for tumor cells, a second lumbar puncture is sometimes helpful.

*g* Patients with exceptionally chemosensitive tumors (e.g., small cell lung cancer, lymphoma) may be treated.
### NCCN Guidelines™ Version 1.2011
Leptomeningeal Metastases

#### RISK STATUS

<table>
<thead>
<tr>
<th>Poor risk&lt;sup&gt;g&lt;/sup&gt;</th>
<th>Good risk:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low KPS</td>
<td>High KPS</td>
</tr>
<tr>
<td>Multiple, serious, major neurologic deficits</td>
<td>No major neurologic deficits</td>
</tr>
<tr>
<td>Extensive systemic disease with few treatment options</td>
<td>Minimal systemic disease</td>
</tr>
<tr>
<td>Bulky CNS disease</td>
<td>Reasonable systemic treatment options, if needed</td>
</tr>
</tbody>
</table>

#### TREATMENT

<table>
<thead>
<tr>
<th>Poor risk&lt;sup&gt;g&lt;/sup&gt;</th>
<th>Good risk:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consider fractionated external beam RT&lt;sup&gt;h&lt;/sup&gt; to symptomatic sites&lt;sup&gt;i&lt;/sup&gt; and Best supportive care</td>
<td>Involved field RT&lt;sup&gt;h&lt;/sup&gt; to bulky disease, symptomatic sites</td>
</tr>
<tr>
<td></td>
<td>Consider placing ventricular catheter and subcutaneous reservoir</td>
</tr>
</tbody>
</table>

<sup>g</sup>Patients with exceptionally chemosensitive tumors (eg, SCLC, lymphoma) may be treated.

<sup>h</sup>See Principles of Brain Tumor Radiation Therapy (BRAIN-C).

<sup>i</sup>Usually WBRT and/or partial spine field recommended.

**Note:** All recommendations are category 2A unless otherwise indicated.

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

**PRIMARY TREATMENT**

- **Normal flow**
  - Strongly consider CSF flow scan
  - Flow abnormalities

- **Flow abnormalities**
  - Fractionated external beam RT\(^h\) to sites of involvement\(^k\)

- **Induction intra-CSF chemotherapy\(^i,j\)**
  - for 4-6 wk, if otherwise stable disease
  - or High-dose methotrexate (if breast or lymphoma)
  - or Craniospinal irradiation (CSI) (if breast or lymphoma)

- Reassess CSF from site where CSF cytology was originally positive; if CSF cytology was originally negative reassess from a different site

- Repeat CSF flow scan

**See CSF cytology negative (LEPT-4)**

**See CSF cytology positive (LEPT-4)**

**See pathway for normal flow, above**

**See Treatment for poor risk (LEPT-2)**

---

\(^h\) See Principles of Brain Tumor Radiation Therapy (BRAIN-C).

\(^k\) Usually WBRT and/or partial spine field recommended.

\(^i\) See Principles of Brain Tumor Systemic Therapy (BRAIN-D).

\(^j\) Induction intra-CSF chemotherapy can start with radiation (concomitant) or high-dose methotrexate for lymphoma or CSI.

**Note:** All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
CSF cytology negative → Continue induction intra-CSF chemotherapy \( ^{ij} \) for 1 mo → Maintenance intrathecal chemotherapy\(^ {1} \) 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

Evidence of clinical or radiologic progression of leptomeningeal disease

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

RT\(^ {h} \) to symptom sites or Chemotherapy\(^ {1} \) or Best supportive care

Negative cytology

Continue induction intra-CSF chemotherapy\(^ {1} \) for 4 wk or Consider switching intra-CSF drugs and treat for 4 wks before re-testing CSF

Consider switching intra-CSF drug

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.

\(^ {h} \) See Principles of Brain Tumor Radiation Therapy (BRAIN-C).

\(^ {1} \) See Principles of Brain Tumor Systemic Therapy (BRAIN-D).

\(^ {i} \) Induction intra-CSF chemotherapy can start with radiation (concomitant) or high-dose methotrexate for lymphoma or CSI.
Patient diagnosed with cancer or patient with newly discovered abnormality suspicious for spine metastasis

**PRESENTATION**
- Asymptomatic (Incidental finding)
- Symptomatic: Severe, new or progressive pain or neurologic symptoms

**WORKUP**
- Systemic imaging: (ie, PET, CT, MRI, bone scan)
- Biopsy if it alters management
- Observation (periodic repeat imaging)
- Surgery/focal RT or chemotherapy are options for patients with asymptomatic epidural disease

**TREATMENT**
- Spinal MRI (urgent in the event of neurologic symptoms)
- Spinal cord compression
- No spinal cord compression
- No tumor

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**a** Biopsy if remote history of cancer.

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

**c** 15-20% of patients have additional lesions. Highly recommend complete spine imaging.

**d** Includes cauda equina syndrome.
**PRESENTATION**

No tumor

Spinal cord compression

No spinal cord compression

<table>
<thead>
<tr>
<th>Fracture or spinal instability</th>
<th>Steroids</th>
<th>Surgical stabilization</th>
<th>Vertebral augmentation</th>
<th>Followed by RT</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>No fracture or spinal instability</th>
<th>RT (preferred)</th>
<th>Chemotherapy (if chemosensitive tumor)</th>
<th>Surgery (selective cases) followed by RT</th>
<th>Consider surgery or stereotactic radiotherapy if:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Deterioration during RT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Intractable pain</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Tumor progression</td>
</tr>
</tbody>
</table>

**TREATMENT**

Evaluate for other causes of pain and/or neurologic symptoms

Surgery followed by RT (preferred) or Primary RT

In the absence of clinical myelopathy, primary chemotherapy if chemosensitive tumor (eg, lymphoma, germ cell tumor, myeloma)

Surgery followed by RT (preferred)

Primary RT

Chemotherapy (if chemosensitive tumor)

Surgery (selective cases) followed by RT

**ADJUVANT TREATMENT**

Followed by RT

**Note:** All recommendations are category 2A unless otherwise indicated.

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

### FOLLOW-UP

**PRESENTATION**

(Symptom or MRI based)

**TREATMENT FOR RECURRENCE OR PROGRESSIVE DISEASE**

<table>
<thead>
<tr>
<th>MRI/CT</th>
<th>Progressive disease or Recurrent disease</th>
<th>If previously treated with:</th>
<th>Consider surgery(^j) Consider re-irradiation if recurrent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3 mo after treatment, then every 3-6 mo as clinically indicated</td>
<td>If previously treated with: RT or Surgery and RT</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>If previously treated with: Chemotherapy</td>
<td>Consider RT(^k)</td>
<td></td>
</tr>
</tbody>
</table>

\(^j\)See Principles of Brain Tumor Surgery (BRAIN-B).

\(^k\)See Principles of Brain Tumor Radiation Therapy (BRAIN-C).

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Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
**PRINCIPLES OF BRAIN TUMOR IMAGING**

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

- **Enhanced CT of the brain and spine:**
  - Should be used in patients who cannot have an MRI
  - Benefits: Claustrophobia or implantable devices are not an issue, can be done faster than an MRI
  - Limitations: Lacks resolution of MRI, especially in posterior fossa

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

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

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

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

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### PRINCIPLES OF BRAIN TUMOR SURGERY

#### GUIDING PRINCIPLES
- Maximal tumor removal when appropriate
- Minimal surgical morbidity
- Accurate diagnosis

#### FACTORS
- Age
- Performance status (PS)
- Feasibility of decreasing the mass effect with surgery
- Resectability, including number of lesions, location of lesions, time since last surgery (recurrent patients)
- New versus recurrent tumor
- Suspected pathology – benign vs. malignant, possibility of other non-cancer diagnoses, projected natural history

#### OPTIONS
- Gross total resection where feasible
- Stereotactic biopsy
- Open biopsy/debulking followed by planned observation or adjuvant therapy

#### TISSUE
- Maximum to pathologist
- Frozen section analysis when possible to help with intraoperative decision making
- Review by experienced neuropathologist

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

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

Ependymoma
- Limited Fields: Tumor volumes are best defined using pre- and postoperative imaging, usually enhanced T1 and or FLAIR/T2. Anatomic areas touched by preoperative tumor volume plus postoperative signal abnormality on MRI for GTV. CTV (GTV plus 1-2 cm margin) should receive 54-59.4 Gy in 1.8 to 2.0 Gy fractions.
- Craniospinal: Whole brain and spine (to bottom of thecal sac) receive 36 Gy in 1.8 Gy fractions, followed by limited field to spine lesions to 45 Gy. Primary brain site should receive total dose of 54-59.4 Gy in 1.8 to 2.0 Gy fractions.

High Grade Gliomas (Grades III/IV)
- Tumor volume is best defined using pre- and postoperative imaging, by enhanced T1 or FLAIR/T2 when suspicious for tumor rather than edema. The GTV is expanded by 2-3 cm (CTV) to account for sub-diagnostic tumor infiltration. Fields are usually shrunk for the last phase of the treatment (boost). While this is the practice in some institutions (ie, MDACC and UCSF), many follow guidelines from RTOG protocols. There, the initial tumor volume, GTV1, includes any FLAIR or T2 signal abnormality. A CTV expansion of 2cm is applied. Fields are shrunk to GTV2 to exclude likely edema.
- The recommended dose is 60 Gy in 1.8 to 2.0 Gy fractions. A slightly lower dose, 55-57 Gy, can be applied when the tumor volume is very large (gliomatosis) or for Grade III astrocytoma.
- In poorly performing patients or the elderly a hypofractionated accelerated course was found to be effective with the goal of completing the treatment in 3-4 weeks. Total doses vary between 40-50 Gy.

Brain Metastases
- Whole brain radiotherapy (WBRT): Doses vary between 20 and 40 Gy delivered in 5-20 fractions. The standard regimens include 30 Gy in 10 fractions or 37.5 Gy in 15 fractions. Nevertheless 20 Gy in 5 fractions is a good option in poor performers.1
- Stereotactic radiosurgery: Recommend maximum marginal doses of 24, 18, or 15 Gy according to tumor volume is recommended (RTOG 90-05). 2,3

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

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**PRINCIPLES OF BRAIN TUMOR RADIATION THERAPY**

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

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

### Meningiomas
- WHO grade 1 and 2 meningiomas may be treated by fractionated conformal radiotherapy with doses of 45-54 Gy.
- WHO grade 3 meningiomas should be treated as malignant tumors with tumor bed and gross tumor + a margin (2-3 cm) receiving 54-60 Gy in 1.8-2 Gy fractions.
- Small WHO grade 1 meningiomas may also be treated with stereotactic radiosurgery doses of 12-15 Gy in a single fraction.

### Adult Medulloblastoma and Supratentorial PNET:
- Craniospinal radiation:
  - Standard risk for recurrence: 30-36 Gy with boosting primary brain site* to 55.8 Gy
    - OR
    - Craniospinal radiation 23.4 Gy with boosting primary brain site to 55.8 Gy
  - High risk for recurrence: 36 Gy with boosting primary brain site* to 55.8 Gy†

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

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**References on next page**
NCCN Guidelines™ Version 1.2011
Central Nervous System Cancers

PRINCIPLES OF BRAIN TUMOR RADIATION THERAPY
(References)


### PRINCIPLES OF BRAIN AND SPINAL CORD TUMOR SYSTEMIC THERAPY

#### Adult Low-Grade Infiltrative Supratentorial Astrocytoma/Oligodendroglioma (excluding pilocytic astrocytoma)
- **Adjuvant Treatment:**
  - Temozolomide 150-200 mg/m² 5/28 schedule
- **Recurrent or Progressive, Low grade disease:**
  - Temozolomide 5/28 schedule
  - Nitrosourea
  - Combination PCV (CCNU + procarbazine + vincristine)
  - Platinum based regimens

#### Adult Intracranial Ependymoma (excluding subependymoma and myxopapillary)
- **Recurrence**
  - Platinum-based regimens: Single agent or combination
  - Etoposide
  - Nitrosourea
  - Bevacizumab

#### Glioblastoma
- **Adjuvant Treatment:**
  - Temozolomide or PCV with deferred RT
- **Recurrence**
  - Temozolomide
  - Nitrosourea
  - Combination PCV
  - Bevacizumab
  - Bevacizumab + chemotherapy
  - Platinum-based regimens
  - Etoposide

### Anaplastic Gliomas
- **Adjuvant Treatment:**
  - Temozolomide or PCV with deferred RT
- **Recurrence/Salvage therapy**
  - Temozolomide
  - Nitrosourea
  - Combination PCV
  - Bevacizumab
  - Bevacizumab + chemotherapy
  - Platinum-based regimens

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

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*For patients not previously treated.

α Platinum-based regimens include cisplatin or carboplatin.

†† Discontinuation of bevacizumab after progression may be associated with rapid neurological deterioration and bevacizumab may be continued in these circumstances.
**PRINCIPLES OF BRAIN AND SPINAL CORD TUMOR SYSTEMIC THERAPY**

### Leptomeningeal Metastases
- **Treatment**
  - Organ specific systemic chemotherapy; emphasizing drugs with good CNS penetration
  - Intra-CSF chemotherapy\(^3\) (liposomal cytarabine,\(^3\) methotrexate,\(^4\) cytarabine, thiotepa, rituximab\(^5\))
  - High-dose methotrexate for lymphomatous meningitis\(^6\)

### Primary CNS Lymphoma
- **Primary Treatment**
  - High dose methotrexate 3.5 g/m\(^2\) or higher as single agent or in combination\(^7\),\(^8\) with:
    - Vincristine
    - Procarbazine
    - Cytarabine\(^9\)
    - Rituximab

- **Recurrence or Progressive Disease**
  - Retreat with high-dose methotrexate
  - Temozolomide
  - Rituximab ± temozolomide\(^10\)
  - Topotecan
  - Consider high-dose chemotherapy with autologous stem cell reinfusion in patients who achieve a complete response with conventional doses of salvage chemotherapy or have no residual disease after re-resection
  - High-dose ARA-C\(^11\)

### Meningiomas
- **Treatment**
  - Hydroxyurea
  - Alpha-interferon\(^12\)
  - Somatostatin analogue\(^13\)

### Adult Medulloblastoma and Supratentorial PNET
- **Adjuvant Treatment**
  - Weekly vincristine\(^\circ\) during craniospinal radiation therapy followed by either of the following regimens:
    - Cisplatin, cyclophosphamide, and vincristine\(^14,\circ\)
    - Cisplatin, lomustine, and vincristine\(^14,\circ\)
  - Recurrence/Salvage therapy
    - No prior chemotherapy
      - High-dose cyclophosphamide ± etoposide
      - Carboplatin, etoposide, and cyclophosphamide
      - Cisplatin, etoposide, and cyclophosphamide
    - High-dose chemotherapy with autologous stem cell reinfusion\(^16\) in patients who achieve a complete response with conventional doses of salvage chemotherapy or have no residual disease after re-resection
  - Prior chemotherapy
    - High dose cyclophosphamide ± etoposide
    - Oral etoposide\(^17,18\)
    - Temozolomide\(^19\) ± 13-cis retinoic acid
    - High-dose chemotherapy with autologous stem cell reinfusion\(^16\) in patients who achieve a complete response with conventional doses of salvage chemotherapy or have no residual disease after re-resection

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

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\(^\circ\)Use agents active against primary tumor.

\(^\circ\)Other combinations with methotrexate may be used.

\(^\circ\)Omission of vincristine during radiotherapy phase of therapy or dose modification may be required for adults because they do not tolerate this regimen as well.

Data supporting vincristine’s use have been found in pediatric trials only. Patients should be closely monitored for neurologic toxicity with periodic exams.
PRINCIPLES OF BRAIN AND SPINAL CORD TUMOR SYSTEMIC THERAPY (References)


**PRINCIPLES OF BRAIN AND SPINAL CORD TUMOR SYSTEMIC THERAPY**

*References*


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


PRINCIPLES OF BRAIN TUMOR MANAGEMENT

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

Multidisciplinary Care

- During the course of their treatment, most patients will be seen by physicians from more than one specialty. Where possible, use of a local brain tumor board, or multidisciplinary clinic facilitates these interactions and allows for input from each of the major neuro-oncology disciplines, as well as allied services (Physical/Occupational Therapy, Social Work, Psychology) when available, in formulating a plan of care for the patient. When not possible in a single clinic or institution, close and regular communication between the various disciplines involved becomes essential.
- As treatment proceeds, it is important that the patient and family understand the role of each team member. One practitioner should be identified early on as the main point of contact for follow-up care questions. This individual can facilitate referral to the appropriate specialist.
- Offering patients the option of participation in a clinical trial is strongly encouraged. Practitioners should discuss any local, regional and national options for which the patient may be eligible and the advantages and disadvantages of participation. Centers treating neuro-oncology patients are encouraged to participate in large collaborative trials in order to have local options to offer patients.
- As the patient's treatment unfolds, their quality of life is the highest priority and should guide clinical decisions. While responses on imaging are benchmarks of successive therapy, other indicators of success such as overall well being, function in day-to-day activities, social and family interactions, nutrition, pain control, long term consequences of treatment, and psychological issues must be considered.
PRINCIPLES OF BRAIN TUMOR MANAGEMENT

1. Corticosteroids

- Steroid therapy should be carefully monitored. If a patient is asymptomatic, steroids may be unnecessary. Careful questioning for subtle symptoms should be undertaken if edema is extensive on imaging. In general, the lowest dose of steroids should be used for the shortest time possible.\(^2\) Downward titration of the dose should be attempted whenever possible. Patients with extensive mass effect should receive steroids for at least 24h before radiation therapy. Patients with high risk of GI side effects (perioperative patients, prior history of ulcers/GI bleed, receiving NSAIDS or anticoagulation) should receive H\(_2\) blockers or proton pump inhibitors. Care should be taken to watch for development of steroid side effects.\(^3\)

2. Antiepileptic Drugs (AED's)

- Seizures are frequent in patients with primary or metastatic brain tumors. Despite this, studies have shown that the use of older, “traditional” antiepileptic drugs (AED's) including phenytoin, phenobarbital and valproic acid as prophylaxis against seizures in patients who have never had a seizure or who are undergoing neurosurgical procedures is ineffective, and is not recommended. Newer agents (levetiracetam, topiramate, lamotrigine, pregabalin) have not yet been systematically studied. Seizure prophylaxis is not recommended as routine in asymptomatic patients.

- Many AED’s have significant effects on the cytochrome P450 system, and may have effects on the metabolism of numerous chemotherapeutic agents such as irinotecan, gefitinib, erlotinib, temsirolimus among others). Where possible, such enzyme inducing AED's (EIAED's) should be avoided (phenytoin, phenobarbital, carbamazepine), and nonEIAED’s should be used instead (levetiracetam, topiramate, valproic acid). Patients should be closely monitored for any adverse effects of the AED’s or chemotherapeutic agents.

3. Endocrine disorders

- Endocrinopathies are common with brain tumor patients. This may be affected by concomitant steroid use as well as radiotherapy, surgery, and certain medical therapies. Patients who present with a declining sense of well being or quality of life should be evaluated not only for abnormalities related to their hypothalamic pituitary and adrenal axis, but also with regard to thyroid and gonad function.

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

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

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

\(^3\)Refractory hyperglycemia, skin changes, visual changes, fluid retention, and myopathy. If any of these changes occur, it is imperative to evaluate potential palliative treatments for them and also to evaluate the current dose of steroids to see if it can be reduced in an attempt to mitigate these side effects.
5. Psychiatric disorders (Also see the NCCN Distress Management Guidelines)

- Depression is common in brain tumor patients. These symptoms are greater than simple sadness or anxiety associated with the diagnosis of a tumor. The vegetative symptoms associated with depression or severe anxiety may become very disabling for the patient and distressing for the family. These symptoms will respond to psychotropic medications as they do in non-tumor patients. If less severe, strong support from behavioral health allies and other qualified counselors is also extremely beneficial. Physicians, and other members of their healthcare teams, should be sensitive to these symptoms and inquire about them in follow-up visits in order to determine if the patient may be a candidate for psychological or psychiatric treatment. Communication between members of the patient’s health care team regarding the patient’s response to treatment is important.

- Antiepileptic drugs, anxiolytics, some chemotherapy agents, antiemetics and other agents used directly in cancer therapy may affect mental status, alertness and mood. Alterations in thought processes should trigger an investigation for any reversible causes, including endocrine disorders, infection, side effects of medication or tumor progression.

6. Venous thromboembolism (VTE)

- See the NCCN Venous Thromboembolic Disease Guidelines.

Allied Services

- Physical therapy, occupational therapy, and speech therapy may be helpful for many patients with CNS tumors, either benign or malignant. Surgical intervention is not a pre-requisite for referral, and these therapies should not be withheld from patients because of the uncertain course of certain malignant tumors. Many patients with aggressive, malignant primary brain tumors or CNS metastases can benefit from inpatient rehabilitation.

- Practitioners are encouraged to serve as a resource for referrals to social service, tumor support, and educational agencies for their patients. Institutional or community resources that can assist patients and families in dealing with financial, insurance, and legal issues are important.

- Practitioners should be familiar with their state laws concerning seizures and driving so that they can advise patients and families appropriately.

- Practitioners should become familiar with palliative and hospice care resources that are available in their community in order to help educate patients and families that involvement of these services does not indicate a state of hopelessness, of no further treatment or abandonment.
Primary and metastatic brain tumors are a heterogeneous group of neoplasms with varied outcomes and management strategies. Primary brain tumors range from pilocytic astrocytomas (which are very uncommon, noninvasive, and surgically curable) to glioblastoma multiforme, the most common intraparenchymal brain tumor in adults, which is highly invasive and virtually incurable. Likewise, patients with metastatic brain disease may have rapidly progressive systemic disease or no systemic cancer at all. These patients may have one or dozens of brain metastases, and they may have a malignancy that is highly responsive or, alternatively, highly resistant to radiation or chemotherapy. Because of this marked heterogeneity, the prognostic features and treatment options for brain tumors must be carefully reviewed 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.

Overview
In the year 2008, an estimated 21,810 new cases of primary brain and other nervous system neoplasms will be diagnosed in the United States. These tumors will be responsible for approximately 13,070 deaths. The incidence of primary malignant brain tumors has been increasing over the last 30 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.
The surgical options include stereotactic biopsy, open biopsy or debulking procedure, subtotal resection, or gross total tumor resection where feasible. The pathologic diagnosis is critical and often difficult to determine accurately; therefore, as much tissue as possible should be delivered to the pathologist. Review by an experienced neuropathologist is highly recommended. In addition, a postoperative magnetic resonance imaging (MRI) scan, with and without contrast, should be obtained 24 to 72 hours after surgery to document the extent of disease after surgical intervention.

Radiation oncologists use several different treatment approaches in patients with primary brain tumors, including brachytherapy, stereotactic fractionated RT, and stereotactic radiosurgery. Fractionated external beam radiation is the most common approach. RT for patients with primary brain tumors usually involves only the tumor volume and margins. Clinical target volume is commonly defined as the region showing T2-weighted abnormalities on an MRI scan plus a 1 to 2 cm margin. The dose of radiation administered varies depending on the pathology.

**Tumor types**

The NCCN CNS Cancer Guidelines focus on high-grade invasive astrocytomas (including glioblastoma multiforme), 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.

**Anaplastic Gliomas and Glioblastomas**

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. The high-grade astrocytomas diffusely infiltrate surrounding tissues and frequently cross the midline to involve the contralateral brain. Patients with these neoplasms often present with symptoms of increased intracranial pressure, seizures, or focal neurologic findings related to the size and location of the tumor and 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.4
### 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.

Fractionated external beam RT is standard therapy for patients with high-grade astrocytomas after either maximal excision or biopsy. Use of RT is 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. Total doses of 54-60 Gy (in 1.8 to 2.0 Gy fractions) are administered to the gross tumor volume (GTV2). Use of abbreviated courses of radiation in older patients may be considered but has not been studied in combination with modern chemotherapy. Alternative dose-fractionation schedules have been explored without significant improvement 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.

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 2 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 either to radiation alone or to 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, 2 meta-analyses reviewed data from randomized trials of high-grade glioma patients, and both found a modest survival benefit when chemotherapy was added to postoperative radiation. Specifically, in the 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.¹⁴

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 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.¹⁶ 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.¹⁷ MGMT (a DNA repair enzyme) may cause resistance to DNA-alkylating drugs commonly used in the treatment of anaplastic oligodendrogliomas and other malignant gliomas.¹⁸ Note that side effects for temozolomide include nausea, vomiting, headaches, fatigue, and anorexia. Prophylaxis against Pneumocystis carinii pneumonia (PCP) is required when temozolomide is administered with radiotherapy. In elderly patients with glioblastoma multiforme, temozolomide alone may be useful to avoid side effects with RT (for example, excessive fatigue and frequent worsening of neurologic deficits).¹⁹ However, in elderly patients with good PS, adjuvant chemotherapy and RT may be useful.²⁰

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.²¹ 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.²² Additionally, the Medical Research Council study (2001) previously discussed found no improvement in survival when patients with anaplastic astrocytomas were treated with PCV.¹³ 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 (9813); however, no results have been reported yet. Given the better side-effect profile of temozolomide and the 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.¹⁶ 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, platinum-based regimens, or combination PCV.²³, ²⁴ 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.\textsuperscript{25} Bevacizumab with irinotecan was recently shown to be useful for recurrent glioblastoma multiforme in a phase II trial; overall survival at 6 months was 77\%.\textsuperscript{26}

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.\textsuperscript{27} 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.\textsuperscript{28} 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.\textsuperscript{29} This benefit was maintained 2 and 3 years after implantation.\textsuperscript{28-30} 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,\textsuperscript{31-34} such as irinotecan\textsuperscript{35} and paclitaxel.\textsuperscript{36} 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 (including mixed anaplastic oligoastrocytomas) 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; subtotal resection is done if maximal safe resection is not feasible. 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 or subtotal resection should be performed to establish the diagnosis.

After surgical intervention, patients can be treated with or without BCNU wafer followed by fractionated external beam RT with or without chemotherapy (category 1 for anaplastic oligodendroglioma and category 2B for anaplastic astrocytoma). For anaplastic oligodendroglioma, there are 2 randomized trials that show that adjuvant PCV chemotherapy prolonged progression free survival in patients with combined 1p19q deletions.\textsuperscript{37, 38} For patients with good PS who have glioblastoma multiforme, a high level of evidence supports the use of daily temozolomide (75 mg/m\(^2\)) 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. 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. Temozolomide or nitrosourea-based chemotherapy regimens may be appropriate. Thus, testing for 1p19q markers can be done if available. 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 fractionated external beam RT. Because RT can produce additional blood-brain barrier dysfunction, corticosteroid requirements may actually increase; therefore, scans may appear worse during the first 3 months after completion of RT, even though there is no actual tumor progression. Early MRI scans allow for appropriate titration of corticosteroid doses, depending on the extent of mass effect and brain edema. Later scans are used to identify tumor recurrence. Early detection of recurrence is warranted, because local and systemic treatment options are available for patients with recurrent disease. However, MR spectroscopy, MR perfusion, or PET can be considered to rule out radiation necrosis.

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. If the local recurrence is unresectable or surgery is deemed too risky, systemic chemotherapy (using temozolomide or nitrosourea-based regimens) can be administered or reirradiation can be considered. 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 2 consecutive agents have failed to produce a response.

**Low-Grade Infiltrative 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 fractionated external beam 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 oligoastrocytomas. 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.49

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.48 Third, a large tumor burden is removed, which also may enhance the effect of RT. As a result of these considerations, the general recommendation for treating an astrocytoma is to first attempt as complete an excision of tumor as possible without compromising function.

No consensus exists regarding the proper timing of postoperative radiation in low-grade astrocytomas. Some oncologists advocate immediate fractionated external beam 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.43 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.46 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.50 Recent followup of these patients showed that overall survival was not increased in patients who had received early radiotherapy (7.4 versus 7.2 years); however, seizures were controlled better in these patients.51 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 deferred, regular follow-up is essential for patients receiving observation alone after resection.

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, because these tumors enhance weakly or not at all. The clinical target volume is defined by the T2-weighted tumor with a 1-2 cm margin. Every attempt should be made to decrease the radiation dose outside the target volume. Therefore, the use of only 2 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 3-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 45 to 54 Gy, delivered in 1.8 to 2.0 Gy fractions. The selection of 45 to 54 Gy as the standard dose range is based on its relative safety when applied to a limited volume of the brain and on the lack of evidence for increased efficacy with higher doses.52, 53 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.54 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 NCCCTG (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, temozolomide is an option (category 2B) in the treatment of low-grade gliomas; several agents (including temozolomide) are options at recurrence. The RTOG conducted a clinical trial (9802) 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. Preliminary results show that there was no increase in overall survival when adding PCV to RT.

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 fractionated external beam RT is also an option for patients in this age group who have had complete excision. Chemotherapy can be considered (category 2B). 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 stereotactic biopsy, open biopsy, or subtotal excision are more likely to be treated with immediate fractionated external beam 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 fractionated external beam RT are other options.

Patients should be followed using MRI every 3 to 6 months for 5 years and then at least annually. At the time of recurrence, surgery is recommended for resectable lesions followed by chemotherapy if patients have previously had fractionated external beam RT. Reirradiation can follow chemotherapy, 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. Surgery can be followed by radiation, if it was not previously administered, or chemotherapy (category 2B for 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. 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. 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. 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. 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 2 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; 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 or using high-dose versus low-dose radiation. 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. In both the EORTC trial and the intergroup randomized study, no benefit of the high-dose RT compared to the low-dose RT delivered in identical fractionation was
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noted. However, more toxicity in the higher dose arm was documented. Therefore, the current recommended doses for low-grade oligodendrogliomas are in the range of 45 to 54 Gy (in 1.8-2.0 Gy fractions). Delay of radiation for tumors in noneloquent regions and for small asymptomatic tumors in eloquent regions is a viable option based on current information. Because of the improved outcomes with the availability of improved mapping and surgical navigation techniques, an interdisciplinary approach 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. Therefore, chemotherapy is an option (category 2B) in these patients.

In the treatment algorithm for newly diagnosed low-grade oligodendrogliomas, recommendations include postoperative fractionated external beam RT, 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 showed there was no difference in median survival between patients who received PCV before radiation and those who received radiation alone. A phase III trial from the EORTC found similar results. However, patients with tumors demonstrating the 1p19q deletions lived longer with PCV plus RT treatment (7 versus 2.8 years, \( P \leq .001 \)) in the intergroup study, but this was not statistically significant in the EORTC study (40.3 versus 30.6 months, \( P = .23 \)). The RTOG conducted a phase II study (RTOG 0131) 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. Patients with 1p19q deletions who were treated with temozolomide and RT had better survival than those without the deletions. 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.

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 is recommended for adjuvant treatment. 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 study found that temozolomide was effective in patients with progressive low-grade oligodendrogliomas; 51% of patients improved, especially those with uncontrolled epilepsy.

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.

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. The uncertain implication of high histologic grade (or anaplastic ependymoma) similarly favors the use of local fields. Based on dose-response analyses for ependymomas, the typical radiation dose is between 54-59.4 Gy locally using 1.8-2.0 Gy fractions.

For anaplastic ependymomas, researchers have recommended irradiating the entire craniospinal axis or administering WBRT, 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; and (4) spinal metastases may not be prevented by prophylactic treatment. As a result, the routine use of “prophylactic” craniospinal or WBRT does not appear to lead to improvement in survival. The 5-year overall survival rate for patients with grade II and III ependymomas who have received surgery and post-operative RT is about 70%.

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 or RT. Recurrence chemotherapy includes etoposide, temozolomide, nitrosourea, and platinum-based regimens.

**Treatment algorithm**

The treatment algorithm for adult ependymomas revolves around histology, extent of surgical resection, and extent of disease in the craniospinal axis. Spine MRI should be delayed by at least 2 to 3 weeks after surgery to avoid post-surgical artifacts. Lumbar puncture for CSF analysis should be delayed at least 2 weeks after surgery to avoid possible false positive results; lumbar puncture may be contraindicated (for example, posterior fossa mass). 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 or observation (only if supratentorial) fractionated external beam RT is recommended; RT or observation can be considered for infratentorial lesions. However, if a contrast-enhanced spinal MRI scan or CSF analysis reveals disease, craniospinal irradiation should be administered.

Patients with anaplastic ependymoma should also have a contrast enhanced brain and spinal MRI scan after a biopsy or subtotal resection. CSF analysis is recommended. If the MRI scan is negative, limited-field fractionated external beam RT is normally given. For limited fields, the clinical target volume (gross tumor volume plus 1-2 cm margin) should receive 54-59.4 Gy in 1.8 to 2.0 Gy fractions. However, if the spinal MRI scan or CSF analysis is positive, craniospinal irradiation is indicated. For craniospinal RT, whole brain and spine (to bottom of thecal sac) should receive 36 Gy in 1.8 fractions, followed by limited field to spine lesions to 45 Gy. The primary tumor site in the brain should receive a total dose of 54-59.4 Gy in 1.8-2.0 Gy fractions.

Follow-up of ependymoma depends on the extent and location of the disease. For localized disease, contrast-enhanced brain and spine MRI (if initially positive) should be done 2 to 3 weeks postoperatively and then every 3 to 4 months for 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 is recommended, if possible. Surgery should be followed with limited field external beam RT, if radiation was not given originally. If the recurrence is unresectable, radiation is a possible option if radiation was not given originally; consider reirradiation (including stereotactic radiosurgery if geometrically favorable). Chemotherapy should also be considered (because of anecdotal reports of response to chemotherapy) or best supportive care, depending on the histologic type, extent of disease, age of the patient, and PS. Radiation (including stereotactic radiosurgery if geometrically favorable) is considered another option for resectable 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.86 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.79 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.87 Stereotactic radiosurgery can be used in the initial treatment of patients with only one or 2 appropriate brain metastases (that is, small, deep) or in those who relapse. 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,88 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 (for example, 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.89, 90 Temozolomide given on a prolonged schedule plus thalidomide has been studied in patients with brain metastases; however, thromboembolic events can be a problem.91-93

**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. FDG-PET can be considered if there are 2-3 lesions, and no primary has been found. If no other readily accessible tumor is available for biopsy, a stereotactic or open biopsy resection is indicated to establish a diagnosis. Among patients with a known history of cancer, if there are concerns regarding the diagnosis of CNS lesions, a stereotactic or open biopsy resection or subtotal resection is also needed. Surgical resection is limited to those with accessible tumors and limited systemic disease; whenever possible, principles of maximal safe resection are used. Patients with disseminated systemic disease who have poor systemic treatment options should be treated with WBRT rather than surgery; however, surgery should be considered to relieve mass effect. Solid brain metastases with systemic non-PCNS lymphoma are not well defined,
but treatment may include systemic treatment, whole brain radiotherapy, or focal RT.

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 1) surgery followed by WBRT (category 1 for 1 metastasis); 2) stereotactic radiosurgery plus WBRT; (category 1 for 1 metastasis); or 3) stereotactic radiosurgery alone (category 2B). 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.

Although previously controversial, WBRT after a surgical resection of a single brain metastasis was shown to be useful by Patchell and colleagues (1998). 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 2 treatment arms. 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 (for example, 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 whose survival is 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.

Patients should be followed with MRI every 3 months for 1 year and then as clinically indicated. Recurrence on radiograph can be confounded by treatment effects. Strongly consider tumor tissue sampling if there is a high index of suspicion of recurrence. 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. For local recurrences, patients who were previously treated with surgery can receive the following options: 1) surgery; 2) stereotactic radiosurgery; 3) WBRT; or 4) chemotherapy can be considered.

However, patients with local recurrences who previously received WBRT cannot receive WBRT again but can receive all of the other options. If the patient had previous stereotactic radiosurgery with a good response for greater than 6 months, then reconsider stereotactic radiosurgery if imaging supports active tumor and not necrosis. The algorithm for distant brain recurrences branches depending on whether patients have either 1-3 lesions or more than 3 lesions, although these are still considered to be limited lesions. WBRT should be used (30-45 Gy, given in 1.8 to 3.0 Gy fractions depending on the patient’s PS) if this modality was not used for initial therapy. Local or systemic chemotherapy may be considered for select patients, if the multiple lesions cannot be controlled by a combination of surgery and radiosurgery.

If systemic CNS disease progression occurs in the setting of limited systemic treatment options, WBRT (30-45 Gy, given in 1.8 to 3.0 Gy...
fractions) should be administered, if the patients have not been previously irradiated. Surgery should be considered to relieve mass effect. For patients who have received prior WBRT, reirradiation is an option only if they had a positive response to the first course of RT treatment. Best supportive care is also an option.

**Treatment algorithm for multiple metastatic lesions**

Patients diagnosed with multiple (that is, >3) metastatic lesions should be treated with WBRT (30-45 Gy, given in 1.8 to 3.0 Gy fractions) with or without stereotactic radiosurgery in selected cases (that is, 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, 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 or reirradiation. For patients with stable systemic disease, options include surgery, reirradiation, or chemotherapy. The choice of chemotherapy depends on the primary tumor. For example, high-dose methotrexate can be used for CNS metastases from breast cancer, and topotecan can be used for metastases from lung cancer.

**Leptomeningeal Metastases**

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. Depending on whether patients are good or poor risk (see “Patient Stratification for Treatment”), therapy involves either 1) fractionated external beam RT to symptomatic sites of the neuraxis and to disease visible on neuroimaging studies or 2) intra-CSF chemotherapy (intrathecal [intralumbar] or intraventricular [intra-Ommaya]). Chemotherapy includes liposomal cytarabine, high-dose methotrexate, and thiotepa. 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 intra-CSF chemotherapy is being considered. A definitive diagnosis is most commonly made by lumbar puncture if it is safe for the patient. The CSF protein is typically increased, and there may be a pleocytosis or decreased glucose levels. The CSF cytology is positive approximately 50% of the time with the first lumbar puncture, and 85% of the time after 3 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 (for example, increased protein, low glucose, and/or a pleocytosis) combined with suggestive clinical findings (for example, multifocal neuraxis involvement, such as cranial nerve palsies and a lumbar radiculopathy that cannot be explained otherwise); and/or (2) suggestive radiologic features (for example, 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 (for example, 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 2 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. Fractionated external beam RT to symptomatic sites (for example, to the whole brain for increased intracranial pressure or to the lumbosacral spine for a developing cauda equina syndrome) can be considered. If the patient stabilizes or improves, a more aggressive treatment approach may be considered. Patients with exceptionally chemosensitive tumors (for example, small cell lung cancer, lymphoma) may be treated.

Good-risk patients can receive fractionated external beam RT 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. Initially, intrathecal chemotherapy is usually given by lumbar puncture, and the SRVC is placed later to administer the drugs more conveniently.

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.\(^{109}\) 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.\(^{107, 110}\) 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.

If an SRVC is placed, a CSF flow scan should be strongly considered.\(^{104, 111}\) CSF flow abnormalities are common in patients with neoplastic meningitis and often lead to increased intracranial pressure. Administering chemotherapy into the ventricle of a patient with a ventricular outlet obstruction increases the patient’s risk for leukoencephalopathy. In addition, the agent administered will not reach the lumbar subarachnoid space where the original CSF cytology was positive. CSF flow scans are easily performed in most nuclear medicine departments. Indium 111-DTPA is administered into the SRVC, and imaging of the brain and spine is performed immediately after injection and then imaging is done again at 4 and 24 hours. If significant flow abnormalities are seen, fractionated external beam 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 (that is, with supportive measures or RT).

For patients with a normal CSF flow scan and otherwise stable disease, induction intrathecal chemotherapy should be given for 4 to 6 weeks 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 3 options: (1) RT to symptom sites; (2) chemotherapy; or (3) best supportive care.

**Primary CNS Lymphomas**

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.\(^112,113\) 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.\(^114\) In immunocompetent primary CNS lymphoma patients, the mean age at diagnosis is 55 years; in immunocompromised patients, it is often younger (for example, 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.\(^113,115\) 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.\(^112,113,115,116\)

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 (that is, 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 (for example, hemiparesis, dysphasia), which occurs in more than 50% of all patients.\(^112,113\) Alterations of mental status (for example, loss of memory or confusion) and symptoms of increased intracranial pressure (for example, 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.\(^113,116\) 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.\(^117\) It is also important to note that the imaging features of primary CNS lymphoma may be profoundly affected by prior use of steroids (for example, 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. CT of the chest, abdomen, and pelvis is recommended along with a chest x-ray. A body PET scan can be considered and can replace CT, bone marrow, and testicular ultrasound but data for use of PET in primary CNS lymphoma are lacking. 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 prior to a diagnostic procedure unless medically indicated. In addition, a lumbar puncture with evaluation of CSF should be considered, if it can be done safely and without concern for herniation from increased intracranial pressure. 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. If the CSF is negative, consider having 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 brain biopsy for a definitive diagnosis. 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, work-up for other diagnoses (for example, inflammatory processes) or rebiopsy is recommended.

Treatment considerations

Steroid Administration

Steroids are cytolytic for primary CNS lymphomas and can significantly alter the appearance of these tumors on CT scans and MRI. It is recommended that steroids be withheld or used judiciously until diagnostic tissue can be obtained in patients suspected of having primary CNS lymphoma. Not only can steroids alter the CT scan or MRI target used by the surgeon (by decreasing enhancement and lesion size), steroids 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.\textsuperscript{112, 113, 119–121} Currently, most authors recommend stereotactic biopsy as the surgical method of choice.\textsuperscript{118} This approach stems from the fact that data do not demonstrate a survival advantage for patients who have had a complete resection or extensive subtotal resection when compared with those who have had only a stereotactic biopsy. In addition, 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 WBRT plus a 2000-cGy boost to involved regions.\textsuperscript{120} 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,\textsuperscript{112} as well as by other investigators.\textsuperscript{106, 122, 123} Therefore, the currently recommended dose of RT for cerebral primary CNS lymphoma is between 24 and 36 Gy in 1.8 to 2.0 Gy fractions (whole brain), without a boost. However, RT may be withheld in patients older than 60 years to avoid toxicity. For patients with ocular lymphoma, RT is the treatment of choice. However, intraocular chemotherapy (category 2B) 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.\textsuperscript{112, 113, 124} Most 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.\textsuperscript{125} Neuwelt and colleagues suggest withholding RT until recurrence or progression in all patients to decrease the risk of radiation-related neuropsychological sequelae.\textsuperscript{121} Others have similar recommendations but only for primary CNS lymphoma patients older than 50 years.\textsuperscript{112, 126} DeAngelis and associates found that it was very uncommon for patients younger than 50 years to develop radiation-induced neurotoxicity.\textsuperscript{125} However, WBRT can be deferred in older patients to decrease neurotoxicity.\textsuperscript{124}
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 51 months.\textsuperscript{112, 113, 117, 120, 124-126}

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. 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{112} 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{121} 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. Gavrilovic and associates (2006) gave preradiation high-dose methotrexate (intravenous and intrathecal) along with vincristine, procarbazine, and consolidation cytarabine to 57 patients. Overall median survival was 51 months; survival was better for patients younger than 60 years at diagnosis.\textsuperscript{124}

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 have 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; CT of the chest, abdomen, and pelvis; 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 (category 2B for biopsy only). Thus, these more elaborate tests are not necessary unless clinically indicated. Consider doing imaging such as testicular ultrasound for elderly men or body PET scans. Although body PET scan may replace CT, bone marrow, and testicular ultrasound, data for use of PET in primary CNS lymphoma are lacking.

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
Pre-irradiation 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-irradiation chemotherapy is less neurotoxic than postradiation chemotherapy. Additionally, drug delivery to a primary CNS lymphoma may be increased before radiation, when the blood-brain barrier is maximally disrupted by the tumor, than after RT, which results in tumor regression as well as partial repair and closure of the blood-brain barrier behind the regressing tumor. Finally, pre-irradiation 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. High-dose methotrexate (≥3.5 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 pre-irradiation chemotherapy can prolong time to tumor progression and prolong median survival in patients treated with these agents, compared with radiation alone. Most of the trials using pre-irradiation 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 (that is, those with a KPS ≥40 and a creatinine clearance ≥50 mL/min), some type of pre-irradiation chemotherapy is generally recommended; a high-dose methotrexate-based regimen is most commonly used. Whether one performs WBRT after systemic chemotherapy depends on the responsiveness of the disease to chemotherapy (that is, whether a complete response occurs) and on the clinical judgment of the medical and radiation oncologists. WBRT may increase toxicity, especially in patients older than 60 years, and may be withheld in the primary setting.

If a patient is found to have malignant uveitis, radiation to the globe has been the standard recommendation because of poor penetration of systemic chemotherapy into the uveal fluid. However, there are reports of clearance of ocular lymphoma in patients who were treated with systemic high-dose methotrexate. Therefore, with a primary CNS lymphoma patient who has asymptomatic ocular involvement, a reasonable strategy is to delay radiation to the globe in order to see if high-dose methotrexate is effective. Intraocular injection of chemotherapy (category 2B) is also an option. Additionally, if the patient is found to have a malignant pleocytosis in the CSF, direct intrathecal chemotherapy (either via a SRVC or by lumbar puncture) should be considered.

For patients with extremely poor KPS (<40) or moderate to severe renal dysfunction (creatinine clearance 50 mL/min or less), it is recommended that treatment consist of WBRT 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 WBRT and who achieve a reasonable quality of life with improved PS; systemic or intrathecal chemotherapy or re-irradiation 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 patients who are treated with prior WBRT and ultimately relapse, treatment is re-irradiation or best supportive care; further chemotherapy (systemic or intrathecal) can be considered.

For patients who were initially treated with high-dose methotrexate based chemotherapy but did not receive RT, the decision about whether to use more chemotherapy or proceed to radiation at the time of relapse depends on the duration of response to initial chemotherapy. If a patient had experienced a relatively long-term response (that is, >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 either have no response or relapse within a very short time after systemic chemotherapy, recommendations include 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. Topotecan also is active and useful for patients who have failed methotrexate-based chemotherapy. The combination regimen of cisplatin, cytarabine, and dexamethasone is also useful. 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 3 main categories based on the type of symptoms associated with the lesions. 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 (that is, 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 with a 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). A normal neurologic examination implies that there is no spinal 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. A randomized trial supports the use of high-dose steroids. 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. 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. In the event that no tumor is found on MRI, additional tests can be performed (for example, 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. Spinal instability is grossly defined as the presence of significant kyphosis or subluxation (deformity) or of significantly retropulsed bone fragment. Not every pathologic fracture implies 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.

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 (that is, to pinprick) or loss of ambulatory status or bladder/bowel incontinence. 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, no history of cancer, radioresistant tumors (for example, renal carcinoma, melanoma, sarcoma), rapid neurologic deterioration, previous RT, high cervical location, tumor is...
not lymphoma or myeloma, and/or for a single site epidural/spinal cord compression.\textsuperscript{139, 144, 145} Category 1 evidence supports the role of surgery for those willing to undergo surgery.\textsuperscript{144} Surgery can involve tumor resection with or without spinal stabilization; surgery can be through an anterior, posterior, or a circumferential approach.\textsuperscript{146} Spinal instrumentation is recommended if there is preoperative spinal instability or if instability is expected to occur after tumor resection.\textsuperscript{141} Surgery also includes vertebroplasty/kyphoplasty, especially for patients with intractable pain.\textsuperscript{147} It also includes implantation of a subarachnoid pump (morphine pump) for patients with intractable pain who are not candidates for tumor resection/stabilization or vertebroplasty/kyphoplasty. The “all others” category 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{148} Short RT regimens over 2 to 3 weeks or less or consideration of stereotactic RT are options for 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{149, 150} 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{149} 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{151} For patients with multiple myeloma or lymphoma with spinal cord compression, chemotherapy can be considered in lieu of RT.

Patients with slow-growing, symptomatic malignancies (for example, 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 (for example, 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. 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 Adult Cancer Pain Guidelines).\textsuperscript{141}
Reference


Discussion


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