September 16, 2019

The Honorable Seema Verma  
Administrator  
Centers for Medicare & Medicaid Services  
Department of Health and Human Services  
Hubert H. Humphrey Building  
200 Independence Avenue, SW  
Washington, DC 20201

RE: CMS-5527-P Medicare Program; Specialty Care Models to Improve Quality of Care and Reduce Expenditures Proposed Rule

Dear Administrator Verma:

The National Comprehensive Cancer Network® (NCCN®) is pleased to comment on the Centers for Medicare & Medicaid Services (CMS) Proposed Rule Medicare Program; Specialty Care Models to Improve Quality of Care and Reduce Expenditures (CMS-5527-P) as it relates to NCCN’s mission of improving and facilitating, quality, effective, efficient, and accessible cancer care.

NCCN thanks CMS for its efforts to advance value models in oncology through the proposed Radiation Oncology (RO) Model. NCCN also thanks CMS for the support of nationally recognized evidence based clinical guidelines as an important tool and safeguard to ensure clinically appropriate care. NCCN appreciates the opportunity to provide comment on the RO Model and will focus our remarks on the scope of the model and proposed included cancer types, guideline adherence requirements as a quality assurance mechanism, and administrative considerations for implementation, and proposed quality measures within the payment model.

NCCN Background

As an alliance of 28 leading academic cancer centers in the United States that treat hundreds of thousands of patients with cancer annually, NCCN is a developer of authoritative information regarding cancer prevention, screening, diagnosis, treatment, and supportive care that is widely used by clinical professionals and payers alike. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a comprehensive set of guidelines detailing the sequential management decisions and interventions that currently apply to 97 percent of cancers affecting patients in the United States.
NCCN Guidelines® and Library of Compendia products help ensure access to appropriate care, clinical decision-making, and assessment of quality improvement initiatives. The NCCN Drugs & Biologics Compendium (NCCN Compendium®) has been recognized by CMS and clinical professionals in the commercial payer setting since 2008 as an evidence-based reference for establishment of coverage policy and coverage decisions regarding off-label use of anticancer and cancer-related medications. NCCN was recognized by CMS in 2016 as a qualified Provider Led Entity (PLE) for the Medicare Appropriate Use Criteria (AUC) Program for the development of AUC and the establishment of policy and decision-making for diagnostic imaging in patients with cancer.

The NCCN Radiation Therapy Compendium™ includes information designed to support clinical decision-making around the use of radiation therapy in patients with cancer and is based directly on the NCCN Guidelines®. The NCCN Radiation Therapy Compendium™ includes recommendations pertaining to indications, modalities, clinical scenario, purpose, as well as the dosing regimens used for treatment. Additional information includes the clinical notes related to the specific recommendation. The NCCN Radiation Therapy Compendium™ also documents information on disease stage and histology. The NCCN Radiation Therapy Compendium™ includes a full complement of radiation therapy recommendations found in the current NCCN Guidelines, including specific treatment modalities such as 2D/3D conformal external beam radiation therapy (EBRT), intensity modulated radiation therapy (IMRT), intra-operative radiation therapy (IORT), stereotactic radiosurgery (SRS)/stereotactic body radiotherapy (SBRT)/stereotactic ablative body radiotherapy (SABR), image-guided radiation therapy (IGRT), low dose-rate (LDR)/high dose-rate (HDR) brachytherapy, radioisotope, and particle therapy. The NCCN Radiation Therapy Compendium™ is accessible through an easy-to-use, web-based user interface and via an Application Programming Interface (API) for easy integration in Health Information Technology (HIT) including clinical decision support systems (CDSS). The NCCN Radiation Therapy Compendium™ includes a full complement of radiation therapy recommendations found in the current Guidelines. The NCCN Radiation Therapy Compendium™ is reviewed on a continual basis to ensure that the recommendations take into account the most current evidence.

NCCN imposes strict policies to shield the guidelines development processes from external influences. The “firewall” surrounding the NCCN Guidelines processes includes: financial support policies; panel participation and communication policies; guidelines disclosure policies; and policies regarding relationships to NCCN’s other business development activities. The guidelines development is supported exclusively by the Member Institutions’ dues and does not accept any form of industry or other external financial support for the guidelines development program. The NCCN Guidelines are updated at least annually in an evidence-based process integrated with
the expert judgment of multidisciplinary panels of expert physicians from NCCN Member Institutions. The NCCN Guidelines are transparent, continuously updated, available free of charge online for non-commercial use and through a multitude of HIT vendors.

Mechanisms to Ensure Guideline Concordant Care within the RO Model

NCCN thanks CMS for recognizing the importance of nationally recognized evidence based clinical practice guidelines in the proposed rule by requiring that all Professional participants and Dual participants attest through documentation in the medical record that the participant adheres to nationally recognized, evidence-based clinical treatment guidelines when appropriate in treating RO beneficiaries or documents in the medical record the rationale for the departure from these guidelines. NCCN agrees with CMS that adherence to evidence-based clinical practice guidelines is an important tool to ensure quality of care for patients. In the proposed rule, CMS proposes to monitor for guideline adherence through site visits and audits. NCCN would like to note that guideline adherence can be determined today through the use of various HIT systems and real-time clinical decision support applications which can be integrated into electronic health record (EHR) systems.

A peer-reviewed, published study by United, eviCore and NCCN entitled “Transforming Prior Authorization to Decision Support” demonstrated mandatory adherence to NCCN Guidelines and NCCN Compendium®, using a real time CDSM significantly reduced total and episodic costs of care while also reducing denials and increasing access to guideline concordant care.¹ In Florida, United Healthcare adopted a prior authorization tool using NCCN real-time decision support over a one-year period and explored 4,272 eligible cases. At the conclusion of the study, United Healthcare found that adding decision support to prior authorization reduced denials to 1 percent. Additionally, when compared to UnitedHealthcare’s cancer drug costs nationwide, the study found that mere adherence to NCCN Guidelines and Compendium within the pilot reduced chemotherapy drug cost trends by 20 percent; a savings of $5.3 million.

NCCN agrees that guideline concordant care is critically important within value payment models to ensure quality of care and believes this can be accomplished more consistently within this model through the use of HIT. NCCN is happy to serve as a resource to CMS in the implementation of this model as it relates to guideline adherence.

Scope of Model and Implementation Timeline

CMS contends within the proposed rule that mandating participation through randomized selection of RT providers and RT suppliers would provide a more complete evidence base of the model’s impact. While NCCN appreciates CMS concerns that voluntary selection may undermine the data captured from the proposed model, we have concerns that mandating participation may result in the inclusion of practices less capable of navigating model requirements while excluding participation from enthusiastic and prepared providers. Additionally, NCCN has concerns about the proposed timeline and believes that notifying selected providers in November with a proposed start date of January 1, 2020 or April 1, 2020 does not provide sufficient time for practices to prepare for the model directives.

Concerns regarding the mandatory nature of the model are magnified by CMS’ proposed size and scope. CMS notes within the proposed rule that a simulation of the Core Based Statistical Areas (CBSA) selection method captured 616 physician group practices (PGPs) and 541 HOPDS; netting nearly 40 percent of radiation oncology episodes in eligible geographic areas and roughly one-third of practices providing Professional Component (PC) or Technical Component (TC). NCCN has concerns that a sample size of this scale, without appropriate pilot testing, may result in patient access issues.

In light of these considerations, NCCN agrees with the recommendation of the American Society for Radiation Oncology (ASTRO) that CMS implement a voluntary RO Model with an effective date of July 1, 2020 that ultimately shifts to a mandatory model over time. A July start date would provide selected practices and suppliers with adequate time to reallocate resources, both staff and equipment, in a manner to better meet model demands. We also ask that CMS consider reducing the scope of the initial phase of this model to prevent patient access issues and appropriately assess the model’s impact on quality of care prior to bringing the model to scale.

Proposed Included Cancer Types

CMS proposes to include seventeen cancer types within the proposed Radiation Oncology Model representing 84% of all Radiation Therapy (RT) episodes. NCCN is concerned that broad implementation of the model across multiple cancer types without appropriate pilot testing may create significant implementation and operational challenges, ultimately resulting in patient access issues. NCCN encourages CMS to consider piloting of the model across a smaller set of cancer types and, in particular, cancer types for which there is established evidence supporting the use of hypofractionation for improved efficiency and patient convenience while maintaining clinically appropriate care.
CMS notes within the proposed rule that for some cancer types, stages, and characteristics, a shorter course of RT treatment with higher doses of radiation per fraction may be appropriate. CMS specifically highlights existing evidence in the treatment of low-risk breast cancer, low- and intermediate-risk prostate cancer, and bone metastases as examples. Additionally, CMS notes there is some indication that the latest evidence-based guidelines are not incorporated into practices’ treatment protocols in a timely manner. NCCN appreciates CMS’ efforts to ensure timely delivery of guideline concordant care. NCCN is pleased to share the recommendations and evidence for hypofractionation of RT as outlined within NCCN Guidelines to assist CMS in considering which cancer types to include within the model. NCCN Guidelines cite evidence and recommendations specific to hypofractionation within breast cancer, prostate cancer, head and neck cancer, and Central Nervous System (CNS) cancers guidelines as well as in the management of bone and brain metastases.

**Breast Cancer**

Evidence for the use of hypofractionation is most well established within the treatment of breast cancer. NCCN Clinical Practice Guidelines for Breast Cancer recommend that when treating patients receiving whole breast radiation, the whole breast should receive a dose of 45-50.4 gray (Gy) in 25-28 fractions or 40-42.5 Gy in 15-16 fractions.\(^2\) NCCN Guidelines\(^\circledR\) note that hypofractionation is preferred.\(^2\) Evidence supporting this recommendation includes four randomized clinical trials that have investigated hypofractionated whole breast radiation schedules (39-42.9 Gy in single fractions of 2.6-3.3 Gy) compared to standard 50 Gy in single fractions of 2 Gy. Trials reported that local tumor control and breast cosmesis were similar with a regimen of 42.5 Gy in 16 fractions over 3.2 weeks compared with 50 Gy in 25 fractions over 5 weeks. The UK Standardisation of Breast Radiotherapy (START) Trials reported radiation-related effects to normal breast tissue such as breast shrinkage, telangiectasia, and breast edema as less common with the hypofractionated treatment regimens.

Based on convenience and the data from the START trials, the short course of radiation therapy (40-42.5 Gy in 15-16 fractions) is the NCCN-preferred option for treatment of patients receiving radiation therapy to the whole breast only.\(^2\) An additional boost to the tumor bed is recommended in patients with higher risk characteristics (such as age <50, high-grade disease, or patients with focally positive margins) in order to reduce local relapse. Typical boost doses are 10 to 16 Gy in 4 to 8 fractions. Please see appendix 1 for additional information.

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Prostate Cancer

NCCN Clinical Practice Guidelines for Prostate Cancer include several mentions of hypofractionation. Over the past several decades, external beam radiation therapy (EBRT) techniques have evolved to allow higher doses of radiation to be administered safely. More recently, moderately hypofractionated image-guided IMRT regimens (2.4-4 Gy per fraction over 4-6 weeks) have been tested in randomized trials. Toxicity was similar between moderately hypofractionated and conventional regimens in some, but not all, of the trials.\(^3\) In addition, efficacy results varied among the trials, with some showing noninferiority or similar efficacy and others showing that hypofractionation may be less effective than conventional fractionation schemes. These safety and efficacy differences are likely a result of differences in fractionation schedules. Overall, the panel believes that moderately hypofractionated IMRT techniques, which are more convenient for patients, can be considered as an alternative to conventionally fractionated regimens when clinically indicated.\(^3\) The panel lists fractionation schemes that have shown acceptable efficacy and toxicity which can be found in the attached appendix 2.

An ASTRO/ASCO/AUA evidence-based guideline regarding the use of hypofractionated radiation in men with localized prostate cancer concluded that moderately fractionated regimens are justified for routine use in this setting and provides more detail on the topic. RT techniques used in prostate cancer include EBRT, proton radiation therapy, and brachytherapy. EBRT techniques include IMRT and image-guided SBRT, which further seeks to decrease the number of radiation fractions to 5 or less. An analysis that included propensity-score matching of patients showed that, among younger men with prostate cancer, SBRT and IMRT had similar toxicity profiles whereas proton radiation therapy was associated with reduced urinary toxicity but increased bowel toxicity.

Head and Neck Cancer

The NCCN Clinical Practice Guideline for Head and Neck Cancers note that the use of shorter, more hypofractionated treatment courses may be indicated, but the dose tolerance of the spinal cord and neural structures must be evaluated carefully in light of altered fraction size. Additionally, for end-stage disease, patients can be given more

hypofractionated schedules because of the very limited prognosis. Please see appendix 3 for additional information.

Central Nervous System (CNS) Tumors and Brain Metastases

The NCCN Clinical Practice Guideline for Central Nervous System Cancers note that radiation oncologists use several different treatment modalities in patients with primary brain tumors, including brachytherapy, fractionated stereotactic RT, and stereotactic radiosurgery (SRS). Standard fractionated external RT (EBRT) is the most common approach. Hypofractionated radiation is an appropriate option for select patients (ie, older adults and patients with a poor PS). RT for patients with primary brain tumors is administered with a limited volume (tumor and margin), while whole brain RT (WBRT) and SRS are used primarily for brain metastases. Please see appendix 4 for additional detail.

Access to Relevant Technology

NCCN feels it is important to note that to properly perform hypofractionation for certain cancers, including breast cancer, practices must have access to appropriate modalities and planning capabilities. Without certain technologies, a radiation oncologist may not be able to satisfactorily implement a specific hypofractionation scheme. The NCCN Guidelines give a range of radiation dosing in gray (Gy), with varying fractions and modalities, because each case plan is different and each practice may have different resources. NCCN notes that the mandatory nature of the model may hinder access to those patients who do not have access to the modalities and technology that can safely provide hypofractionated care.

NCCN encourages CMS to consider a more manageable and limited subset of cancer types for which there is strong evidence indicating equivalent efficiency with hypofractionation while maintaining clinically appropriate care, prior to expanding the scope of the model beyond cancer types with adequate evidence supporting shorter treatment duration.

Proposed Historical Experience Adjustments and Efficiency Factor

Under the proposed rule, CMS considers an RO Model participant’s historical care patterns in the reimbursement methodology through a historical experience adjustment.

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The historical experience adjustment is expressed mathematically as historical experience adjustment = (winsorized payments – Predicted payments)/Expected payments. Based on this calculation, if a participant’s historic episodic payments are less than or equal to the predicted payments, the practice would have an historical experience adjustment of 0.0 or less and be categorized as historically efficient. Participants with historic episodic payment greater than predicted payments have an historical experience adjustment value more than 0.0 and are categorized as historically inefficient. CMS proposes to use this historical efficiency figure to adjust the weight (efficiency factor) applied to the practice over the course of the RO Model. Efficient practices will receive an efficiency factor of .90 over the course of the RO Model; inefficient practices would see a punitive weight reduction over the course of the model (0.90 in PY1, 0.85 in PY2, 0.80 in PY3, 0.75 in PY4 and 0.70 in PY5).

NCCN is concerned that the efficiency factor as currently proposed does not appropriately account for practices that have been historically efficient. According to an ASTRO analysis, in certain example scenarios, under the current proposal historically efficient providers would be reimbursed 21.8% less than historically inefficient providers. In light of these concerns, NCCN echoes ASTRO’s recommendation that CMS should adjust the efficiency factor to avoid penalizing historically efficient practices.

**Quality Measures**

CMS outlines a pay-for-performance methodology that influences reimbursement rates for participating practices and suppliers. The Aggregate Quality Score (AQS) is comprised of five data elements that participants are mandated to collect. CMS proposes the following measures in the proposed rule:

- Oncology: Medical and Radiation—Plan of Care for Pain—NQF #0383; CMS Quality ID #144
- Preventive Care and Screening: Screening for Depression and Follow-Up Plan—NQF #0418; CMS Quality ID #134
- Advance Care Plan—NQF #0326; CMS Quality ID #047
- Treatment Summary Communication—Radiation Oncology
- CAHPS® Cancer Care Survey

NCCN recognizes the importance of implementing quality measures in value based payment models and thanks CMS for seeking to include quality measures that are consensus and evidence-based. NCCN agrees that these measures are important and worthy of reporting. NCCN notes that the individual assigned to report on these measures should be the primary treating clinician and should not be required of those providers delivering only palliative treatment.
Administrative Burden Considerations and Request for Further Clarification

CMS has outlined numerous monitoring and compliance requirements within the proposed rule. NCCN appreciates the need to put safeguards in place protecting quality of care for Medicare beneficiaries within the proposed model. However, in line with Administrator Verma’s push to reduce duplicative and burdensome administrative requirements, NCCN encourages CMS to consider using requirements that can be easily incorporated into current work streams. Aligning these requirements with current practice will ensure patient access to quality care while reducing administrative burden. As noted in previous sections, NCCN believes requiring guideline adherence through a real time clinical decision support mechanism, integrated into EHR systems, is one way to ensure quality care without adding significant administrative burden.

The RO Model requires Professional and Dual participants to notify beneficiaries of their participation in the model through written notice. NCCN has learned from Member Institutions that this requirement as implemented in current value models has been costly, administratively burdensome, and confusing to beneficiaries. Members note that the information provided has not been meaningful or useful to patients and has caused significant confusion. NCCN supports the CMS goal of informing beneficiaries of their cost-sharing responsibilities and right to refuse having their data shared. However, in light of challenges implementing this requirement in current value models, NCCN encourages CMS to work with patient advocates and providers to develop an alternative notification requirement that is less costly, less onerous, and more useful to patients.

NCCN appreciates the opportunity to respond to the Specialty Care Models to Improve Quality of Care and Reduce Expenditures (CMS-5527-P) proposed rule. NCCN urges CMS to consider a more measured roll out by reducing the breadth of the model, prioritizing included cancer types by evidence supporting the safe and effective use of shorter treatment lengths, and reducing administrative burden by using current work streams wherever possible. We welcome the opportunity to discuss our comments further and look forward to working together to ensure Medicare beneficiary timely access to high-quality cancer care.

Sincerely,

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Chief Executive Officer  
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Optimizing Delivery of Individual Therapy

- It is important to individualize radiation therapy planning and delivery.
  > CT-based treatment planning is encouraged to delineate target volumes and adjacent organs at risk.
  > Radiation to the breast/chest wall and nodal regions is generally delivered with photons ± electrons.
  > Greater target dose homogeneity and sparing of normal tissues can be accomplished using compensators such as wedges, forward planning using segments, and intensity-modulated radiation therapy (IMRT).
  > Respiratory control techniques including deep inspiration breath-hold and prone positioning may be used to further reduce dose to adjacent normal tissues, in particular heart and lung.
  > Boost treatment in the setting of breast conservation can be delivered using enface electrons, photons, or brachytherapy. Chest wall scar boost when indicated is typically treated with electrons or photons.
  > Verification of daily setup consistency is done with weekly imaging. In certain circumstances, more frequent imaging may be appropriate. Routine use of daily imaging is not recommended.

Whole Breast Radiation

- Target definition is the breast tissue in entirety.
- RT dosing:
  > The whole breast should receive a dose of 45–50.4 Gy in 25–28 fractions or 40–42.5 Gy in 15–16 fractions (hypofractionation is preferred).
  > A boost to the tumor bed is recommended in patients at higher risk for recurrence. Typical boost doses are 10–16 Gy in 4–8 fractions.
  > All dose schedules are given 5 days per week.

Chest Wall Radiation (including breast reconstruction)

- The target includes the ipsilateral chest wall, mastectomy scar, and drain sites when indicated.
- Depending on whether or not the patient has had breast reconstruction, several techniques using photons and/or electrons are appropriate.
- CT-based treatment planning is encouraged in order to identify lung and heart volumes and minimize exposure of these organs.
- Special consideration should be given to the use of bolus material to ensure that the skin dose is adequate.
- RT Dosing:
  > Dose is 45–50.4 Gy in 25–28 fractions to the chest wall ± scar boost, at 1.8–2 Gy per fraction, to a total dose of approximately 60 Gy.
  > All dose schedules are given 5 days per week.

Regional Nodal Radiation

- Target delineation is best achieved by the use of CT-based treatment planning.
  > For the paraclavicular and axillary nodes, prescription depth varies based on the patient anatomy.
  > For internal mammary node identification, the internal mammary artery and vein can be used as a surrogate for the nodal location (as the nodes themselves are not usually visible on planning imaging). Based on the post-mastectomy radiation randomized studies and recent trials, radiation therapy of the internal mammary lymph nodes should be strongly considered when delivering regional nodal irradiation. CT treatment planning should be utilized when treating the internal mammary lymph nodal volume to evaluate dose to normal tissues, especially the heart and lung, and dose constraints respected.
  > RT Dosing:
  > Dose is 45–50.4 Gy in 25–28 fractions to the regional nodal fields.
  > All dose schedules are given 5 days per week.

Accelerated Partial Breast Irradiation (APBI)

- Preliminary studies of APBI suggest that rates of local control in selected patients with early-stage breast cancer may be comparable to those treated with standard whole breast RT. However, compared to standard whole breast radiation, several recent studies document an inferior cosmetic outcome with APBI. Follow-up is limited and studies are ongoing.
- Patients are encouraged to participate in clinical trials.
- The NCCN Panel accepts the updated 2016 version of the ASTRO APBI guideline, which now defines patients "suitable" for APBI to be one of the following:
  > 1) 50 years or older with invasive ductal carcinoma measuring ≤2 cm (T1 disease) with negative margin widths of ≥2 mm, no LVI, ER positive, and BRCA negative; or
  > 2) low/intermediate nuclear grade, screening-detected DCIS measuring ≥2.5 cm with negative margin widths of ≥3 mm.
- RT Dosing:
  > A course of 34 Gy in 10 fractions delivered twice per day with brachytherapy or 38.5 Gy in 10 fractions delivered twice per day with external beam photon therapy is typically prescribed to the tumor bed.
  > Other fractionation schemes are currently under investigation.

Preoperative Systemic Therapy

- In patients treated with preoperative systemic therapy, indications for radiation therapy and treatment fields should be based on the maximum stage from the pre-therapy clinical stage, pathologic stage, and tumor characteristics.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
particularly favorable tumors, patients for whom the selection of adjuvant systemic therapy will not be affected by the results of the procedure, elderly patients, and patients with serious comorbid conditions. Women who do not undergo ALN dissection or ALN irradiation are at increased risk for ipsilateral lymph node recurrence. Radiation Therapy

Planning Techniques, Targets, and Doses
It is important to individualize radiation therapy planning and delivery. CT-based treatment planning is encouraged to delineate target volumes and adjacent organs at risk. Greater target dose homogeneity and sparing of normal tissues can be accomplished using compensators such as wedges, forward planning using segments, and intensity-modulated radiation therapy (IMRT). Respiratory control techniques including deep inspiration breath-hold and prone positioning may be used to try to further reduce dose to adjacent normal tissues, particularly heart and lung. Boost treatment in the setting of breast conservation can be delivered using enface electrons, photons, or brachytherapy. Chest wall scar boost when indicated is typically treated with electrons or photons. Verification of daily setup consistency is done with weekly imaging. In certain circumstances, more frequent imaging may be appropriate. Routine use of daily imaging is not recommended.

Whole Breast Radiation
Whole breast radiation reduces the risk of local recurrence and has shown to have a beneficial effect on survival. Randomized trials have demonstrated decreased in-breast recurrences with an additional boost dose of radiation (by photons, brachytherapy, or electron beam) to the tumor bed. The panel recommends whole breast irradiation to include breast tissue in its entirety. CT-based treatment planning is recommended to limit irradiation exposure of the heart and lungs, and to assure adequate coverage of the breast and lumpectomy site.

For greater homogeneity of target dose and to spare normal tissues using compensators such as tissue wedges, forward planning using segments, and IMRT may be used. Respiratory control techniques including deep inspiration breath-hold and prone positioning may be used to try to further reduce dose to adjacent normal tissues, particularly heart and lung. Radiation boost treatment in the setting of breast conservation can be delivered using enface electrons, photons, or brachytherapy.

Dose and Fractionation
Four randomized clinical trials have investigated hypofractionated whole breast radiation schedules (39-42.9 Gy in single fractions of 2.6-3.3 Gy) compared to standard 50 Gy in single fractions of 2 Gy. The 10-year follow-up data from the START trials are consistent with the 10-year results of the Canadian trial, which reported that local tumor control and breast cosmesis were similar with a regimen of 42.5 Gy in 16 fractions over 3.2 weeks compared with 50 Gy in 25 fractions over 5 weeks. The START trials reported radiation-related effects to normal breast tissue such as breast shrinkage, telangiectasia, and breast edema as less common with the hypofractionated fraction regimen.

The NCCN Panel recommends whole breast irradiation, a dose of 46 to 50 Gy in 23 to 25 fractions, or a dose of 40 to 42.5 Gy in 15 to 16 fractions. Based on convenience and the data from the START trials, the short course of radiation therapy (40-42.5 Gy in 15-16 fractions) is the NCCN-preferred option for treatment of patients receiving radiation therapy to the whole breast only. A boost to the tumor bed is recommended in patients with higher risk characteristics (such as age <50, high-grade disease, or patients with locally positive margins) in order to reduce local relapse. Typical boost doses are 10 to 16 Gy in 4 to 8 fractions.

Chest Wall Radiation (Including Breast Reconstruction)
The target includes the ipsilateral chest wall, mastectomy scar, and drain sites when indicated. Depending on whether the patient has had breast reconstruction, several techniques using photons and/or electrons are appropriate. The NCCN Panel recommends a dose of 46 to 50 Gy in 23 to 25 fractions to the chest wall. A boost at the scar with a dose of 2 Gy per fraction to a total dose of approximately 60 Gy may be considered in some cases based on risk.

**Regional Nodal Irradiation**

The NCCN Guidelines include updated recommendations for regional lymph node irradiation in patients treated with lumpectomy and mastectomy depending on lymph node involvement (see Principles of Radiation Therapy in the NCCN Guidelines for Breast Cancer).

Two studies, MA.20 and EORTC 22922/10925, evaluated the addition of regional nodal irradiation to the internal mammary nodes and the upper axillary nodes including the supraclavicular region in addition to whole breast irradiation or chest wall irradiation after lumpectomy or mastectomy, respectively. In MA.20, regional recurrences were reduced from 2.7% with breast irradiation only to 0.7% with the addition of nodal irradiation.\(^\text{195}\) The distant recurrences were reduced from 17.3% to 13.4%.\(^\text{195}\) An improvement in DFS was seen from 77% to 82% at 10 years in those who received regional nodal irradiation compared to those who did not.\(^\text{193}\) In EORTC 22922/10925, regional radiation therapy reduced the incidence of regional recurrences from 4.2% to 2.7% and decreased the rate of distant metastases from 19.6% to 15.9% at a median follow-up of 10.9 years.\(^\text{196}\)

**Accelerated Partial Breast Irradiation**

Several studies have been reported using accelerated partial breast irradiation (APBI) rather than whole breast irradiation following complete surgical excision of in-breast disease. The panel generally views the use of APBI as investigational, and encourages its use within the confines of a high-quality, prospective clinical trial.\(^\text{197}\) For patients who are not trial eligible, recommendations from ASTRO indicate that APBI may be suitable in selected patients with early-stage breast cancer and may be comparable to treatment with standard whole-breast RT.\(^\text{198}\) Patients who may be suitable for APBI are women 60 years of age and older who are not carriers of a known BRCA1/2 mutation and who have been treated with primary surgery for a unifocal stage I, ER-positive cancer. Tumors should be infiltrating ductal or have a favorable histology, should not be associated with an extensive intraductal component or LCIS, and should have negative margins. Thirty-four Gy in 10 fractions delivered twice per day with brachytherapy or 38.5 Gy in 10 fractions delivered twice per day with external beam photon therapy to the tumor bed is recommended. Other fractionation schemes are under investigation. Studies have suggested that the ASTRO stratification guidelines may not adequately predict ipsilateral breast tumor recurrences following APBI.\(^\text{199,200}\) Follow-up is limited and studies are ongoing.

**Radiation Therapy in Patients Receiving Preoperative Systemic Therapy**

The panel recommends that decisions related to administration of radiation therapy for patients receiving preoperative systemic chemotherapy should be made based on maximal stage from pre-chemotherapy tumor characteristics and/or pathological stage, irrespective of tumor response to preoperative systemic therapy.

**Radiation Therapy After Lumpectomy**

After lumpectomy, whole breast irradiation is strongly recommended with or without boost to tumor bed for node-positive disease (category 1 for those with positive nodes; category 2A for those with negative axillary nodes). This recommendation is supported by the results of a
meta-analysis by the EBCTCG showing reduction in 10-year risk of recurrence in those who received whole breast irradiation versus those who did not (19% vs. 35%; RR 0.52; 95% CI, 0.48–0.56). In addition, a significant reduction in 15-year risk of breast cancer death (21% vs. 25%; RR 0.82; 95% CI, 0.75–0.90) was also observed.

Regional Nodal Irradiation
The reduction in the risk of locoregional and distant recurrence and improvement in DFS seen in the MA.20 and EORTC 22922/10925 trials support the importance of regional nodal irradiation after lumpectomy. The NCCN Panel strongly recommends irradiation of infraclavicular and supraclavicular areas, internal mammary nodes, and any part of the axillary bed that may be suspicious (category 1 for ≥4 positive nodes). Irradiation of the regional nodal area is generally not recommended by the panel for those with negative axillary nodes.

If adjuvant chemotherapy is indicated after lumpectomy, radiation should be given after chemotherapy is completed. This recommendation is based on results of the "Upfront-Outback" trial in which patients who had undergone breast-conserving surgery and axillary dissection were randomly assigned to receive chemotherapy following radiation therapy or radiation therapy following chemotherapy. The initial results showed an increased rate of local recurrence in the group with delayed radiotherapy at a median follow-up of 58 months; however, differences in rates of distant or local recurrence were not statistically significant when the two arms were compared at 135-month follow-up.

Radiation Therapy After Lumpectomy in Older Adults
Whole breast irradiation as a component of breast-conserving therapy is not always necessary in selected women 70 years of age or older. In a study of women with clinical stage I, ER-positive breast cancer who were greater than or equal to 70 years of age at diagnosis, patients were randomized to receive lumpectomy with whole breast radiation or lumpectomy alone, both with tamoxifen for five years. Locoregional recurrence rates were 1% in the lumpectomy, radiation, and tamoxifen arm and 4% in the lumpectomy plus tamoxifen arm. There were no differences in OS, DFS, or need for mastectomy. These results were confirmed in an updated analysis of this study with a median follow-up of 12.6 years. At 10 years, a statistically significant reduction in ipsilateral breast recurrences was seen with radiation therapy with 90% of patients in the lumpectomy and tamoxifen arm compared with 98% in the lumpectomy plus radiation and tamoxifen arm who were free from locoregional recurrence. Similar results were obtained in other studies of similar design. Whether the difference in tumor control is clinically significant and the patient receives breast radiotherapy should be individualized based upon discussion between the patient and her care team.

The NCCN Guidelines allow for the use of lumpectomy (pathologically negative margin required) plus tamoxifen or an aromatase inhibitor without breast irradiation in women greater than or equal to 70 years of age with clinically negative lymph nodes and ER-positive, T1 breast cancer (category 1).

Radiation Therapy After Mastectomy
Node-Positive Disease: Randomized clinical trials have shown that a DFS and OS advantage is conferred by the irradiation of chest wall and regional lymph nodes in women with positive ALNs after mastectomy and ALN dissection. In these trials, the ipsilateral chest wall and the ipsilateral locoregional lymph nodes were irradiated. The results of EBCCTCG meta-analyses show that radiotherapy after mastectomy and axillary node dissection reduced both recurrence and breast cancer mortality in the women with 1 to 3 positive lymph nodes even when
systemic therapy was administered.\textsuperscript{196} Based on these studies, the current guidelines recommend postmastectomy chest wall irradiation in women with positive ALNs (category 1). Two retrospective analyses have provided evidence for benefit of radiation therapy for only selected patients (patients presenting with clinical stage III disease and patients with four or more positive nodes) receiving preoperative systemic therapy prior to mastectomy.\textsuperscript{213,214}

Regional Nodal Irradiation
The use of regional nodal irradiation for patients undergoing mastectomy is supported by a subgroup analysis of studies from the Danish Breast Cancer Cooperative Group.\textsuperscript{215} In this analysis, a substantial survival benefit was associated with postmastectomy radiation therapy for women with 1 to 3 positive ALNs. In addition, data from the EORTC 22922/10925 trial supports the role of regional RT in this population based on the inclusion of patients who had undergone mastectomy in this study. Based on the above data, the NCCN Panel recommends irradiation of infraclavicular and supraclavicular areas, internal mammary nodes, and any part of the axillary bed that may be suspicious (category 1 for ≥4 positive nodes; 2A for 1–3 positive nodes).

Node-Negative Disease: Features in node-negative tumors that predict a high rate of local recurrence include primary tumors greater than 5 cm or positive pathologic margins. Chest wall irradiation is recommended for these patients.\textsuperscript{216} Consideration should be given to radiation to the ipsilateral supraclavicular area and to the ipsilateral internal mammary lymph nodes, especially in patients with tumors greater than 5 cm, or positive surgical margins. In patients with tumors less than or equal to 5 cm and negative margins but less than or equal to 1 mm, chest wall irradiation should be considered.

In patients with negative nodes, tumor less than or equal to 5 cm, and clear margins (≥1 mm), post-mastectomy radiation therapy is usually not recommended. However, the panel has noted that it may be considered only for patients with high risk of recurrence. A retrospective analysis suggests benefit of post-mastectomy radiation therapy in reducing risk of recurrence in patients with node-negative disease with high-risk factors such as close margins, tumors greater than or equal to 2 cm, premenopausal status, and lymphovascular invasion.\textsuperscript{217} Another study showed increased risk of locoregional recurrence in women with node-negative triple-negative breast cancer with tumors less than or equal to 5 cm.\textsuperscript{218}

Breast Reconstruction
Breast reconstruction may be an option for any woman receiving surgical treatment for breast cancer. Therefore, all women undergoing breast cancer treatment should be educated about breast reconstructive options as adapted to their individual clinical situation and be offered an opportunity to consult with a reconstructive plastic surgeon. Breast reconstruction should not interfere with the appropriate surgical management. This may increase the risk of overall and cancer-related death, especially in those with late-stage disease.\textsuperscript{219} Coordinating consultation and surgical treatment with a reconstructive surgeon should be executed within a reasonable timeframe.

Several reconstructive approaches are summarized for these patients in the NCCN Guidelines for Breast Cancer under Principles of Breast Reconstruction Following Surgery.

The decision regarding type of reconstruction includes patient preference, body habitus, smoking history, comorbidities, plans for irradiation, and expertise and experience of the reconstruction team. Smoking and obesity increase the risk of complications for all types of

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APPENDIX 2
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Prostate Cancer

Version 4.2019 — August 19, 2019

NCCN.org

NCCN Guidelines for Patients® available at www.nccn.org/patients

Continue
PRINCIPLES OF RADIATION THERAPY

Definitive Radiation Therapy General Principles
- Highly conformal RT techniques should be used to treat localized prostate cancer.
- Photon or proton EBRT are both effective at achieving highly conformal radiotherapy with acceptable and similar biochemical control and long-term side effect profiles (See Discussion).
- Brachytherapy boost, when added to EBRT plus ADT in men with NCCN intermediate and high/very high risk prostate cancer, has demonstrated improved biochemical control over EBRT plus ADT alone in randomized trials, but with higher toxicity.
- Ideally, the accuracy of treatment should be verified by daily prostate localization, with any of the following: techniques of IGRT using CT, ultrasound, implanted fiducials, or electromagnetic targeting/tracking. Endorectal balloons may be used to improve prostate immobilization. Perirectal spacer materials may be employed when the previously mentioned techniques are insufficient to improve oncologic cure rates and/or reduce side effects due to anatomic geometry or other patient related factors, such as medication usage and/or comorbid conditions. Patients with obvious rectal invasion or visible T3 and posterior extension should not undergo perirectal spacer implantation.
- Various fractionation and dose regimens can be considered depending on the clinical scenario (See Table 1). Dose escalation has been proven to achieve the best biochemical control in men with Intermediate and high risk disease.

Definitive Radiation Therapy by Risk Group
- Very low risk
  - Men with NCCN very low risk prostate cancer are encouraged to pursue active surveillance.
- Low risk
  - Men with NCCN low-risk prostate cancer are encouraged to pursue active surveillance.
  - Prophylactic lymph node radiation should NOT be performed routinely. ADT or antiandrogen therapy should NOT be used routinely
- Favorable intermediate risk
  - Prophylactic lymph node radiation is not performed routinely, and ADT or antiandrogen therapy is not used routinely. Prophylactic lymph node radiation and/or ADT use is reasonable if additional risk assessments suggest aggressive tumor behavior.

For brachytherapy:
- Patients with a very large prostate or very small prostate, symptoms of bladder outlet obstruction (high IPSS), or a previous TURP are more difficult to implant and may suffer increased risk of side effects. Neoadjuvant ADT may be used to shrink the prostate to an acceptable size; however, increased toxicity would be expected from ADT and prostate size may not decline in some men despite neoadjuvant ADT. Potential toxicity of ADT must be balanced against the potential benefit of target reduction.
- Post-implant dosimetry must be performed to document the quality of the low dose-rate implant.
PRINCIPLES OF RADIATION THERAPY

- Unfavorable intermediate risk
  - Prophylactic nodal radiation can be considered if additional risk assessments suggest aggressive tumor behavior. ADT should be used unless additional risk assessments suggest less-aggressive tumor behavior or if medically contraindicated. The duration of ADT can be reduced when combined with EBRT and brachytherapy. Brachytherapy combined with ADT (without EBRT), or SBRT combined with ADT can be considered when delivering longer courses of EBRT would present medical or social hardship.

- High risk
  - Prophylactic nodal radiation can be considered. ADT is required unless medically contraindicated. The duration of ADT may be reduced when EBRT is combined with brachytherapy. Brachytherapy combined with ADT (without EBRT), or SBRT combined with ADT, can be considered when delivering longer courses of EBRT would present a medical or social hardship.

- Very high risk
  - Prophylactic nodal radiation should be considered. ADT is required unless medically contraindicated.

- Regional disease
  - Nodal radiation should be performed. Clinically positive nodes should be dose-escalated as dose-volume histogram parameters allow. ADT is required unless medically contraindicated, and the addition of abiraterone and prednisone or abiraterone with methylprednisolone (category 2B) to ADT can be considered.

- Low-volume metastatic disease
  - Radiation therapy to the prostate is an option in patients with low-volume castration-naive metastatic disease, without contraindications to radiotherapy. ADT is required unless medically contraindicated.
  - This recommendation is based on the STAMPEDE phase 3 randomized trial, which randomized 2,061 men to standard systemic therapy with or without radiotherapy to the primary. The overall cohort had a significant improvement from the addition of radiotherapy to the primary in failure-free survival, but not overall survival. The prespecified low-volume subset had a significant improvement in both failure-free survival and overall survival.
  - Minimizing toxicity is paramount when delivering radiation therapy to the primary in patients with metastatic disease.
  - Whether treatment of regional nodes in addition to the primary improves outcomes remains uncertain; nodal treatment should be performed in the context of a clinical trial.
  - Dose escalation beyond biologically effective dose equivalents of the two dose prescriptions used in STAMPEDE (55 Gy in 20 fractions or 6 Gy x 6 fractions) is not recommended given the known increase in toxicity from dose intensification without overall survival improvement in localized disease.
  - Brachytherapy is not recommended outside of a clinical trial as safety and efficacy have not been established in this patient population.

- High-volume metastatic disease
  - Radiation therapy to the prostate should NOT be performed in men with high-volume metastatic disease outside the context of a clinical trial unless for palliative intent.
  - This recommendation is based on two randomized trials, HORRAD and STAMPEDE, neither of which showed an improvement in overall survival from the addition of radiotherapy to the primary when combined with standard systemic therapy.

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

Table 1: Regimens that have shown acceptable efficacy and toxicity. The optimal regimen for an individual patient warrants evaluation of comorbid conditions, voiding symptoms and toxicity of therapy. Additional fractionation schemes may be used as long as sound oncologic principles and appropriate estimate of BED are considered.

<table>
<thead>
<tr>
<th>Regimen for Definitive Therapy</th>
<th>NCCN Risk Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Very Low&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Beam Therapies</td>
<td></td>
</tr>
<tr>
<td>72–80 Gy at 2 Gy per fraction</td>
<td>✓</td>
</tr>
<tr>
<td>75.6–81.0 Gy at 1.8 Gy per fraction</td>
<td>✓</td>
</tr>
<tr>
<td>70.2 Gy at 2.7 Gy per fraction</td>
<td>✓</td>
</tr>
<tr>
<td>70 Gy at 2.5 Gy per fraction</td>
<td>✓</td>
</tr>
<tr>
<td>60 Gy at 3 Gy per fraction</td>
<td>✓</td>
</tr>
<tr>
<td>51.6 Gy at 4.3 Gy per fraction</td>
<td>✓</td>
</tr>
<tr>
<td>37 Gy at 7.4 Gy per fraction</td>
<td>✓</td>
</tr>
<tr>
<td>40 Gy at 8 Gy per fraction</td>
<td>✓</td>
</tr>
<tr>
<td>36.25 Gy at 7.25 Gy per fraction</td>
<td>✓</td>
</tr>
<tr>
<td>Brachytherapy Monotherapy</td>
<td></td>
</tr>
<tr>
<td>Iodine 125 implant at 145 Gy</td>
<td>✓</td>
</tr>
<tr>
<td>Palladium 103 implant at 125 Gy</td>
<td>✓</td>
</tr>
<tr>
<td>Cesium implant at 115 Gy</td>
<td>✓</td>
</tr>
<tr>
<td>HDR 27 Gy at 13.5 Gy in 2 implants</td>
<td>✓</td>
</tr>
<tr>
<td>HDR 38 Gy at 9.5 Gy BID in 2 implants</td>
<td>✓</td>
</tr>
<tr>
<td>Combined EBRT and Brachytherapy (EBRT 45–50.4 Gy at 1.8–2.0 Gy/fx, unless otherwise noted)</td>
<td>✓</td>
</tr>
<tr>
<td>Iodine 125 Implant at 110–115 Gy</td>
<td>✓</td>
</tr>
<tr>
<td>Palladium 103 implant at 90–100 Gy</td>
<td>✓</td>
</tr>
<tr>
<td>Cesium Implant at 85 Gy</td>
<td>✓</td>
</tr>
<tr>
<td>HDR 21.5 Gy at 10.75 Gy x 2</td>
<td>✓</td>
</tr>
<tr>
<td>EBRT 37.5 Gy at 2.5 Gy + 12–15 Gy single HDR</td>
<td>✓</td>
</tr>
</tbody>
</table>

<sup>a</sup> Active surveillance is preferred for men with very low risk and life expectancy ≥ 20 y and for men with low risk and life expectancy ≥ 10 y.

<sup>b</sup> "Good" or "Poor" prognostic is not strictly defined. Predictive nomograms and/or molecular testing can be used to prognosticate PSA persistence/recurrence, prostate cancer-specific mortality, and metastasis-free survival after definitive external beam radiation therapy. Although the prognostic value has been established, the predictive value of these tests remains unknown.

<sup>c</sup> Prophylactic nodal radiation may be considered if estimate of nodal metastasis is high.

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

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

Salvage Brachytherapy
- Permanent LDR or temporary HDR brachytherapy is a treatment option for pathologically confirmed local recurrence after EBRT or brachytherapy. Subjects should have restaging imaging according to the NCCN high-risk stratification group to rule out regional nodal or metastatic disease. Patients should be counseled that salvage brachytherapy significantly increases the probability of urologic, sexual, and bowel toxicity compared to primary brachytherapy.

Post-Prostatectomy Radiation Therapy
- The panel recommends use of nomograms and consideration of age and comorbidities, clinical and pathologic information, PSA levels, and PSADT to individualize treatment discussion. The panel recommends consultation with the American Society for Radiation Oncology (ASTRO)/AUA Guidelines. Evidence supports offering adjuvant/salvage RT in most men with adverse pathologic features or detectable PSA and no evidence of disseminated disease.
- Indications for adjuvant RT include pT3 disease, positive margin(s), or seminal vesicle involvement. Adjuvant RT is usually given within 1 year after RP and after operative side effects have improved/stabilized. Patients with positive surgical margins may benefit the most.
- Indications for salvage RT include an undetectable PSA that becomes subsequently detectable and increases on 2 measurements or a PSA that remains persistently detectable after RP. Treatment is more effective when pre-treatment PSA is low and PSADT is long.
- The recommended prescribed doses for adjuvant/salvage post-prostatectomy RT are 64–72 Gy in standard fractionation. Biopsy-proven gross recurrence may require higher doses.
- EBRT with two years of anti-androgen therapy with 150 mg/daily of bicalutamide demonstrated improved overall and metastasis-free survival on a prospective randomized trial (RTOG 9601) versus radiation alone in the salvage setting. EBRT with 6 months of ADT improved biochemical or clinical progression at 5 years on a prospective randomized trial (GETUG-16) versus radiation alone.
- Nuclear medicine advanced imaging techniques can be useful for localizing disease with PSA levels as low as 0.5 ng/mL (see Discussion)
- Nomograms, and tumor-based molecular assays, can be used to prognosticate risk of metastasis and prostate cancer-specific mortality in men with adverse risk features after RP.
- Target volumes include the prostate bed and may include the whole pelvis according to physician discretion.

Oligometastatic and Palliative Radiotherapy
- 8 Gy as a single dose is as effective for pain palliation at any bony site as longer courses of radiation, but re-treatment rates are higher.
- Widespread bone metastases can be palliated using strontium-89 or samarium-153 with or without focal external beam radiation.
- SBRT can be considered, and enrollment on clinical trials is encouraged for oligometastatic disease where durable local control is desirable.
- Treatment of the primary site in men with metastatic disease can be used to palliate obstructive symptoms due to tumor. Definitive external beam dosing regimens, or traditional palliative regimens (eg, 30 Gy/10 fx or 37.5 Gy/15 fx), can be used depending on clinical scenario.

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

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**Radiopharmaceutical Therapy**

- Radium-223 is an alpha-emitting radiopharmaceutical that has been shown to extend survival in men who have castration-resistant prostate cancer (CRPC) with symptomatic bone metastases, but no visceral metastases. Radium-223 alone has not been shown to extend survival in men with visceral metastases or bulky nodal disease (>3 to 4 cm). Radium-223 differs from beta-emitting agents, such as samarium 153 and strontium 89, which are palliative and have no survival advantage. Radium-223 causes double-strand DNA breaks and has a short radius of activity. Grade 3–4 hematologic toxicity (2% neutropenia, 3% thrombocytopenia, 6% anemia) occurs at low frequency.
- Radium-223 is administered intravenously once a month for 6 months by an appropriately licensed facility, usually in nuclear medicine or RT departments.
- Prior to the initial dose, patients must have absolute neutrophil count $\geq 1.5 \times 10^9/L$, platelet count $\geq 100 \times 10^9/L$, and hemoglobin $\geq 10$ g/dL.
- Prior to subsequent doses, patients must have absolute neutrophil count $\geq 1 \times 10^9/L$ and platelet count $\geq 50 \times 10^9/L$ (per label, although this may be too low in practice). Radium-223 should be discontinued if a delay of 6–8 weeks does not result in the return of blood counts to these levels.
- Non-hematologic side effects are generally mild, and include nausea, diarrhea, and vomiting. These symptoms may occur because radium-223 is eliminated predominantly by fecal excretion.
- Radium-223 is not intended to be used in combination with chemotherapy due to the potential for additive myelosuppression, except in a clinical trial.
- Concomitant use of denosumab or zoledronic acid does not interfere with the beneficial effects of radium-223 on survival.
postoperative management and additional cancer therapies were not standardized between the groups.291

An analysis of the Prostate Cancer Outcomes Study on 1655 men with localized prostate cancer compared long-term functional outcomes after radical prostatectomy or EBRT.293 At 2 and 5 years, patients who underwent radical prostatectomy reported higher rates of urinary incontinence and erectile dysfunction but lower rates of bowel urgency. However, no significant difference was observed at 15 years. In a large retrospective cohort study involving 32,465 patients, those who received EBRT had a lower 5-year incidence of urological procedures than those who underwent radical prostatectomy, but higher incidence for hospital admissions, rectal or anal procedures, open surgical procedures, and secondary malignancies.294

Return of urinary continence after radical prostatectomy may be improved by preserving the urethra beyond the prostatic apex and by avoiding damage to the distal sphincter mechanism. Bladder neck preservation may allow more rapid recovery of urinary control.295 Anastomotic strictures that increase the risk of long-term incontinence are less frequent with modern surgical techniques. Recovery of erectile function is related directly to the degree of preservation of the cavernous nerves, age at surgery, and preoperative erectile function. Improvement in urinary and sexual function has been reported with nerve-sparing techniques.296,297 Replacement of resected nerves with nerve grafts does not appear to be effective for patients undergoing wide resection of the neurovascular bundles.298 The ability of mpMRI to detect extracapsular extension can aid in decision-making in nerve-sparing surgery.158

Pelvic Lymph Node Dissection

The decision to perform PLND should be guided by the probability of nodal metastases. The NCCN Guidelines Panel chose 2% as the cutoff for PLND because this avoids 47.7% of PLNDs at a cost of missing 12.1% of positive pelvic lymph nodes.112 A more recent analysis of 26,713 patients in the SEER database treated with radical prostatectomy and PLND between 2010 and 2013 found that the 2% nomogram threshold would avoid 22.3% of PLNDs at a cost of missing 3.0% of positive pelvic lymph nodes.299 The panel recommends use of a nomogram developed at Memorial Sloan Kettering Cancer Center that uses pretreatment PSA, clinical stage, and Gleason sum to predict the risk of pelvic lymph node metastases.112

PLND should be performed using an extended technique.300,301 An extended PLND includes removal of all node-bearing tissue from an area bounded by the external iliac vein anteriorly, the pelvic side wall laterally, the bladder wall medially, the floor of the pelvis posteriorly, Cooper's ligament distally, and the internal iliac artery proximally. Removal of more lymph nodes using the extended technique has been associated with increased likelihood of finding lymph node metastases, thereby providing more complete staging.302-304 A survival advantage with more extensive lymphadenectomy has been suggested by several studies, possibly due to elimination of microscopic metastases;303,355-357 although definitive proof of oncologic benefit is lacking.308 PLND can be performed safely laparoscopically, robotically, or as an open procedure, and complication rates should be similar among the three approaches.

Radiation Therapy

RT techniques used in prostate cancer include EBRT, proton radiation, and brachytherapy. EBRT techniques include IMRT and hypofractionated, image-guided SBRT. An analysis that included propensity-score matching of patients showed that, among younger men with prostate cancer, SBRT and IMRT had similar toxicity profiles whereas proton radiation was associated with reduced urinary toxicity and increased bowel toxicity. The
cost of proton therapy was almost double that of IMRT, and SBRT was slightly less expensive.\textsuperscript{309}

The panel believes that highly conformal RT (CRT) techniques should be used to treat localized prostate cancer. Photon and proton beam radiation are both effective at achieving highly CRT with acceptable and similar biochemical control and long-term side effect profiles. Radiation techniques are discussed in more detail below.

**External Beam Radiation Therapy**

Over the past several decades, EBRT techniques have evolved to allow higher doses of radiation to be administered safely. Three-dimensional (3D) CRT (3D-CRT) uses computer software to integrate CT images of the patients' internal anatomy in the treatment position, which allows higher cumulative doses to be delivered with lower risk of late effects.\textsuperscript{123,310-312} The second-generation 3D technique, intensity-modulated RT (IMRT), has been used increasingly in practice.\textsuperscript{313} IMRT reduced the risk of gastrointestinal toxicities and rates of salvage therapy compared to 3D-CRT in some but not all older retrospective and population-based studies, although treatment cost is increased.\textsuperscript{314-317} More recently, moderately hypofractionated image-guided IMRT regimens (2.4–4 Gy per fraction over 4–6 weeks) have been tested in randomized trials, and their efficacy has been similar or non-inferior to conventionally fractionated IMRT, with one trial showing fewer treatment failures with a moderately fractionated regimen.\textsuperscript{318-327} Toxicity was similar between moderately hypofractionated and conventional regimens in some\textsuperscript{318,322,325,326} but not all of the trials.\textsuperscript{320,323,324} In addition, efficacy results varied among the trials, with some showing noninferiority or similar efficacy and others showing that hypofractionation may be less effective than conventional fractionation schemes. These safety and efficacy differences are likely a result of differences in fractionation schedules.\textsuperscript{328} Overall, the panel believes that hypofractionated IMRT techniques, which are more convenient for patients, can be considered as an alternative to conventionally fractionated regimens when clinically indicated. The panel lists fractionation schemes that have shown acceptable efficacy and toxicity on PROS-D page 3 of 5 in the algorithm above. An ASTRO/ASCO/AUA evidence-based guideline regarding the use of hypofractionated radiation in men with localized prostate cancer concluded that moderately fractionated regimens are justified for routine use in this setting and provides more detail on the topic.\textsuperscript{329}

Daily prostate localization using image-guided RT (IGRT) is essential with either 3D-CRT or IMRT for target margin reduction and treatment accuracy. Imaging techniques, such as ultrasound, implanted fiducials, electromagnetic targeting and tracking, or endorectal balloon, can improve cure rates and decrease complications.

These techniques have permitted safer dose escalation, and results of randomized trials have suggested that dose escalation is associated with improved biochemical outcomes.\textsuperscript{330-335} Kuban and colleagues\textsuperscript{333} published an analysis of their dose-escalation trial of 301 patients with stage T1b to T3 prostate cancer. Freedom from biochemical or clinical recurrence was higher in the group randomized to 78 Gy compared to 70 Gy (78% vs. 59%, \(P = .004\)) at a median follow-up of 8.7 years. The difference was even greater among patients with diagnostic PSA \(>10\) ng/mL (78% vs. 39%, \(P = .001\)). An analysis of the National Cancer Database found that dose escalation (75.6–90 Gy) resulted in a dose-dependent improvement in OS for men with intermediate- or high-risk prostate cancer.\textsuperscript{336} In light of these findings, the conventional 70 Gy dose is no longer considered adequate. A dose of 75.6 to 79.2 Gy in conventional fractions to the prostate (with or without seminal vesicles) is appropriate for patients with low-risk cancers. Intermediate-risk and high-risk patients should receive doses of up to 81.0 Gy.\textsuperscript{314,327,328}
Contraindications to EBRT include prior pelvic irradiation, active inflammatory disease of the rectum, or a permanent indwelling Foley catheter. Relative contraindications include very low bladder capacity, chronic moderate or severe diarrhea, bladder outlet obstruction requiring a suprapubic catheter, and inactive ulcerative colitis.

**EBRT for Early Disease**

EBRT is one of the principal treatment options for clinically localized prostate cancer. The NCCN Guidelines Panel consensus was that modern EBRT and surgical series show similar progression-free survival in patients with low-risk disease treated with radical prostatectomy or EBRT. In a study of 3546 patients treated with brachytherapy plus EBRT, disease-free survival (DFS) remained steady at 73% between 15 and 25 years of follow-up. The panel lists several acceptable dosing schemas in the guidelines. The NRG Oncology/RTG 0126 randomized clinical trial compared 79.2 Gy (44 fractions) and 70.2 Gy (39 fractions), both in 1.8 Gy fractions, in 1499 men with intermediate-risk prostate cancer. After a median follow-up of 8.4 years, the escalated dose reduced biochemical recurrences, but increased late toxicity and had no effect on OS.

**EBRT for Patients with High-Risk or Very-High-Risk Disease**

EBRT has demonstrated efficacy in patients at high risk and very high risk. One study randomized 415 patients to EBRT alone or EBRT plus 3-year ADT. In another study (RTG 8531), 977 patients with T3 disease treated with EBRT were randomized to adjuvant ADT or ADT at relapse. Two other randomized phase 3 trials evaluated long-term ADT with or without radiation in a population of patients who mostly had T3 disease. In all four studies, the combination group showed improved disease-specific survival and OS compared to single-modality treatment. Patients with a PSA nadir >0.5 ng/mL after radiation and 6 months of ADT have an adjusted hazard ratio (HR) for all-cause mortality of 1.72 (95% CI, 1.17–2.52; P = .01) compared with patients who received radiation only.
EBRT for Node-Positive Disease

See Adjuvant or Salvage Therapy After Radical Prostatectomy under NCCN Recommendations.

EBRT to the Primary Tumor in Low-Volume M1 Disease

Patients with newly diagnosed, low-volume metastatic prostate cancer can be considered for ADT with EBRT to the primary tumor based on results from the randomized controlled phase 3 STAMPEDE trial. In this multicenter, international study, 2061 patients were randomized to lifelong ADT with or without EBRT to the primary tumor (either 55 Gy in 20 daily fractions over 4 weeks or 36 Gy in 6 weekly fractions over 6 weeks). The primary outcome of OS by intention-to-treat analysis was not met (HR, 0.92; 95% CI, 0.80–1.06; P = .266), but EBRT improved the secondary outcome of failure-free survival (FFS; HR, 0.76; 95% CI, 0.68–0.84; P < .0001). In a pre-planned subset analysis, outcomes of patients with high metastatic burden (defined as visceral metastases ≥4 bone metastases with ≥1 outside the vertebral bodies or pelvis; or both) and those with low metastatic burden (all others) were determined. EBRT improved OS (adjusted HR, 0.68; 95% CI, 0.52–0.90), prostate cancer-specific survival (adjusted HR, 0.65; 95% CI, 0.47–0.90), FFS (adjusted HR, 0.59; 95% CI, 0.49–0.72), and progression-free survival (adjusted HR, 0.78; 95% CI, 0.63–0.98) in patients with low metastatic burden, but not in patients with high metastatic burden. Randomized clinical trials are ongoing to better test the value of removal or radiation of the primary tumor in patients with low metastatic burden who are beginning ADT.

The panel recommends against EBRT to the primary tumor in the case of high-volume M1 disease based on the HORRAD and STAMPEDE trials. No improvement in OS was seen from the addition of EBRT to the primary when combined with standard systemic therapy in patients with high-volume M1 disease in either trial.

Stereotactic Body Radiation Therapy

The relatively slow proliferation rate of prostate cancer is reflected in a low α/β ratio, most commonly reported between 1 and 4. These values are similar to that for the rectal mucosa. Because the α/β ratio for prostate cancer is similar to or lower than the surrounding tissues responsible for most of the toxicity reported with radiation, appropriately designed radiation treatment fields and schedules using extremely hypofractionated regimens should result in similar cancer control rates without increased risk of late toxicity.

Stereotactic body RT (SBRT) is a technique that delivers highly conformal, high-dose radiation in 5 or fewer treatment fractions, which are safe to administer only with precise, image-guided delivery. Single-institution series with median follow-up as long as 6 years report excellent biochemical progression-free survival and similar early toxicity (bladder, rectal, and QOL) compared to standard radiation techniques. According to a pooled analysis of phase 2 trials, the 5-year biochemical relapse-free survival is 95%, 84%, and 81% for patients with low-, intermediate-, and high-risk disease, respectively. A study of individual patient data from a cohort of 2142 patients with low or intermediate-risk prostate cancer from 10 single institution phase 2 trials and 2 multi-institutional phase 2 trials found that the 7-year cumulative rates of biochemical recurrence were 4.5%, 8.6%, and 14.9% for low-risk disease, favorable intermediate risk disease, and unfavorable intermediate risk disease, respectively. Severe acute toxicity was rare, at 0.6% for grade 3 or higher genitourinary toxic events and 0.09% for grade 3 or higher gastrointestinal toxic events. Late (7-year cumulative incidence) toxicity rates were 2.4% and 0.4% for grade 3 or higher genitourinary toxic events and gastrointestinal toxic events, respectively.

SBRT may be associated with more toxicity than moderately fractionated IMRT. One retrospective study of 4005 patients reported higher...
genitourinary toxicity at 24 months after SBRT than IMRT (44% vs. 36%; \( P = .001 \)). Another phase 2 trial found increased toxicity with doses >47.5 Gy delivered in 5 fractions. An analysis using the SEER database also reported that SBRT was more toxic than IMRT.

A phase 3 trial has been initiated that is comparing 38 Gy in 5 fractions with 79.2 Gy in 44 fractions. Preliminary results show that the cumulative incidence of grade 2 or higher genitourinary and bowel toxicity was similar between the arms after median follow-up of 36 months in 75 patients.

SBRT/extremely hypofractionated image-guided IMRT regimens (6.5 Gy per fraction or greater) can be considered as an alternative to conventionally fractionated regimens at clinics with appropriate technology, physics, and clinical expertise. Longer follow-up and prospective multi-institutional data are required to evaluate longer-term results, especially because late toxicity theoretically could be worse in hypofractionated regimens compared to conventional fractionation (1.8–2.0 Gy per fraction).

Brachytherapy

Brachytherapy involves placing radioactive sources into the prostate tissue. Brachytherapy has been used traditionally for low-risk cases because earlier studies found it less effective than EBRT for high-risk disease. However, increasing evidence suggests that technical advancements in brachytherapy may provide a role for contemporary brachytherapy in high-risk localized and locally advanced prostate cancer.

The advantage of brachytherapy is that the treatment is completed in 1 day with little time lost from normal activities. In appropriate patients, the cancer-control rates appear comparable to radical prostatectomy (over 90%) for low-risk prostate cancer with medium-term follow-up. In addition, the risk of incontinence is minimal in patients without a previous transurethral resection of the prostate (TURP), and erectile function is preserved in the short term. Disadvantages of brachytherapy include the requirement for general anesthesia and the risk of acute urinary retention. Irritative voiding symptoms may persist for as long as 1 year after implantation. The risk of incontinence is greater after TURP because of acute retention and bladder neck contractures, and many patients develop progressive erectile dysfunction over several years. IMRT causes less acute and late genitourinary toxicity and similar freedom from biochemical recurrence compared with iodine-125 or palladium-103 permanent seed implants. Current brachytherapy techniques attempt to improve the radioactive seed placement and radiation dose distribution.

There are currently two methods for prostate brachytherapy: low dose-rate (LDR) and high dose-rate (HDR). LDR brachytherapy consists of placement of permanent seed implants in the prostate. The short range of the radiation emitted from these low-energy sources allows delivery of adequate dose levels to the cancer within the prostate, with excessive irradiation of the bladder and rectum avoided. Post-implant dosimetry should be performed to document the quality of an LDR implant. HDR brachytherapy, which involves temporary insertion of a radiation source, is a newer approach.

Two groups have observed a lower risk of urinary frequency, urgency, and rectal pain with HDR brachytherapy compared with LDR brachytherapy (permanent seed implant). Vargas and colleagues reported that HDR brachytherapy results in a lower risk of erectile dysfunction than LDR brachytherapy. Commonly prescribed doses for LDR and HDR brachytherapy are listed in the guidelines.

For patients with very large or very small prostates, symptoms of bladder outlet obstruction (high International Prostate Symptom Score), or a previous TURP, seed implantation may be more difficult. These patients...
also have an increased risk of side effects. Neoadjuvant ADT may be used to shrink the prostate to an acceptable size; however, increased toxicity is expected from ADT, and prostate size may not decline in some men. The potential toxicity of ADT must be weighed against the possible benefit of target reduction.

Ideally, the accuracy of brachytherapy treatment should be verified by daily prostate localization with techniques of ICRT: CT, ultrasound, Implanted fiducials, or electromagnetic targeting/tracking. Endorectal balloons may be used to improve prostate immobilization. Perirectal spacer materials (discussed under External Beam Radiation Therapy, above) may be employed when the previously mentioned techniques are insufficient to improve oncologic cure rates and/or reduce side effects due to anatomic geometry or other patient-related factors (e.g., medication usage, comorbid conditions). Patients with obvious rectal invasion or visible T3 and posterior extension should not undergo perirectal spacer implantation.

Brachytherapy Alone for Localized Disease
Brachytherapy alone is an option for patients with very low, low, or favorable intermediate-risk prostate cancer, depending on life expectancy. Patients with high-risk cancers are generally considered poor candidates for brachytherapy alone. Either LDR or HDR brachytherapy can be used in this setting.

Retrospective analyses show that LDR or HDR brachytherapy alone can be effective and well tolerated in this population. A phase 2 trial in 300 patients with intermediate-risk prostate cancer also found LDR brachytherapy alone to be safe and effective. However, randomized controlled trials comparing brachytherapy to radical prostatectomy or EBRT in this population are limited. In a single-center trial, 165 patients with low-risk prostate cancer were randomized to LDR brachytherapy with iodine-125 seeds or radical prostatectomy. The 2-year biochemical FFS rates were similar between the groups at 96.1% after brachytherapy and 97.4% after radical prostatectomy (P = .35). At 6 months follow-up, continence was better in the brachytherapy group whereas potency was better in the radical prostatectomy group.

Brachytherapy Boost
LDR or HDR brachytherapy can be added as a boost to EBRT plus ADT in men with unfavorable intermediate-, high-, or very-high-risk prostate cancer being treated with curative intent. Combining EBRT and brachytherapy allows dose escalation while minimizing acute or late toxicity in patients with high-risk localized or locally advanced cancer.

This combination has demonstrated improved biochemical control over EBRT plus ADT alone in randomized trials, but with higher toxicity. An analysis of a cohort of 12,745 patients with high-risk disease found that treatment with brachytherapy (HR, 0.66; 95% CI, 0.49–0.86) or brachytherapy plus EBRT (HR, 0.77; 95% CI, 0.66–0.90) lowered disease-specific mortality compared to EBRT alone.

The randomized ASCEND-RT trial compared 2 methods of dose escalation in 398 men with intermediate- or high-risk prostate cancer; dose-escalated EBRT boost to 78 Gy or LDR brachytherapy boost. All men were initially treated with 12 months of ADT and pelvic EBRT to 46 Gy. An intention-to-treat analysis found that the primary endpoint of biochemical progression-free survival was 89% versus 84% at 5 years; 86% versus 75% at 7 years; and 83% versus 62% at 9 years for the LDR versus EBRT boost arms (log-rank P < .001). Toxicity was higher in the brachytherapy arm, with the cumulative incidence of grade 3 genitourinary events at 5 years of 18.4% for brachytherapy boost and 5.2% for EBRT boost (P < .001). A trend for increased gastrointestinal toxicity with brachytherapy boost was also seen (cumulative incidence of grade 3 events at 5 years, 8.1% vs. 3.2%; P = .12). However, at 6-year follow-up, health-related QOL was similar between the groups in most domains,
except that physical and urinary function scales were significantly lower in the LDR arm.\textsuperscript{401} Whereas the toxicity is increased with the use of brachytherapy boost, this and other randomized controlled trials have failed to show an improvement in overall or cancer-specific survival.\textsuperscript{402}

Addition of ADT (2 or 3 years) to brachytherapy and EBRT is common for patients at high risk of recurrence. The outcome of trimodality treatment is excellent, with 9-year progression-free survival and disease-specific survival reaching 87% and 91%, respectively.\textsuperscript{403,404} However, it remains unclear whether the ADT component contributes to outcome improvement. D'Amico and colleagues studied a cohort of 1342 patients with PSA over 20 ng/mL and clinical T3/T4 and/or Gleason score 8 to 10 disease.\textsuperscript{405} Addition of either EBRT or ADT to brachytherapy did not confer an advantage over brachytherapy alone. The use of all three modalities reduced prostate cancer-specific mortality compared to brachytherapy alone (adjusted HR, 0.32; 95% CI, 0.14–0.73). Other analyses did not find an improvement in recurrence rate when ADT was added to brachytherapy and EBRT.\textsuperscript{406,407}

A large, multicenter, retrospective cohort analysis that included 1809 men with Gleason score 9–10 prostate cancer found that multimodality therapy with EBRT, brachytherapy, and ADT was associated with improved prostate cancer-specific mortality and longer time to distant metastasis than either radical prostatectomy or EBRT with ADT.\textsuperscript{408} In addition, an analysis of outcomes of almost 43,000 men with high-risk prostate cancer in the National Cancer Database found that mortality was similar in men treated with EBRT, brachytherapy, and ADT versus those treated with radical prostatectomy, but was worse in those treated with EBRT and ADT.\textsuperscript{409}

**Salvage Brachytherapy**

Brachytherapy can be considered in men with biochemical recurrence after EBRT. In a retrospective study of 24 men who had EBRT as primary therapy and permanent brachytherapy after biochemical recurrence, the cancer-free and biochemical relapse-free survival rates were 96% and 88%, respectively, after a median follow-up of 30 months.\textsuperscript{410} Results of a phase 2 study of salvage HDR brachytherapy after EBRT included relapse-free survival, distant metastases-free survival, and cause-specific survival rates of 68.5%, 81.5%, and 90.3%, respectively, at 5 years.\textsuperscript{411} Toxicities were mostly grade 1 and 2 and included gastrointestinal toxicity and urethral strictures, and one case of Grade 3 urinary incontinence. In another prospective phase 2 trial, the primary endpoint of grade ≥3 late treatment-related gastrointestinal and genitourinary adverse events at 9 to 24 months post salvage brachytherapy was below the unacceptable threshold, at 14%.\textsuperscript{412}

Data on the use of brachytherapy after permanent brachytherapy are limited, but the panel agrees that it can be considered for carefully selected patients. Decisions regarding the use of brachytherapy in the recurrent-disease setting should consider comorbidities, extent of disease, and potential complications. Brachytherapy in this setting is best performed at high-volume centers.

**Proton Therapy**

Proton beam RT has been used to treat patients with cancer since the 1950s. Proponents of proton therapy argue that this form of RT could have advantages over x-ray (photon)-based radiation in certain clinical circumstances. Proton therapy and x-ray-based therapies like IMRT can deliver highly conformal doses to the prostate. Proton-based therapies will deliver less radiation dose to some of the surrounding normal tissues like muscle, bone, vessels, and fat not immediately adjacent to the prostate. These tissues do not routinely contribute to the morbidity of prostate radiation and are relatively resilient to radiation injury; therefore, the benefit of decreased dose to these types of normal, non-critical tissues has not been apparent. The critical normal structures adjacent to the
prostate that can create prostate cancer treatment morbidity include the bladder, rectum, neurovascular bundles, and occasionally small bowel.

The weight of the current evidence about prostate cancer treatment morbidity supports the notion that the volume of the rectum and bladder that receives radiobiologically high doses of radiation near the prescription radiation dose accounts for the likelihood of long-term treatment morbidity, as opposed to higher volume, lower dose exposures. Numerous dosimetric studies have been performed trying to compare x-ray-based IMRT plans to proton therapy plans to illustrate how one or the other type of treatment can be used to spare the bladder or rectum from higher dose parts of the exposure. These studies suffer from the biases and talents of the investigators who plan and create computer models of dose deposition for one therapy or the other. Although dosimetric studies in-silico can suggest that the right treatment planning can make an IMRT plan beat a proton therapy plan and vice-versa, they do not accurately predict clinically meaningful endpoints.

Comparative effectiveness studies have been published in an attempt to compare toxicity and oncologic outcomes between proton and photon therapies. Two comparisons between men treated with proton therapy or EBRT report similar early toxicity rates. A prospective QOL comparison of patient-reported outcomes using the EPIC instrument between IMRT (204 patients) and proton therapy (1234 patients) concluded that “No differences were observed in summary score changes for bowel, urinary incontinence, urinary irritative/obstructive, and sexual domains between the 2 cohorts” after up to 2 years of follow-up. A Medicare analysis of 421 men treated with proton therapy and a matched cohort of 842 men treated with IMRT showed less genitourinary toxicity at 6 months for protons, although the difference disappeared after 1 year. No other significant differences were seen between the groups. In contrast, a single-center report of prospectively collected QOL data revealed significant problems with incontinence, bowel dysfunction, and impotence at 3 months, 12 months, and >2 years after treatment with proton therapy. In that report, only 28% of men with normal erectile function maintained it after therapy. The largest retrospective comparative effectiveness analysis to date comparing IMRT to proton therapy was performed using SEER-Medicare claims data for the following long-term endpoints: gastrointestinal morbidity, urinary incontinence, non-incontinence urinary morbidity, sexual dysfunction, and hip fractures. With follow-up as mature as 80 months and using both propensity scoring and instrumental variable analysis, the authors concluded that men receiving IMRT therapy had statistically significantly lower gastrointestinal morbidity than patients receiving proton therapy, whereas rates of urinary incontinence, non-incontinence urinary morbidity, sexual dysfunction, hip fractures, and additional cancer therapies were statistically indistinguishable between the cohorts. However, firm conclusions regarding differences in toxicity or effectiveness of proton and photon therapy cannot be drawn because of the limitations inherent in retrospective/observational studies.

The costs associated with proton beam facility construction and proton beam treatment are high compared to the expense of building and using the more common photon linear accelerator-based practice. The American Society for Radiation Oncology (ASTRO) evaluated proton therapy and created a model policy to support the society’s position on payment coverage for proton beam therapy in 2014. This model policy was updated in 2017 and recommends coverage of proton therapy for the treatment of non-metastatic prostate cancer if the patient is enrolled in either an institutional review board (IRB)-approved study or a multi-institutional registry that adheres to Medicare requirements for Coverage with Evidence Development (CED). The policy states: “In the treatment of prostate cancer, the use of [proton beam therapy] is evolving as the comparative efficacy evidence is still being developed. In order for an
informed consensus on the role of [proton beam therapy] for prostate cancer to be reached, it is essential to collect further data, especially to understand how the effectiveness of proton therapy compares to other RT modalities such as IMRT and brachytherapy. There is a need for more well-designed registries and studies with sizable comparator cohorts to help accelerate data collection. Proton beam therapy for primary treatment of prostate cancer should only be performed within the context of a prospective clinical trial or registry.

An ongoing prospective randomized trial is accruing patients to compare prostate proton therapy and prostate IMRT. The NCCN Panel believes no clear evidence supports a benefit or decrement to proton therapy over IMRT for either treatment efficacy or long-term toxicity. Conventionally fractionated prostate proton therapy can be considered a reasonable alternative to x-ray–based regimens at clinics with appropriate technology, physics, and clinical expertise.

Radiation for Distant Metastases
Radiation is an effective means of palliating bone metastases from prostate cancer. Isolated symptomatic bone metastases can be managed with EBRT. Recent studies have confirmed the common practice in Canada and Europe of managing prostate cancer with bone metastases with a short course of radiation. A short course of 8 Gy x 1 is as effective as, and less costly than, 30 Gy in 10 fractions. In a randomized trial of 898 patients with bone metastases, grade 2–4 acute toxicity was observed less often in the 8-Gy arm (10%) than the 30-Gy arm (17%) \(P = .002\); however, the relapse rate was higher in the 8-Gy group (18%) than in the 30-Gy group (9%) \(P < .001\). In another study of 425 patients with painful bone metastases, a single dose of 8 Gy was non-inferior to 20 Gy in multiple fractions in terms of overall pain response to treatment. Most patients should be managed with a single fraction of 8 Gy for non-vertebral metastases based on therapeutic guidelines from the American College of Radiology.\(^{423}\)

Radium-223 and Other Radiopharmaceuticals
In May 2013, the U.S. Food and Drug Administration (FDA) approved radium-223 dichloride, an alpha particle-emitting radioactive agent. This first-in-class radiopharmaceutical was approved for treatment of metastatic CRPC in patients with symptomatic bone metastases and no known visceral metastatic disease. Approval was based on clinical data from a multicenter, phase 3, randomized trial (ALSYMPCA) that included 921 men with symptomatic CRPC, 2 or more bone metastases, and no known visceral disease.\(^{424}\) Fifty-seven percent of the patients received prior docetaxel and all patients received best supportive care. Patients were randomized in a 2:1 ratio to 6 monthly radium-223 intravenous injections or placebo. Compared to placebo, radium-223 significantly improved OS (median 14.9 months vs. 11.3 months; HR, 0.70; 95% CI, 0.58–0.83; \(P < .001\)) and prolonged time to first skeletal-related event (SRE) (median 15.6 months vs. 9.8 months). Preplanned subset analyses showed that the survival benefit of radium-223 was maintained regardless of prior docetaxel use.\(^{425}\) Intent-to-treat analyses from ALSYMPCA showed that radium-223 also may reduce the risk of symptomatic SREs.\(^{426}\) Grade 3/4 hematologic toxicity was low (3% neutropenia, 6% thrombocytopenia, and 13% anemia), likely due to the short range of radioactivity.\(^{424}\) Fecal elimination of the agent led to generally mild non-hematologic side effects, which included nausea, diarrhea, and vomiting. Radium-223 was associated with improved or slower decline of QOL in ALSYMPCA.\(^{427}\)

An international, open-label, single-arm phase 3b trial of radium-223 in symptomatic and asymptomatic patients treated in an early access program showed that radium-223 can be combined safely with abiraterone or enzalutamide and suggested that it can be administered safely to asymptomatic patients.\(^{428}\) A phase 2 U.S. expanded access program also
Beta-emitting radiopharmaceuticals are an effective and appropriate option for patients with widespread metastatic disease, particularly if they are no longer candidates for effective chemotherapy. Because many patients have multifocal bone pain, systemic targeted treatment of skeletal metastases offers the potential of pain relief with minimal side effects. Unlike the alpha-emitting agent radium-223, beta emitters confer no survival advantage and are palliative. Beta-emitting radiopharmaceuticals developed for the treatment of painful bone metastases most commonly used for prostate cancer include strontium-89 (89Sr) or samarium-153 (153Sm).\(^{33,34}\)

**Comparison of Treatment Options for Localized Disease**

Several large prospective, population/cohort-based studies have compared the outcomes of patients with localized prostate cancer treated with EBRT, brachytherapy, radical prostatectomy, observation, and/or active surveillance. Barocas et al compared radical prostatectomy, EBRT, and active surveillance in 2550 men and found that, after 3 years, radical prostatectomy was associated with a greater decrease in urinary and sexual function than either EBRT or active surveillance.\(^{32}\) Active surveillance, however, was associated with an increase in urinary irritative symptoms. Health-related QOL measures including bowel and hormonal function were similar among the groups, as was disease-specific survival.

Chen et al compared radical prostatectomy, EBRT, and brachytherapy against active surveillance in 1141 men.\(^{33}\) As in the Barocas study, radical prostatectomy was associated with greater declines in sexual and urinary function than other treatments at 3 months. In this study, EBRT was associated with worse short-term bowel function, and both EBRT and brachytherapy were associated with worsened urinary obstructive and irritative symptoms. By 2 years, however, differences among the groups compared with active surveillance were insignificant. Results of a systematic review showed similar findings to these studies.\(^{34}\)

**Other Local Therapies**

Many therapies have been investigated for the treatment of localized prostate cancer in the initial disease and recurrent settings, with the goals of reducing side effects and matching the cancer control of other therapies. At this time, the panel recommends only cryosurgery and high-intensity focused ultrasound (HIFU) as options for RT recurrence in the absence of metastatic disease.

Cryoablation, also known as cryotherapy or cryoablation, is an evolving minimally invasive therapy that damages tumor tissue through local freezing. In the initial disease setting, the reported 5-year biochemical disease-free rate after cryotherapy ranged from 65% to 92% in patients with low-risk disease using different definitions of biochemical recurrence. A report suggests that cryotherapy and radical prostatectomy give similar oncologic results for unilateral prostate cancer. A study by Donnelly and colleagues randomly assigned 244 men with T2 or T3 disease to either cryotherapy or EBRT. All patients received neoadjuvant ADT. There was no difference in 3-year OS or DFS. Patients who received cryotherapy reported poorer sexual function. For patients with locally advanced cancer, cryoablation was associated with lower 8-year biochemical progression-free rate compared to EBRT in a small trial of 62 patients, although disease-specific survival and OS were similar.\(^{39}\)

Cryosurgery has been assessed in patients with recurrent disease after RT. In one registry-based study of 91 patients, the biochemical DFS rates at 1, 3, and 5 years were 95.3%, 72.4%, and 46.5%, respectively.


NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Head and Neck Cancers

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**NCCN Guidelines Version 3.2019**  
**Cancer of the Lip (Mucosa)**

## PRINCIPLES OF RADIATION THERAPY

### DEFINITIVE:
- **RT Alone**
  - Planning target volume (PTV)
    - **High risk:** Primary tumor and involved lymph nodes [this includes possible local subclinical infiltration at the primary site and at the high-risk level lymph node(s)]
      - $66 \text{ Gy (2.2 Gy/fraction)}$ to $70 \text{ Gy (2.0 Gy/fraction)}$; daily
      - Monday–Friday in 6–7 weeks
  - **Low to intermediate risk:** Sites of suspected subclinical spread
    - $44–50 \text{ Gy (2.0 Gy/fraction)}$ to $54–63 \text{ Gy (1.6–1.8 Gy/fraction)}$
  - External beam RT (EBRT) ± brachytherapy
  - **Brachytherapy**
    - Intermittent brachytherapy is considered for selected cases
      - **Low dose-rate (LDR) brachytherapy (0.4–0.5 Gy per hour)**
        - Consider LDR boost 20–35 Gy if combined with 50 Gy EBRT or 60–70 Gy over several days if using LDR as sole therapy
      - **High dose-rate (HDR) brachytherapy**
        - Consider HDR boost 21 Gy at 3 Gy/fraction if combined with 40–50 Gy EBRT or 45–60 Gy at 3–6 Gy/fraction if using HDR as sole therapy

Either intensity-modulated RT (IMRT) or 3D conformal RT is recommended.

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### CONCURRENT CHEMORADIATION

#### PTV:
- **High risk:** Typically $70 \text{ Gy (2.0 Gy/fraction)}$
- **Low to intermediate risk:** $44–50 \text{ Gy (2.0 Gy/fraction)}$ to $54–63 \text{ Gy (1.6–1.8 Gy/fraction)}$

#### POSTOPERATIVE:
- Preferred interval between resection and postoperative RT is ≤6 weeks
- **PTV**
  - **High risk:** Adverse features such as positive margins (see footnote j on LIP-3)
    - $60–66 \text{ Gy (2.0 Gy/fraction)}$ daily Monday–Friday in 6–6.5 weeks
  - **Low to intermediate risk:** Sites of suspected subclinical spread
    - $44–50 \text{ Gy (2.0 Gy/fraction)}$ to $54–63 \text{ Gy (1.6–1.8 Gy/fraction)}$
  - For T1–T2 simple lesions, treat with postoperative RT as per non-melanoma skin cancers. See the NCCN Guidelines for Non-Melanoma Skin Cancers.

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*See Radiation Techniques (RAD-A) and Discussion.*

1. For doses >70 Gy, some clinicians feel that the fractionation should be slightly modified (eg, <2.0 Gy/fraction for at least some of the treatment) to minimize toxicity. An additional 2–3 doses can be added depending on clinical circumstances.

2. Suggest 44–50 Gy in 3D conformal RT and sequentially planned IMRT or 54–63 Gy with IMRT dose painting technique (dependent on dose per fraction).


5. The interval between EBRT and brachytherapy should be at least 6 hours, but at least 1–2 weeks, depending on recovery from acute toxicity. The interval between LDR fractions should be at least 6 hours.


7. Based on published data, concurrent chemoradiation most commonly uses conventional fractionation at 2.0 Gy per fraction to a typical dose of 70 Gy in 7 weeks with single-agent cisplatin given every 3 weeks at 100 mg/m²; 2–3 cycles of chemotherapy are used depending on the radiation fractionation scheme (RTOG 0129) (Arg KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 2010;363:24–35). When carboplatin and 5-FU are used, the recommended regimen is standard fractionation plus 3 cycles of chemotherapy. (Bourhis J, Sire C, Graff P, et al. Concomitant chemoradiotherapy versus acceleration of radiotherapy with or without concomitant chemotherapy in locally advanced head and neck carcinoma (GORTEC 99-02): an open-label phase 3 randomised trial. Lancet Oncol 2012;13:145-153.) Other fraction sizes (eg, 1.8 Gy, conventional), multiagent chemotherapy, other dosing schedules of cisplatin, or altered fractionation with chemotherapy are efficacious, and there is no consensus on the optimal approach. In general, the use of concurrent chemoradiation carries a high toxicity burden; altered fractionation or multiagent chemotherapy will likely further increase the toxicity burden. For any chemoradiation approach, close attention should be paid to published reports for the specific chemotherapy agent, dose, and schedule of administration. Chemoradiation should be performed by an experienced team and should include substantial supportive care.

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

DEFINITIVE:
RT Alone

• PTV:
  ▶ High risk: Primary tumor and involved lymph nodes [this includes possible local subclinical infiltration at the primary site and at the high-risk level lymph node(s)]:
    ◦ Fractionation:
      - 66 Gy (2.2 Gy/fraction) to 70 Gy (2.0 Gy/fraction); daily Monday–Friday in 6–7 weeks
      - Concomitant boost accelerated RT:
        - 72 Gy/6 weeks (1.8 Gy/fraction, large field; 1.5 Gy boost as second daily fraction during last 12 treatment days)
        - 66–70 Gy (2.0 Gy/fraction; 6 fractions/wk accelerated)
      - Hyperfractionation: 81.6 Gy/7 weeks (1.2 Gy/fraction, twice daily)
  ▶ Low to intermediate risk: Sites of suspected subclinical spread
    ◦ 44–50 Gy (2.0 Gy/fraction) to 54–63 Gy (1.6–1.8 Gy/fraction)

• Brachytherapy
  ▶ Interstitial brachytherapy is considered for selected cases.
    ◦ LDR brachytherapy (0.4–0.5 Gy per hour):
      - Consider LDR boost 20–35 Gy if combined with 50 Gy EBRT or 60–70 Gy over several days if using LDR as sole therapy.
    ◦ HDR brachytherapy:
      - Consider HDR boost 21 Gy at 3 Gy/fraction if combined with 40–50 Gy EBRT or 45–60 Gy at 3–6 Gy/fraction if using HDR as sole therapy.

For unresectable disease, see ADV-1.
Either IMRT or 3D conformal RT is recommended.

1See Radiation Techniques (RAD-A) and Discussion.
2For doses >70 Gy, some clinicians feel that the fractionation should be slightly modified (eg, <2.0 Gy/fraction for at least some of the treatment) to minimize toxicity. An additional 2–3 doses can be added depending on clinical circumstances.
3Suggest 44–50 Gy in 3D conformal RT and sequentially planned IMRT or 54–63 Gy with IMRT dose painting technique (dependent on dose per fraction).
5The interval between EBRT and brachytherapy should be as short as possible (1–2 weeks) depending on recovery from acute toxicity. The interval between HDR fractions should be at least 6 hours.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
PRINCIPLES OF RADIATION THERAPY¹

POSTOPERATIVE:
RT or Concurrent Systemic Therapy/RT⁰¹⁰
- Preferred interval between resection and postoperative RT is ≤6 weeks.
- PTV
  - High risk: Adverse features such as positive margins (see footnote j on OR-3)
    - 60–66 Gy (2.0 Gy/fraction); daily Monday–Friday in 6–6.5 weeks
  - Low to intermediate risk: Sites of suspected subclinical spread
    - 44–50 Gy (2.0 Gy/fraction) to 54–63 Gy (1.6–1.8 Gy/fraction)²

Either IMRT or 3D conformal RT is recommended.

¹See Radiation Techniques (RAD-A) and Discussion.
²Suggest 44–50 Gy in 3D conformal RT and sequentially planned IMRT or 54–63 Gy with IMRT dose painting technique (dependent on dose per fraction).
³See Principles of Systemic Therapy (CHEM-A).

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PRINCIPLES OF RADIATION THERAPY

DEFINITIVE:
RT Alone
• PTV
  ▶ High risk: Primary tumor and involved lymph nodes (this includes possible local subclinical infiltration at the primary site and at the high-risk level lymph node(s)
    ◊ Fractionation:
      - 66 Gy (2.2 Gy/fraction) to 70 Gy (2.0 Gy/fraction);
        daily Monday–Friday in 6–7 weeks
      - Concomitant boost accelerated RT:
        * 72 Gy/6 weeks (1.8 Gy/fraction, large field; 1.5 Gy boost as second daily fraction during last 12 treatment days)
        * 66–70 Gy (2.0 Gy/fraction; 6 fractions/wk accelerated)
        - Hyperfractionation: 81.6 Gy/7 weeks (1.2 Gy/fraction, twice daily)
          - 69.6 Gy (2.12 Gy/fraction) daily Monday–Friday in 6–7 weeks
  ▶ Low to intermediate risk: Sites of suspected subclinical spread
    ◊ 44–50 Gy (2.0 Gy/fraction) to 54–63 Gy (1.6–1.8 Gy/fraction)
• Treatment de-intensification is an area of active research, with several published phase II studies demonstrating promising rates of progression-free survival with dose-reduced radiotherapy.

CONCURRENT CHEMORADIATION:5,6
• PTX:
  ▶ High risk: Typically 70 Gy (2.0 Gy/fraction)
  ▶ Low to intermediate risk: 44–50 Gy (2.0 Gy/fraction) to 54–63 Gy (1.6–1.8 Gy/fraction)

Either IMRT (preferred) or 3D conformal RT is recommended for cancers of the oropharynx in order to minimize dose to critical structures. Use of proton therapy is an area of active investigation. Proton therapy may be considered when normal tissue constraints cannot be met by photon-based therapy.

6Based on published data, concurrent chemoradiation most commonly uses conventional fractionation at 2.0 Gy per fraction to a typical dose of 70 Gy in 7 weeks with single-agent cisplatin given every 3 weeks at 100 mg/m2; 2–3 cycles of chemotherapy are used depending on the radiation fractionation scheme (RTOG 0129) (Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 2010;363:24–35). When carboplatin and 5-FU are used, the recommended regimen is standard fractionation plus 3 cycles of chemotherapy. (Bourhis J, Siro C, Graff P, et al. Concomitant chemoradiotherapy versus acceleration of radiotherapy with or without concomitant chemotherapy in locally advanced head and neck carcinoma (GORTEC 99-02): an open-label phase 3 randomised trial. Lancet Oncol 2012;13:145–153). Other fraction sizes (eg, 1.8 Gy, conventional), multiagent chemotherapy, other dosing schedules of cisplatin, or altered fractionation with chemotherapy are efficacious, and there is no consensus on the optimal approach. In general, the use of concurrent chemoradiation carries a high toxicity burden; altered fractionation or multiagent chemotherapy will likely further increase the toxicity burden. For any chemoradiation approach, close attention should be paid to published reports for the specific chemotherapy agent, dose, and schedule of administration. Chemoradiation should be performed by an experienced team and should include substantial supportive care.

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

POSTOPERATIVE:

RT or Concurrent Systemic Therapy/RT

- Preferred interval between resection and postoperative RT is ≤6 weeks.
- PTV

High risk: Adverse features such as positive margins (See footnote m on ORPH-A)
  ◯ 60–66 Gy (2.0 Gy/fraction); daily Monday–Friday in 6–6.5 weeks
  ◯ Low to intermediate risk: sites of suspected subclinical spread
  ◯ 44–50 Gy (2.0 Gy/fraction) to 54–63 Gy (1.6–1.8 Gy/fraction)\textsuperscript{5}

Either IMRT (preferred) or 3D conformal RT is recommended for cancers of the oropharynx in order to minimize dose to critical structures. Use of proton therapy is an area of active investigation. Proton therapy may be considered when normal tissue constraints cannot be met by photon-based therapy.

\textsuperscript{1}See Radiation Techniques (RAD-A) and Discussion.
\textsuperscript{2}Suggest 44–50 Gy in 3D conformal RT and sequentially planned IMRT or 54–63 Gy with IMRT dose painting technique (dependent on dose per fraction).
\textsuperscript{3}See Principles of Systemic Therapy (CHEM-A).
Cancer of the Hypopharynx

PRINCIPLES OF RADIATION THERAPY

DEFINITIVE:
RT Alone
• PTV
  › High risk: Primary tumor and involved lymph nodes (this includes possible local subclinical infiltration at the primary site and at the high-risk level lymph node(s))
    ◦ Fractionation:
      – 66 Gy (2.2 Gy/fraction) to 70 Gy (2.0 Gy/fraction); daily Monday–Friday in 6–7 weeks
      – 69.6 Gy (2.12 Gy/fraction) daily Monday–Friday in 6–7 weeks
      – Concomitant boost accelerated RT:
        ◦ 72 Gy/6 weeks (1.8 Gy/fraction, large field; 1.5 Gy boost as second daily fraction during last 12 treatment days)
        ◦ 66–70 Gy (2.0 Gy/fraction; 6 fractions/wk accelerated)
        – Hyperfractionation: 81.6 Gy/7 weeks (1.2 Gy/fraction, twice daily)
  › Low to intermediate risk: Sites of suspected subclinical spread
    ◦ 44–50 Gy (2.0 Gy/fraction) to 54–63 Gy (1.6–1.8 Gy/fraction)

CONCURRENT CHEMORADIATION
• PTV
  › High risk: typically 70 Gy (2.0 Gy/fraction)
  › Low to intermediate risk: 44–50 Gy (2.0 Gy/fraction) to 54–63 Gy (1.6–1.8 Gy/fraction)

Either IMRT or 3D conformal RT is recommended.

1See Radiation Techniques (RAD-A) and Discussion.
2Particular attention to speech and swallowing is needed during therapy.
3For doses >70 Gy, some clinicians feel that the fractionation should be slightly modified (eg. <2.0 Gy/fraction for at least some of the treatment) to minimize toxicity. An additional 2–3 doses can be added depending on clinical circumstances.
5Suggest 44–50 Gy in 3D conformal RT and sequentially planned IMRT or 54–63 Gy with IMRT dose painting technique (dependent on dose per fraction).
6See Principles of Systemic Therapy (CHEM-A).
7Based on published data, concurrent chemoradiation most commonly uses conventional fractionation at 2.0 Gy per fraction to a typical dose of 70 Gy in 7 weeks with single-agent cisplatin given every 3 weeks at 100 mg/m2; 2–3 cycles of chemotherapy are used depending on the radiation fractionation scheme (RTOG 0129) (Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 2010;363:24-35). When carboplatin and 5-FU are used, the recommended regimen is standard fractionation plus 3 cycles of chemotherapy, (Bourhis J, Sire C, Graff P, et al. Concomitant chemoradiotherapy versus acceleration of radiotherapy with or without concomitant chemotherapy in locally advanced head and neck carcinoma (GORTEC 99-02): an open-label phase 3 randomised trial. Lancet Oncol 2012;13:145-153). Other fraction sizes (eg. 1.8 Gy, conventional), multiagent chemotherapy, other dosing schedules of cisplatin, or altered fractionation with chemotherapy are efficacious, and there is no consensus on the optimal approach. In general, the use of concurrent chemoradiation carries a high toxicity burden; altered fractionation or multiagent chemotherapy will likely further increase the toxicity burden. For any chemoradiation approach, close attention should be paid to published reports for the specific chemotherapy agent, dose, and schedule of administration. Chemoradiation should be performed by an experienced team and should include substantial supportive care.

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

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

RT or Concurrent Systemic Therapy/RT\(^6,8-11\)

- Preferred interval between resection and postoperative RT is ≤6 weeks.
- PTV
  - High risk: Adverse features such as positive margins (See footnote h on HYPO-3).
    - 60–66 Gy (2.0 Gy/fraction; daily Monday–Friday) in 6–6.5 weeks
  - Low to intermediate risk: sites of suspected subclinical spread
    - 44–50 Gy (2.0 Gy/fraction) to 54–63 Gy (1.6–1.8 Gy/fraction)\(^2\)

Either IMRT or 3D conformal RT is recommended.

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\(^1\) See Radiation Techniques (RAD-A) and Discussion.

\(^2\) Particular attention to speech and swallowing is needed during therapy.

\(^3\) Suggest 44–50 Gy in 3D conformal RT and sequentially planned IMRT or 54–63 Gy with IMRT dose painting technique (dependent on dose per fraction).

\(^4\) See Principles of Systemic Therapy (CHEM-A).


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

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

DEFINITIVE:
RT Alone (for T1, N0 or patients who are not eligible to receive chemotherapy)
• PTV
  › High risk: Primary tumor and involved lymph nodes [this includes possible local subclinical infiltration at the primary site and at the high-risk level lymph node(s)]
    ◦ 66 Gy (2.2 Gy/fraction) to 70–70.2 Gy (1.8–2.0 Gy/fraction); daily Monday–Friday in 6–7 weeks\(^2,3\)
    ◦ 69.96 Gy (2.12 Gy/fraction) daily Monday–Friday in 6–7 weeks\(^4\)
  › Low to intermediate risk: Sites of suspected subclinical spread
    › 44–50 Gy (2.0 Gy/fraction) to 54–63 Gy (1.6–1.8 Gy/fraction)\(^5\)

CONCURRENT CHEMORADIATION:\(^5\)
(preferred for patients eligible for chemotherapy)
• PTV
  › High risk: typically 70–70.2 Gy (1.8–2.0 Gy/fraction); daily Monday–Friday in 7 weeks\(^2\)
  › Low to intermediate risk: 44–50 Gy (2.0 Gy/fraction) to 54–63 Gy (1.6–1.8 Gy/fraction)\(^5\)

Either IMRT (preferred) or 3D conformal RT is recommended for cancers of the nasopharynx to minimize dose to critical structures. Proton therapy can be considered when normal tissue constraints cannot be met by photon-based therapy.

\(^1\)See Radiation Techniques (RAD-A) and Discussion.
\(^2\)Care should be taken to avoid critical neural structures; therefore, 1.8 Gy/fraction can be considered.
\(^3\)For doses >70 Gy, some clinicians feel that the fractionation should be slightly modified (eg, <2.0 Gy/fraction for at least some of the treatment) to minimize toxicity. An additional 2–3 doses can be added depending on clinical circumstances.
\(^5\)Suggest 44–50 Gy in 3D conformal RT and sequentially planned IMRT or 54–63 Gy with IMRT dose painting technique (dependent on dose per fraction).
\(^6\)See Principles of Systemic Therapy (CHEM-A).

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

CONCURRENT CHEMORADIATION

- PTV
  - High risk: typically 70 Gy (2.0 Gy/fraction)
  - Low to intermediate risk: 44–50 Gy (2.0 Gy/fraction) to 54–63 Gy (1.6–1.8 Gy/fraction)²

Either IMRT or 3D conformal RT is recommended.

¹See Radiation Techniques (RAD.A) and Discussion.
²For doses >70 Gy, some clinicians feel that the fractionation should be slightly modified (eg, <2.0 Gy/fraction for at least some of the treatment) to minimize toxicity. An additional 2–3 doses can be added depending on clinical circumstances.
³Suggest 44–50 Gy in 3D conformal RT and sequentially planned IMRT or 54–63 Gy with IMRT dose painting technique (dependent on dose per fraction).
⁴See Principles of Systemic Therapy (CHEM.A).
⁵Based on published data, concurrent chemoradiation most commonly uses conventional fractionation at 2.0 Gy per fraction to a typical dose of 70 Gy in 7 weeks with single-agent cisplatin given every 3 weeks at 100 mg/m²; 2–3 cycles of chemotherapy are used depending on the radiation fractionation scheme (RTOG 0129) (Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 2010;363:24-35). When carboplatin and 5-FU are used, then the recommended regimen is standard fractionation plus 3 cycles of chemotherapy. (Bourhis J, Sere C, Graff P, et al. Concomitant chemoradiotherapy versus acceleration of radiotherapy with or without concomitant chemotherapy in locally advanced head and neck carcinoma (GORTEC 99-02): an open-label phase 3 randomised trial. Lancet Oncol 2012;13:145-153). Other fraction sizes (eg, 1.8 Gy, conventional), multiagent chemotherapy, or other dosing schedules of cisplatin, or altered fractionation with chemotherapy are efficacious, and there is no consensus on the optimal approach. In general, the use of concurrent chemoradiation carries a high toxicity burden; altered fractionation or multiagent chemotherapy will likely further increase the toxicity burden. For any chemoradiation approach, close attention should be paid to published reports for the specific chemotherapy agent, dose, and schedule of administration. Chemoradiation should be performed by an experienced team and should include substantial supportive care.
**PRINCIPLES OF RADIATION THERAPY**

**POSTOPERATIVE:**
RT or Concurrent Systemic Therapy/RT

- Preferred interval between resection and postoperative RT is ≤6 weeks.
- PTV
  - High risk: Adverse features such as positive margins (See footnote j on GLOT-3).
    - 60–66 Gy (2.0 Gy/fraction); daily Monday–Friday in 6–6.5 weeks
  - Low to intermediate risk: sites of suspected subclinical spread
    - 44–50 Gy (2.0 Gy/fraction) to 54–63 Gy (1.6–1.8 Gy/fraction)

Either IMRT or 3D conformal RT is recommended.

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1. See Radiation Techniques (RAD-A) and Discussion.
2. Suggest 44–50 Gy in 3D conformal RT and sequentially planned IMRT or 54–63 Gy with IMRT dose painting technique (dependent on dose per fraction).
3. See Principles of Systemic Therapy (CHEM-A).

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

**DEFINITIVE:**
- RT Alone
  - T1-3, N0-1: 66–70 Gy conventional (2.0 Gy/fraction)
  - PTV
    - High risk: Primary tumor and involved lymph nodes [this includes possible local subclinical infiltration at the primary site and at the high-risk level lymph node(s)]
      - Fractionation: 66 Gy (2.2 Gy/fraction) to 70 Gy (2.0 Gy/fraction); daily Monday–Friday in 6–7 weeks
      - Concomitant boost accelerated RT:
        - 72 Gy/6 weeks (1.8 Gy/fraction, large field; 1.5 Gy boost as second daily fraction during last 12 treatment days)
        - 66–70 Gy (2.0 Gy/fraction; 6 fractions/wk accelerated)
      - Hyperfractionation: 79.2–81.6 Gy/7 weeks (1.2 Gy/fraction twice daily)
  - Low to intermediate risk: Sites of suspected subclinical spread
    - 44–50 Gy (2.0 Gy/fraction) to 54–63 Gy (1.6–1.8 Gy/fraction)

**CONCURRENT CHEMORADIATION:**
- PTV
  - High risk: typically 70 Gy (2.0 Gy/fraction)
  - Low to intermediate and low risk: 44–50 Gy (2.0 Gy/fraction) to 54–63 Gy (1.6–1.8 Gy/fraction)

Either IMRT or 3D conformal RT is recommended. Use of proton therapy is an area of active investigation. Proton therapy may be considered when normal tissue constraints cannot be met by photon-based therapy.

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

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**POSTOPERATIVE:**

RT or Concurrent Systemic Therapy/RT\(^5,7-10\)

- Preferred interval between resection and postoperative RT is ≤ 6 weeks.
- PTV
  - **High risk:** Adverse features such as positive margins (See footnote h on SUPRA-3).
    - 60–66 Gy (2.0 Gy/fraction); daily Monday–Friday in 6–6.5 weeks
  - **Low to intermediate risk:** sites of suspected subclinical spread
    - 44–50 Gy (2.0 Gy/fraction) to 54–63 Gy (1.6–1.8 Gy/fraction)\(^4\)

Either IMRT or 3D conformal RT is recommended. Use of proton therapy is an area of active investigation. Proton therapy may be considered when normal tissue constraints cannot be met by photon-based therapy.

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\(^1\)See Radiation Techniques (RAD-A) and Discussion.

\(^4\)Suggest 44–50 Gy in 3D conformal RT and sequentially planned IMRT or 54–63 Gy with IMRT dose painting technique (dependent on dose per fraction).

\(^5\)See Principles of Systemic Therapy (CHEM-A).


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Ethmoid Sinus Tumors

PRINCIPLES OF RADIATION THERAPY

DEFINITIVE:
RT Alone
• PTV
  ▶ High risk: Primary tumor and involved lymph nodes [this includes possible local subclinical infiltration at the primary site and at the high-risk level lymph node(s)]
    ◦ Fractionation:
      - 66 Gy (2.2 Gy/fraction) to 70–70.2 Gy (1.8–2.0 Gy/fraction); daily Monday–Friday in 6–7 weeks
      - Concomitant boost accelerated RT:
        ◦ 72 Gy/6 weeks (2 Gy once daily and then 1.8 Gy/fraction, large field; 1.5 Gy boost as second daily fraction during last 12 treatment days)
        ◦ 66–70 Gy (2.0 Gy/fraction; 6 fractions/wk accelerated)
        ◦ Hyperfractionation: 81.6 Gy/7 weeks (1.2 Gy/fraction, twice daily)
  ▶ Low to intermediate risk: Sites of suspected subclinical spread
    ◦ 44–50 Gy (2.0 Gy/fraction) to 54–63 Gy (1.6–1.8 Gy/fraction)

POSTOPERATIVE:
RT or Concurrent Systemic Therapy/RT
• Preferred interval between resection and postoperative RT is ≤6 weeks
• PTV
  ▶ High risk: Adverse features such as positive margins
    (See footnote I on ETHM-A)
    ◦ 60–66 Gy (1.8–2.0 Gy/fraction); daily Monday–Friday in 6–6.5 weeks
  ▶ Low to intermediate risk: sites of suspected subclinical spread
    ◦ 44–50 Gy (2.0 Gy/fraction) to 54–63 Gy (1.6–1.8 Gy/fraction)

CONCURRENT CHEMORADIATION:
• PTV
  ▶ High risk: typically 70–70.2 Gy (1.8–2.0 Gy/fraction); daily Monday–Friday in 7 weeks
  ▶ Low to intermediate risk: 44–50 Gy (2.0 Gy/fraction) to 54–63 Gy (1.6–1.8 Gy/fraction)

Either IMRT (preferred) or 3D conformal RT is recommended for maxillary sinus or paranasal/ethmoid sinus tumors to minimize dose to critical structures. Proton therapy can be considered when normal tissue constraints cannot be met by photon-based therapy.

1See Radiation Techniques (RAD-A) and Discussion.
2In the paranasal sinus area, care should be taken to avoid critical neural structures; therefore, 1.8 Gy/fraction can be considered.
3For doses >70 Gy, some clinicians feel that the fractionation should be slightly modified (eg, <2.0 Gy/fraction for at least some of the treatment) to minimize toxicity. An additional 2–3 doses can be added depending on clinical circumstances.
4Suggest 44–50 Gy in 3D conformal RT and sequentially planned IMRT or 54–63 Gy with IMRT dose painting technique (dependent on dose per fraction).
5Treatment to sites of suspected subclinical spread is not consistently performed at all institutions. (Le QT, Fu KK, Kaplan MJ, et al. Lymph node metastasis in maxillary sinus carcinoma. Int J Radiat Oncol Biol Phys 2000;46:541–549.)
6See Principles of Systemic Therapy (CHEMA).

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

DEFINITIVE:
RT Alone
• PTV
  ‣ High risk: Primary tumor and involved lymph nodes [this includes possible local subclinical infiltration at the primary site and at the high-risk level lymph node(s)]
    ◦ Fractionation:
      ‣ 66 Gy (2.2 Gy/fraction) to 70–70.2 Gy (1.8–2.0 Gy/fraction) daily Monday–Friday in 6–7 weeks
      ‣ Concomitant boost accelerated RT:
        ‣ 72 Gy/6 weeks (2 Gy once daily and then 1.8 Gy/fraction, large field; 1.5 Gy boost as second daily fraction during last 12 treatment days)
        ‣ 66–70 Gy (2.0 Gy/fraction; 6 fractions/wk accelerated)
        ‣ Hyperfractionation: 81.6 Gy/7 weeks (1.2 Gy/fraction, twice daily)
  ‣ Low to intermediate risk: Sites of suspected subclinical spread
    ◦ 44–50 Gy (2.0 Gy/fraction) to 54–63 Gy (1.6–1.8 Gy/fraction)

POSTOPERATIVE:
RT or Concurrent Systemic Therapy/RT
• Preferred interval between resection and postoperative RT is ≤6 weeks
• PTV
  ‣ High risk: Adverse features such as positive margins (See footnote 1 on MAXI-3)
    ◦ 60–66 Gy (1.8–2.0 Gy/fraction); daily Monday–Friday in 6–6.5 weeks
  ‣ Low to intermediate risk: sites of suspected subclinical spread
    ◦ 44–50 Gy (2.0 Gy/fraction) to 54–63 Gy (1.6–1.8 Gy/fraction)

CONCURRENT CHEMORADIATION:
• PTV
  ‣ High-risk: typically 70–70.2 Gy (1.8–2.0 Gy/fraction); daily Monday–Friday in 7 weeks
  ‣ Low to intermediate risk: 44–50 Gy (2.0 Gy/fraction) to 54–63 Gy (1.6–1.8 Gy/fraction)

Either IMRT (preferred) or 3D conformal RT is recommended for maxillary sinus or paranasal/ethmoid sinus tumors to minimize dose to critical structures. Proton therapy can be considered when normal tissue constraints cannot be met by photon-based therapy.

1See Radiation Techniques (RAD-A) and Discussion.
2In the paranasal sinus area, care should be taken to avoid critical neural structures; therefore, 1.8 Gy/fraction can be considered.
3For doses >70 Gy, some clinicians feel that the fractionation should be slightly modified (eg, <2.0 Gy/fraction for at least some of the treatment) to minimize toxicity. An additional 2–3 doses can be added depending on clinical circumstances.
4Suggest 44–50 Gy in 3D conformal RT and sequentially planned IMRT or 54–63 Gy with IMRT dose painting technique (dependent on dose per fraction).
6See Principles of Systemic Therapy (CHEM-A).
CONCURRENT CHEMORADIATION³ (preferred for patients eligible for chemotherapy):

- PTW
  - High risk: typically 70 Gy (2.0 Gy/fraction)
  - Low to intermediate risk: Sites of suspected subclinical spread
    - 44–50 Gy (2.0 Gy/fraction) to 54–63 Gy (1.6–1.8 Gy/fraction)⁴

CHEMORADIATION³

Based on published data, concurrent chemoradiation most commonly uses conventional fractionation at 2.0 Gy per fraction to a typical dose of 70 Gy in 7 weeks with single-agent cisplatin given every 3 weeks at 100 mg/m²; 2–3 cycles of chemotherapy are used depending on the radiation fractionation scheme (RTOG 0129) (Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 2010;363:24-35). When carboplatin and 5-FU are used, then the recommended regimen is standard fractionation plus 3 cycles of chemotherapy (Bourhis J, Sire C, Graff P, et al. Concomitant chemoradiotherapy versus acceleration of radiotherapy with or without concomitant chemotherapy in locally advanced head and neck carcinoma (GORTEC 99-02): an open-label phase 3 randomised trial. Lancet Oncol 2012;13:145-53). Other fraction sizes (eg, 1.8 Gy, conventional), multigent chemotherapy, other dosing schedules of cisplatin, or altered fractionation with chemotherapy are efficacious, and there is no consensus on the optimal approach.⁵ Data indicate that accelerated fractionation does not offer improved efficacy over conventional fractionation.⁶,⁷ In general, the use of concurrent chemoradiation carries a high toxicity burden; altered fractionation or multigent chemotherapy will likely further increase the toxicity burden. For any chemoradiation approach, close attention should be paid to published reports for the specific chemotherapeutic agent, dose, and schedule of administration. Chemoradiation should be performed by an experienced team and should include substantial supportive care.

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¹See Radiation Techniques (RAD-A) and Discussion.
²In general, the reirradiated population of head and neck cancer patients described in current literature represents a diverse but highly selected group of patients treated in centers where there is high level of expertise and systems in place for managing acute and long-term toxicities. When the goal of treatment is curative and surgery is not an option, reirradiation strategies can be considered for patients who: develop locoregional failures or second primaries at ≥6 months after the initial radiotherapy; receive additional doses of radiotherapy of at least 60 Gy; and can tolerate concurrent chemotherapy. Organs at risk for toxicity should be carefully analyzed through review of dose-volume histograms, and consideration for acceptable doses should be made on the basis of time interval since original radiotherapy, anticipated volumes to be included, and patient's life expectancy. For reirradiation dosing, see Radiation Techniques (RAD-A). Proton therapy can be considered when normal tissue constraints cannot be met by photon-based therapy. (Taklar V, Garden AS, Ma D, et al. Reirradiation of head and neck cancers with intensity modulated radiation therapy: Outcomes and analyses. Int J Radiat Oncol Biol Phys 2016;95:1117-1131.)
³See Principles of Systemic Therapy (CHEM-A).
⁴Suggest 44–50 Gy in 3D conformal RT and sequentially planned IMRT or 54–63 Gy with IMRT dose painting technique (dependent on dose per fraction).
PRINCIPLES OF RADIATION THERAPY

**DEFINITIVE:**
RT Alone

- PTV
  - High risk: Primary tumor and involved lymph nodes [this includes possible local subclinical infiltration at the primary site and at the high-risk level lymph node(s)]
    - Fractionation:
      - 70–72 Gy (2.0 Gy/fraction) daily Monday–Friday in 7–7.5 weeks
      - Concomitant boost accelerated RT:
        - 72 Gy/6 weeks (1.8 Gy/fraction, large field; 1.5 Gy boost as second daily fraction during last 12 treatment days)
        - 66–70 Gy (2.0 Gy/fraction; 6 fractions/wk accelerated)
      - Hyperfractionation: 81.6 Gy/7 weeks
        - (1.2 Gy/fraction, twice daily)
      - Modified fractionation: total dose >70 Gy and treatment course <7 weeks
  - Low to intermediate risk: sites of suspected subclinical spread
    - 44–50 Gy (2.0 Gy/fraction) to 54–63 Gy (1.6–1.8 Gy/fraction)

Either IMRT or 3D conformal RT is recommended.

**POSTOPERATIVE:**
RT or Concurrent Systemic Therapy/RT

- Preferred interval between resection and postoperative RT is ≤6 weeks.
- PTV
  - High risk: Adverse features such as positive margins (See footnote f on ADV-3)
    - 60–66 Gy (2.0 Gy/fraction); daily Monday–Friday in 6–6.5 weeks
  - Low to intermediate risk: sites of suspected subclinical spread
    - 44–50 Gy (2.0 Gy/fraction) to 54–63 Gy (1.6–1.8 Gy/fraction)

4Suggest 44–50 Gy in 3D conformal RT and sequentially planned IMRT or 54–63 Gy with IMRT dose painting technique (dependent on dose per fraction).
8For doses >70 Gy, some clinicians feel that the fractionation should be slightly modified (eg, <2.0 Gy/fraction for at least some of the treatment) to minimize toxicity. An additional 2–3 doses can be added depending on clinical circumstances.
PRINCIPLES OF RADIATION THERAPY

DEFINITIVE:
RT Alone
• PTV
  ▶ High risk: Involved lymph nodes [this includes possible local subclinical infiltration at the high-risk level lymph node(s)]
  - Fractionation:
    - 66 Gy (2.2 Gy/fraction) to 70 Gy (2.0 Gy/fraction): daily Monday–Friday in 6–7 weeks
    - Mucosal dosing: 50–66 Gy (2.0 Gy/fraction) to putative mucosal sites, depending on field size. Consider higher dose to 60–66 Gy to particularly suspicious areas
  ▶ Low to intermediate risk: Sites of suspected subclinical spread
    - 54–63 Gy (1.6–1.8 Gy/fraction)

CONCURRENT CHEMORADIATION
• PTV
  ▶ High risk: typically 70 Gy (2.0 Gy/fraction)
  ▶ Mucosal dosing: 50–66 Gy (2.0 Gy/fraction) to putative mucosal primary sites, depending on field size and use of chemotherapy. Consider higher dose to 60–66 Gy to particularly suspicious areas
  ▶ Low to intermediate risk: 44–50 Gy (2.0 Gy/fraction) to 54–63 Gy (1.6–1.8 Gy/fraction)

Either IMRT or 3D conformal RT is recommended when targeting the oropharynx to minimize the dose to critical structures. Use of proton therapy is an area of active investigation. Proton therapy may be considered when normal tissue constraints cannot be met by photon-based therapy.

1For squamous cell carcinoma, adenocarcinoma, and poorly differentiated carcinoma.
2See Radiation Techniques (RAD-A) and Discussion.
3For doses >70 Gy, some clinicians feel that the fractionation should be slightly modified (eg, <2.0 Gy/fraction for at least some of the treatment) to minimize toxicity. An additional 2–3 doses can be added depending on clinical circumstances.
4Suggest 44–50 Gy in 3D conformal RT and sequentially planned IMRT or 54–63 Gy with IMRT dose painting technique (dependent on dose per fraction).
5See Principles of Systemic Therapy (CHEM-A).
6Based on published data, concurrent chemoradiation most commonly uses conventional fractionation at 2.0 Gy per fraction to a typical dose of 70 Gy in 7 weeks with single-agent cisplatin given every 3 weeks at 100 mg/m²; 2–3 cycles of chemotherapy are used depending on the radiation fractionation scheme (RTOG 0129) (Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 2010;363:24-35). When carboplatin and 5-FU are used, the recommended regimen is standard fractionation plus 3 cycles of chemotherapy. (Bourhis J, Sire C, Graff P, et al. Concomitant chemoradiotherapy versus acceleration of radiotherapy with or without concomitant chemotherapy in locally advanced head and neck carcinoma (GORTEC 99-02): an open-label phase III randomised trial. Lancet Oncol 2012;13:145-153). Other fraction sizes (eg, 1.8 Gy, conventional), multiagent chemotherapy, other dosing schedules of cisplatin, or altered fractionation with chemotherapy are efficacious, and there is no consensus on the optimal approach. In general, the use of concurrent chemoradiation carries a high toxicity burden; altered fractionation or multiagent chemotherapy will likely further increase the toxicity burden. For any chemoradiation approach, close attention should be paid to published reports for the specific chemotherapy agent, dose, and schedule of administration. Chemoradiation should be performed by an experienced team and should include substantial supportive care.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
POSTOPERATIVE:
RT or Concurrent Systemic Therapy/RT\(^5,7-10\)
- Preferred interval between resection and postoperative RT is ≤6 weeks
- PTV
  - High risk: Adverse features such as extranodal extension (See OCC-4)
    - Mucosal dose: 50–66 Gy (2.0 Gy/fraction) to putative mucosal sites, depending on field size. Consider higher dose to 60–66 Gy to particularly suspicious areas
  - Low to intermediate risk: Sites of suspected subclinical spread
    - 44–50 Gy (2.0 Gy/fraction) to 54–63 Gy (1.6–1.8 Gy/fraction)\(^4\)

Either IMRT or 3D conformal RT is recommended when targeting the oropharynx to minimize the dose to critical structures. Use of proton therapy is an area of active investigation. Proton therapy may be considered when normal tissue constraints cannot be met by photon-based therapy.

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\(^1\)For squamous cell carcinoma, adenocarcinoma, and poorly differentiated carcinoma.

\(^2\)See Radiation Techniques (RAD-A) and Discussion.

\(^3\)Suggest 44–50 Gy in 3D conformal RT and sequentially planned IMRT or 54–63 Gy with IMRT dose painting technique (dependent on dose per fraction).

\(^4\)See Principles of Systemic Therapy (CHEM-A).


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Salivary Gland Tumors

PRINCIPLES OF RADIATION THERAPY\textsuperscript{1,2,3}

DEFINITIVE:
RT Alone or concurrent systemic therapy/RT
- Photon or photon/electron therapy or highly conformal radiation therapy techniques
- PTV:
  \> High risk: Primary tumor and involved lymph nodes [this includes possible local subclinical infiltration at the primary and at the high-risk level lymph node(s)]
    \> Fractionation: 66 Gy (2.0 Gy/fraction) to 70–70.2 Gy (1.8–2.0 Gy/fraction); daily Monday–Friday in 6–7 weeks\textsuperscript{4}
  \> Low to intermediate risk: Sites of suspected subclinical spread
    \> 44–50 Gy (2.0 Gy/fraction) to 54–63 Gy (1.6–1.8 Gy/fraction)\textsuperscript{5}

POSTOPERATIVE RT:
RT Alone or concurrent systemic therapy/RT
- Preferred interval between resection and postoperative RT is \leq 6 weeks
- Photon or photon/electron therapy
- PTV
  \> High risk: Adverse features such as positive margins (see SALI-3)
    \> 60–66 Gy (2.0 Gy/fraction); daily Monday–Friday in 6–7 weeks
  \> Low to intermediate risk: Sites of suspected subclinical spread
    \> 44–50 Gy (2.0 Gy/fraction) to 54–63 Gy (1.6–1.8 Gy/fraction)\textsuperscript{5}

Either IMRT or 3D conformal RT is recommended. Proton therapy can be considered when normal tissue constraints cannot be met by photon-based therapy.

\textsuperscript{1}See Radiation Techniques (RAD-A) and Discussion.

\textsuperscript{2}Neutron therapy was historically considered a promising solution for unresectable salivary gland cancers, but this therapy is currently offered at only one center in the United States. Pfister DG, Spencer S, Brizel DM, et al. NCCN Head and Neck Cancers, Version 1.2015. J Natl Compr Canc Netw 2015;13:847-856.

\textsuperscript{3}In general, the reirradiated population of head and neck cancer patients described in current literature represents a diverse but highly selected group of patients treated in centers where there is high level of expertise and systems in place for managing acute and long-term toxicities. When the goal of treatment is curative and surgery is not an option, reirradiation strategies can be considered for patients who: develop locoregional failures or second primaries at \geq 6 months after the initial radiotherapy; can receive additional doses of radiotherapy of at least 60 Gy; and can tolerate concurrent chemotherapy. Organs at risk for toxicity should be carefully analyzed through review of dose-volume histograms, and consideration for acceptable doses should be made on the basis of time interval since original radiotherapy, anticipated volumes to be included, and patient's life expectancy. For reirradiation dosing, see Radiation Techniques (RAD-A). Proton therapy can be considered when normal tissue constraints cannot be met by photon-based therapy. (Takiar V, Garden AS, Ma D, et al. Reirradiation of head and neck cancers with intensity modulated radiation therapy: Outcomes and analyses. Int J Radiat Oncol Biol Phys 2016;95:1117-1131.)

\textsuperscript{4}For doses >70 Gy, some clinicians feel that the fractionation should be slightly modified (eg, <2.0 Gy/fraction for at least some of the treatment) to minimize toxicity. An additional 2–3 doses can be added depending on clinical circumstances.

\textsuperscript{5}Suggest 44–50 Gy in 3D conformal RT and sequentially planned IMRT or 54–63 Gy with IMRT dose painting technique (dependent on dose per fraction).

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

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
DEFINITIVE:
RT Alone (unresectable locally advanced melanoma):
- PTV:
  - High risk: Primary tumor and involved lymph nodes (this includes possible local subclinical infiltration at the primary site and at the high-risk level lymph node(s))
    - 66 Gy (2.2 Gy/fraction) to 70 Gy (2.0 Gy/fraction) daily Monday–Friday in 6–7 weeks
  - Low to intermediate risk: Sites suspected of subclinical spread
    - 44–50 Gy (2.0 Gy/fraction) to 54–63 Gy (1.8–1.6 Gy/fraction)
- Palliative RT doses and schedules may be considered.
- Optional dosing schedules may be considered.¹

POSTOPERATIVE:
RT:
- Preferred interval between resection and postoperative RT is <6 weeks.
- PTV
  - High risk: adverse features >2 nodes, single node >3 cm, extranodal extension, recurrence in nodal basin after previous surgery²
    - 60–66 Gy (2.0 Gy/fraction; daily Monday–Friday) in 6–6.5 weeks
  - Low to intermediate risk: sites of suspected subclinical spread
    - 44–50 Gy (2.0 Gy/fraction) to 54–63 Gy (1.8–1.6 Gy/fraction)
- Optional dosing schedules may be considered.³

Either IMRT or 3D conformal RT is recommended. Proton therapy can be considered when normal tissue constraints cannot be met by photon-based therapy.

¹See Radiation Techniques (RAD-A) and Discussion.
²Recent studies suggest that increased toxicity may occur when RT is used in combination with BRAF inhibitors. (Anker CJ, Grossmann KF, Atkins MB, et al. Avoiding severe toxicity from combined BRAF inhibitor and radiation treatment: Consensus guidelines from the Eastern Cooperative Oncology Group (ECOG). Int J Radiat Oncol Biol Phys 2016;95:632-646.)

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

Assessment of Radiotherapy

- All patients should be evaluated by a radiation oncologist prior to treatment to assure the following:
  - Review staging and imaging to determine the extent of disease, exclude the presence of a synchronous primary tumor, assess functional status, and evaluate for potential radiation therapy options.
  - Participate in the multidisciplinary team discussions regarding patient treatment options with the goal of maximizing survival with preservation of form and function.
  - Develop a prospective surveillance plan that includes adequate dental, swallowing, nutritional, and health behavior evaluation and intervention and any other ancillary evaluations that would provide for comprehensive rehabilitation.

General Principles

- Target delineation and optimal dose distribution require experience in head and neck imaging and a thorough understanding of patterns of disease spread. Standards for target definition, dose specification, fractionation (with and without concurrent chemotherapy), and normal tissue constraints are still evolving. Published contouring guidelines referenced are in patients who have not been operated upon.9,10
  - IMRT or other conformal techniques (3D conformal RT, helical tomotherapy, volumetric modulated arc therapy [VMAT], and proton beam therapy [PBT]) may be used as appropriate depending on the stage, tumor location, physician training/experience, and available physics support.*
  - Close interplay exists between radiation technology, techniques, fractionation, cumulative radiation dose, surgery, and chemotherapy options resulting in a large number of combinations that may impact toxicity or tumor control.
  - FDG-PET/CT or MRI with contrast can be used for fusion in treatment planning.
  - Advanced radiation therapy technologies such as IMRT, tomotherapy, VMAT, image-guided radiation therapy (IGRT), and PBT may offer clinically relevant advantages in specific instances to spare important organs at risk (OARs), such as the brain, brain stem, cochlea, semicircular canals, optic chiasm and cranial nerves, retina, lacrimal glands, cornea, spinal cord, brachial plexus, mucosa, salivary glands, bone (skull base and mandible), pharyngeal constrictors, larynx, and esophagus, and decrease the risk for late, normal tissue damage while still achieving the primary goal of local tumor control.
  - The demonstration of clinically significant dose sparing of these OARs reflects best clinical practice.
  - Since the advantages of these techniques include tightly conformal doses and steep gradients next to normal tissues, target definition and delineation and treatment delivery verification require careful monitoring to avoid the risk of tumor geographic miss and subsequent decrease in local tumor control.
  - Initial diagnostic imaging with contrast-enhanced CT, MRI, PET, and other imaging modalities facilitate target definition.
  - Image guidance is required to provide assurance of accurate daily delivery. Anatomical changes including rapidly shrinking tumors, changes in air cavities, or significant weight loss may necessitate repeat diagnostic imaging and replanning (adaptive treatment).
  - Randomized studies to test these concepts are unlikely to be done since the above specific clinical scenarios represent complex combinations of multiple variables. In light of that, the modalities and techniques that are found best to reduce the dosing to the clinically relevant OARs without compromising target coverage should be considered.

*For additional resources regarding the technical details of radiation, see the American College of Radiology Guidelines: http://www.acr.org/Quality-Safety/Standards-Guidelines/Practice-Guidelines-by-Modality/Radiation-Oncology.

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RADIATION TECHNIQUES*

Techniques/Dosing

- IMRT
  - IMRT has been shown to be useful in reducing long-term toxicity in oropharyngeal, nasal cavity, paranasal sinus, salivary gland, and nasopharyngeal cancers by reducing the dose to salivary glands, temporal lobes, auditory structures (including cochlea), and optic structures. IMRT is useful for thyroid cancers because of its ability to spare the larynx, brachial plexus, and esophagus.
  - The application of IMRT to other sites (e.g., oral cavity, larynx, hypopharynx) is evolving and may be used at the discretion of treating physicians.
  - Helical tomotherapy and VMAT are advanced forms of IMRT.

- PBT11-31
  - Achieving highly conformal dose distributions is especially important for patients whose primary tumors are pericranial in location and/or invade the orbit, skull base, and/or cavernous sinus; extend intracranially or exhibit extensive perineural invasion; and who are being treated with curative intent and/or who have long life expectancies following treatment. Nonrandomized single institution clinical reports and systematic comparisons demonstrate safety and efficacy of PBT in the above-mentioned specific clinical scenarios.
  - Proton therapy can be considered when normal tissue constraints cannot be met by photon-based therapy.

- IMRT, PBT, and Fractionation32-34
  - A number of ways exist to integrate IMRT or PBT, target volume dosing, and fractionation.
    - The Simultaneous Integrated Boost (SIB) technique uses differential “dose painting” (66–72 Gy to gross disease; 44–63 Gy to subclinical disease) for each fraction of treatment throughout the entire course of radiation.4 SIB is commonly used in the conventional (5 fractions/ wk) and the “6 fractions/wk accelerated” schedule.5
    - The Sequential (SEQ) technique typically delivers the initial (lower dose) phase (weeks 1–5) followed by the high-dose boost volume phase (weeks 6–7) using 2–3 separate dose plans, and is commonly applied in standard fractionation and hyperfractionation.
    - The Concomitant Boost Accelerated schedule may utilize a “Modified SEQ” dose plan by delivering the dose to the subclinical targets once a day for 6 weeks, and a separate boost dose plan as a second daily fraction for the last 12 treatment days.6
    - Another accelerated approach, aside from concomitant boost, is to simply treat 6 fractions per week.5
  - Altered fractionation has not proven to be beneficial in the context of concurrent chemotherapy. The best available evidence is that the benefit of AFX is specific to hyperfractionation, HR = 0.83 for overall survival. The benefit of other methods of altered fractionation is not clearly advantageous on meta-analysis.35

*For additional resources regarding the technical details of radiation, see the American College of Radiology Guidelines: http://www.acr.org/Quality-Safety/Standards-Guidelines/Practice-Guidelines-by-Modality/Radiation-Oncology.
RADIATION TECHNIQUES*

- Palliative 3D Conformal RT, IMRT, and SBRT
  - Palliative radiation should be considered in the advanced cancer setting when curative-intent treatment is not appropriate.
  - No general consensus exists for appropriate palliative RT regimens in head and neck cancer. For those who are either medically unsuitable for standard RT or who have widely metastatic disease, palliative RT should be considered for relief or prevention of locoregional symptoms if the RT toxicities are acceptable. RT regimens should be tailored individually; severe RT toxicities should be avoided when treatment is for palliation.
  - Some recommended RT regimens include:
    - 50 Gy in 20 fractions;\(^{38}\)
    - 37.5 Gy in 15 fractions (if well tolerated, consider adding 5 additional fractions to 50 Gy);
    - 30 Gy in 10 fractions;
    - 30 Gy in 5 fractions:** give 2 fractions/wk with ≥3 days between the 2 treatments; and\(^{37}\)
    - 44.4 Gy in 12 fractions, in 3 cycles (for each cycle, give 2 fractions six hours apart for 2 days in a row, and treatments must exclude the spinal cord after second cycle);\(^{38,39}\) Reassessment should be done at 1- to 3-week intervals.
  - The use of shorter more hypofractionated treatment courses may be indicated, but the dose tolerance of the spinal cord and neural structures must be evaluated carefully in light of fraction size.
  - Carefully evaluate the patient’s performance status, treatment tolerance, tumor response, and/or any systemic progression. Other palliative/supportive care measures include analgesics, nutrition support, targeted therapy, Immunotherapy, or chemotherapy, if indicated (see the NCCN Guidelines for Supportive Care).

*For additional resources regarding the technical details of radiation, see the American College of Radiology Guidelines: http://www.aacr.org/Quality-Safety/Standards-Guidelines/Practice-Guidelines-by-Modality/Radiation-Oncology.

**For end-stage disease, patients can be given more hypofractionated schedules because of the very limited prognosis.

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

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

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RADIATION TECHNIQUES*

- Reirradiation with 3D Conformal RT, SBRT, PBT, or IMRT\(^\text{50-51}\)
  - If the area in consideration overlaps with the previously radiated volume, the prior radiotherapy should have been more than 6 months from the appearance of new disease.
  - In certain rare circumstances, reirradiation with IORT or brachytherapy may be considered in high-volume centers with expertise in these techniques.
  - Before reirradiation, the patient should have a reasonable ECOG performance status of 0-1. Patients who are more than 2 years from prior radiation, who have surgery to remove gross disease prior to reirradiation and who are free of organ dysfunction (e.g., laryngectomy, feeding tube) have better outcomes.\(^\text{52}\)
  - The incidence of myelopathy is thought to increase after a cumulative BED of 120 Gy,\(^\text{53}\) but this risk is increased if large fraction sizes (≥2.5 Gy/fraction) are used.
  - Radiation volumes should include known disease only to minimize the volume of tissue receiving very high doses in regions of overlap.
  - Prophylactic treatment of subclinical disease (e.g., elective nodal irradiation) is therefore not routinely indicated.
  - When using SBRT techniques for reirradiation, careful selection of patients is advised. The best outcomes are seen in patients with smaller tumors and no skin involvement. Caution should be exercised in cases of circumferential carotid artery involvement.
  - Reirradiation dosing:
    - Conventional fractionation
      - Postoperative: 56–60 Gy at 1.8–2 Gy/fraction
      - Definitive: 66–70 Gy at 1.8–2 Gy/fraction
    - Accelerated fractionated: 60–70 Gy at 1.2–1.5 Gy/fraction twice daily
    - Current SBRT schedules being used or investigated are in the range of 35–44 Gy using 5 fractions.
    - Clinical trials should be strongly considered for patients receiving reirradiation.


**For end-stage disease, patients can be given more hypofractionated schedules because of the very limited prognosis.

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

References


RADIATION TECHNIQUES

References


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Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
Surgery for Relapsed/Refractory Disease
Patients with advanced carcinoma (any T, N2–3) who undergo nonsurgical treatment, such as concurrent chemotherapy and RT, need very close follow-up both to evaluate for local recurrence and to assess for ipsilateral or contralateral neck recurrence (see Follow-up Recommendations in the NCCN Guidelines for Head and Neck Cancers). For patients who do not have a complete clinical response to systemic therapy/RT, surgery plus neck dissection is recommended as indicated. However, all panel members emphasized that it may be difficult to detect local or regional recurrence due to radiation-related tissue changes, and this may result in a delayed diagnosis of persistent or recurrent disease.

Panel members also emphasized the increased risk of complications when surgery in patients with relapsed/refractory disease is attempted. Some of these patients may require microvascular free flap reconstruction to cover the defects at the primary site. The patients undergoing neck dissection may develop complications related to delayed wound healing, skin necrosis, or carotid exposure. Laryngectomy may be indicated to obtain clear surgical margins or to prevent aspiration (eg, in patients with advanced oropharyngeal cancer). After laryngectomy for relapsed/refractory disease, patients may have a higher incidence of pharyngocutaneous fistula, pharyngeal and stomal stenosis, and other wound complications. Flaps may be advantageous (either a free flap reconstruction of the laryngopharyngeal defect, or a myocutaneous flap to buttress the suture line if the pharynx can be closed primarily).

Head and Neck Radiation Therapy
RT for H&N cancers has grown increasingly complex. The availability and technical precision of techniques such as intensity-modulated RT (IMRT) has markedly increased, perhaps beyond our ability to estimate the location of small subsites of microscopic disease. A thorough understanding of natural history, anatomy, clinical circumstances, and imaging continue to guide the use of radiation as primary or adjuvant treatment. Principles regarding radiation techniques as described in the NCCN Guidelines for Head and Neck Cancers are not all-inclusive. Although technical guidelines are rapidly evolving and becoming more specific, advanced technologies provide much opportunity for variations and individualization in targeting and dose delivery, challenging traditional notions of standard fields and targets. Guidelines from the American College of Radiology may be useful for technical details (http://www.acr.org/Quality-Safety). Frequently used and cited contouring guidelines for treatment of head and neck cancers are based on patients who have not undergone surgical resection. The maximum dose limits are 70 Gy (2 Gy/fraction) for the following sites: lip, oral cavity, oropharynx, hypopharynx, glottic larynx, supraglottic larynx, occult primary, salivary gland tumors, and MM. For patients with cancer of the pharynx and who have high-risk subclinical disease, a fractionation schedule of 69.86 Gy at 2.12 Gy/fraction daily (Monday–Friday) for 6 to 7 weeks is recommended.

Although several palliative RT regimens are provided, no single regimen is preferred; specific regimens vary widely among NCCN Member Institutions. Any palliative RT regimen that might cause severe toxicities should be avoided. More hypofractionated regimens may be useful for patients with end-stage disease. For example, the QUAD SHOT regimen consists of a dose of 44.4 Gy, delivered in 12 fractions over 3 cycles.

Radiation Doses
Selection of radiation total dose depends on the primary tumor and neck node size, fractionation, and clinical circumstances, including whether to use concurrent systemic therapy (see Radiation Techniques in the NCCN Guidelines for Head and Neck Cancers).
Guidelines for Head and Neck Cancers and see the individual Principles of Radiation Therapy for each primary site). The demonstration of clinically significant dose sparing of organs at risk (eg, brain, cochlea, optic chiasm and nerves, spinal cord) reflects best clinical practice. Target definition and delineation is crucial, and imaging should be used to ensure accurate radiation delivery. Anatomical changes (eg, rapidly shrinking tumors, changes in air cavities, significant weight loss) may necessitate repeat imaging and treatment replanning.

When using conventional definitive fractionation, the primary tumor and involved lymph nodes (ie, high-risk sites) generally require a total of 66 Gy (2.2 Gy/fraction) to 70 Gy (2.0 Gy/fraction).\textsuperscript{138,141} For doses greater than 70 Gy, some clinicians feel that the fractionation should be slightly modified (eg, <2.0 Gy/fraction for at least some of the treatment) to minimize toxicity; an additional 2 to 3 doses can be added depending on clinical circumstances. External-beam radiation doses exceeding 72 Gy using conventional fractionation (2.0 Gy/fraction) may lead to unacceptable rates of normal tissue injury.\textsuperscript{138,142} When using hyperfractionation, high-risk sites generally require up to 81.6 Gy (1.2 Gy/fraction).\textsuperscript{138,139} In contrast, elective irradiation to low-risk and intermediate-risk sites requires 44 Gy (2.0 Gy/fraction) to 63 Gy (1.6–1.8 Gy/fraction), depending on the estimated level of tumor burden, and on whether 3D conformal RT (3D-CRT) or IMRT is used. For 3D-CRT and sequentially planned IMRT, 44 to 50 Gy (2.0 Gy/fraction) is suggested.\textsuperscript{143,144} For IMRT, 54 to 63 Gy (1.6–1.8 Gy/fraction) is suggested.\textsuperscript{144–148} Delivery of 6 fractions per week is an acceptable accelerated schedule.\textsuperscript{140}

Postoperative irradiation is recommended based on stage, histology, and surgical-pathologic findings. In general, postoperative RT is recommended for selected risk factors, including advanced T-stage, depth of invasion, multiple positive nodes (without extranodal extension), or perineural/lymphatic/vascular invasion. Higher doses of postoperative RT alone (60–66 Gy), or with systemic therapy, are recommended for the high-risk features of extranodal extension and/or positive margins.\textsuperscript{119,120,141} The preferred interval is 6 weeks or less, between resection and commencement of postoperative RT. Dosing schedules are the same regardless of whether or not systemic therapy is administered concurrently with postoperative RT.

Fractionation in RT Alone

No single fractionation schedule has proven to be best for all tumors. Data strongly indicate that squamous cancers of the H&N can grow rapidly and may compensate for RT-induced cell loss through the mechanism of accelerated repopulation.\textsuperscript{147,148} Especially in RT alone settings, schedules delivering at least 1000 cGy per week are recommended,\textsuperscript{149–151} with the exception of salivary gland tumors, which may have slower cell kinetics. Trials in early-stage glottic laryngeal cancer have shown higher recurrence rates with daily fraction sizes <200 cGy where the cumulative weekly dose is <1000 cGy.\textsuperscript{152,153}

Two large, randomized trials from Europe have reported improved locoregional control using altered fractionation. The EORTC protocol 22791 compared hyperfractionation (1.15 Gy twice daily, or 80.5 Gy over 7 weeks) with conventional fractionation (2 Gy once daily, or 70 Gy over 7 weeks) in the treatment of T2, T3, N0-1 oropharyngeal carcinoma excluding base of tongue primaries. At 5 years, a statistically significant increase in local control was observed in the hyperfractionation arm (38% vs. 56%; \( P = .01 \)) and no increase in late complications was observed.\textsuperscript{154} A long-term follow-up analysis has also shown a small survival advantage for hyperfractionation (\( P = .05 \)).\textsuperscript{155} Another EORTC protocol (22851) compared accelerated fractionation (1.6 Gy 3 times daily, or 72 Gy over 5 weeks) with conventional fractionation (1.8–2.0 Gy once daily, or 70 Gy over 7–8 weeks) in various intermediate to advanced H&N cancers.
fractionation (HR, 0.83; 95% CI, 0.74–0.92; P < .001), in patients with locally advanced squamous cell cancers of the H&N.\textsuperscript{162}

Consensus regarding altered fractionation schedules with concomitant boost or hyperfractionation for stage III or IV oral cavity, oropharynx, supraglottic larynx, and hypopharyngeal squamous cell cancers has not yet emerged among NCCN Member Institutions.\textsuperscript{158,163,164}

**Fractionation in Concurrent Chemoradiation**

Panel members do not agree about the optimal radiation dose fractionation scheme to use with concurrent systemic therapy in the definitive treatment setting. Most published studies have used conventional fractionation (at 2.0 Gy/fraction to a typical dose of 70 Gy in 7 weeks) with single-agent high-dose cisplatin (given every 3 weeks at 100 mg/m\textsuperscript{2}).\textsuperscript{25} Other fraction sizes (e.g., 1.8 Gy, conventional), other dosing schedules of cisplatin, other single agents, multiagent systemic therapy, and altered fractionation with systemic therapy have been evaluated alone or in combination. Numerous trials have shown that modified fractionation and concurrent chemotherapy are more efficacious than modified fractionation alone.\textsuperscript{154-163} RTOG 0129 assessed accelerated fractionation with 2 cycles of concurrent cisplatin versus standard fractionation with 3 cycles of concurrent cisplatin. There was no significant difference in OS between the two arms,\textsuperscript{167,168} indicating that accelerated fractionation is not more efficacious than conventional fractionation when concurrent chemotherapy is added.

Concurrent chemoradiation increases acute toxicity compared to radiation alone, although an increase in late toxicity beyond that caused by RT alone is less clear.\textsuperscript{169-171} Altered fractionation and/or multiagent systemic therapy may further increase the toxicity burden.\textsuperscript{172} For any chemotherapeutic approach, close attention should be paid to published reports for the specific chemotherapy agent, dose, and schedule of
administration. Chemoradiation should be performed by an experienced team and should include substantial supportive care.

**Radiation Techniques**

**IMRT**
The intensity of the radiation beam can be modulated to decrease doses to normal structures without compromising the doses to the cancer targets. Over the last 15 years, IMRT has displaced other techniques in the treatment of most H&N malignancies. IMRT is an advanced form of CRT permitting more precise cancer targeting while reducing dose to normal tissues.

**IMRT dose painting** refers to the method of assigning different dose levels to different structures within the same treatment fraction (eg, 2.0 to gross tumor, 1.7 to microscopic tumor, <1.0 Gy to parotid gland) resulting in different total doses to different targets (eg, 70 Gy, 65 Gy, <26 Gy). Although dose painting has been used to simplify radiation planning, hot spots associated with higher toxicity can occur. Alternatively separate dose plans for the low versus higher dose targets can be delivered sequentially (reduce target size and boost) or on the same day as separate fractions in twice-daily schemas (see Radiation Techniques in the NCCN Guidelines for Head and Neck Cancers).

IMRT is now widely used in H&N cancers and is the predominant technique used at NCCN Member Institutions. It is useful in reducing long-term toxicity in oropharyngeal, paranasal sinus, and nasopharyngeal cancers by reducing the dose to one or more major salivary glands, temporal lobes, mandible, auditory structures (including cochlea), and optic structures. OS is similar between patients treated with IMRT and those receiving conventional RT. A prospective Korean study showed that 3D and IMRT techniques were superior to 2D radiation for both PFS and OS in patients with nasopharyngeal carcinoma (NPC), and IMRT was associated with improved survival in multivariate analysis, particularly in T3-T4 tumors. In-field recurrences, low-grade mucositis in areas away from the cancer targets, and posterior neck hair loss can occur with IMRT. The application of IMRT to other sites (eg, oral cavity, larynx, hypopharynx) is evolving.

IMRT may be useful to preserve the optic pathway in patients with sinonasal malignancies. Retrospective analyses including 2,993 patients who received RT for treatment of H&N cancer showed that patients who received IMRT had a shorter duration of feeding tube placement, compared to those who received 3D-RT \( (P = .03) \). However, IMRT can create new unexpected acute toxicities to organs radiated in the beam path. In addition, the long-term effects, even with using IMRT, can still result in a substantial decrease in quality of life.

Xerostomia is a common long-term side effect of RT, which can be reduced with use of IMRT, drug therapy (eg, pilocarpine, cevimeline), salivary substitutes, and other novel approaches (eg, acupuncture). Reports indicate that xerostomia has decreased due to the transition from older 2D and 3D radiotherapy techniques, such as IMRT. Numerous phase II studies show a decrease in late toxicity (xerostomia) without compromising tumor control for nasopharyngeal, sinonasal, and other sites.

Three randomized trials have supported the clinical benefits of IMRT in H&N cancers with regard to the reduction in xerostomia. Pow et al evaluated treatment of early-stage NPC with conventional RT techniques versus with IMRT. The results showed a statistical improvement in salivary flow and in patient-reported quality-of-life parameters. In the study by Kam et al, patients with NPC were randomly assigned to either IMRT or conventional 2D-RT. At one year after treatment, patients in the IMRT arm had significantly lower rates of clinician-rated severe xerostomia than patients in the 2D-RT arm (39.3% vs. 82.1%; \( P = .001 \)). Salivary flow...
rates were also higher with IMRT. The mean parotid dose was 32 Gy in the IMRT group and 62 Gy in the conventional group. Although a trend for improvement in patient-reported dry mouth was observed after IMRT, recovery was incomplete and there was no significant difference in patient-reported outcomes between the 2 arms. The authors concluded that other salivary glands may also be important and merit protection. Finally, data from a phase III randomized trial (PARSPORT) indicate that IMRT decreases xerostomia when compared with conventional RT in patients with non-NPC.\(^{175}\) In this trial, patients with T1-T4, N0-N3, M0 disease were treated to a total dose of 60 or 65 Gy in 30 fractions either with conventional RT (ie, parallel opposed technique) or with IMRT; 80 patients with oropharyngeal and 14 patients with hypopharyngeal tumors were included. Grade 2 or worse (LENT-SOMA scale) xerostomia 2 years after treatment was seen in 83% of patients receiving conventional RT versus 29% of patients in the IMRT group \((P < .0001)\). No differences were seen in the rates of locoregional control or survival.

**Proton Beam Therapy**

At present, proton therapy is the predominant particle therapy under active clinical investigation in the United States.\(^{220-233}\) Proton therapy has been used to treat oropharyngeal cancers, sinonasal malignancies, adenoid cystic carcinomas, and MMs.\(^{234-242}\) Proton therapy has typically been used to treat patients with the most challenging disease, for which other RT options were not felt to be safe or of any benefit.\(^{235,236,243}\)

Data supporting the use of PBT come mainly from nonrandomized institutional reports and a small number of systematic reviews. A systematic review and meta-analysis of non-comparative observation studies concluded that patients with malignant diseases of the nasal cavity and paranasal sinuses who received proton therapy appeared to have better outcomes than those receiving photon therapy.\(^{244}\) A review of proton therapy in patients with H\&N cancers included 14 retrospective reviews and 4 prospective nonrandomized studies.\(^{231}\) The 2- to 5-year local control rates were as low as 17.5% for T4 or recurrent paranasal sinus cancers and as high as 95% for other types of tumors.

In institutional reports, outcomes for proton therapy have been reported, including good locoregional control, freedom from distant metastasis, and acceptable toxicity.\(^{231,240,245-248}\) PBT may be associated with greater normal tissue sparing without sacrificing target coverage, which may be associated with reduced toxicity compared to IMRT.\(^{246}\)

Occasional fatal outcomes have been reported with proton therapy, including 3 deaths secondary to brainstem injury.\(^{249-251}\) However, clinicians have reported low rates of serious toxicities when using strict dose limits for proton therapy.\(^{252}\) In patients with tumors that are pericranial in location and/or invade the orbit, skull base, and/or cavernous sinus, and tumors that extend intracranially or exhibit extensive perineural invasion, as well as in patients being treated with curative intent and/or have long life expectancies, achieving highly conformal dose distributions is crucial.

As described above, nonrandomized institutional reports and a small number of systematic reviews have shown that PBT may be safe to use in some settings. Without high-quality prospective comparative data, it is premature to conclude that proton therapy has been established as superior to other modern radiation techniques such as IMRT, particularly with regard to tumor control. An accurate comparison of benefits to other RT options should ideally take place in the controlled setting of randomized clinical trials. An alternative approach may be to develop prospectively maintained databases to raise the quality of institutional reports of clinical experiences.\(^{251}\) In cancers of the oropharynx, supraglottic larynx, paranasal sinus, and salivary glands, as well as MM and unknown primary tumors of the H\&N, proton therapy can be considered when normal tissue constraints cannot be met by photon-based therapy.
Brachytherapy

Brachytherapy is now being used less often because of improved local control obtained with concurrent chemoradiation. However, brachytherapy still has a role for lip and oral cavity cancers (see Principles of Radiation Therapy in the NCCN Guidelines for Cancer of the Lip and Cancer of the Oral Cavity).253

Stereotactic Body Radiation Therapy

Stereotactic body RT (SBRT) is an advanced technique of external beam RT (EBRT) that delivers large ablative doses of radiation. Advantages of SBRT include shorter treatment time, promising local control rates, and acceptable toxicity.254 There is currently insufficient evidence to recommend SBRT for treatment of H&N cancers, but the NCCN Panel acknowledges that it might be beneficial for palliation or for older adults.265,266

Follow-up After RT

For patients whose cancer has been treated with RT, the recommended follow-up (see Follow-up Recommendations in the NCCN Guidelines for Head and Neck Cancers) includes an assessment of thyroid function (i.e., the thyroid-stimulating hormone [TSH] level should be determined every 6–12 months). Increased TSH levels have been detected in 20% to 25% of patients who have received neck irradiation; patients are at increased risk of hypothyroidism.257-259

Principles of Nutrition and Supportive Care

The Principles of Nutrition section in the NCCN Guidelines for Head and Neck Cancers outlines nutritional management and supportive care for patients with H&N cancers who are prone to weight loss, which can often be severe, as a result of treatment-related toxicity, disease, and health behaviors such as poor nutritional habits.51,260,261 Patients with H&N cancers are also at risk for dehydration. The multidisciplinary expertise of a registered dietitian and a speech-language/swallowing therapist should be utilized throughout the continuum of care.

Patients who have had significant weight loss (5% body weight loss over 1 month, or 10% body weight loss over 6 months) need nutritional evaluation and close monitoring of their weight to prevent further weight loss.262,263 In addition, all patients should receive nutritional evaluation before and after treatment to assess the need for interventions (e.g., enteral support via feeding tubes).264-266 Patients are also at risk for problems with speech. Treatment and/or the progression of their disease may cause deterioration in their ability to speak and/or swallow.267-270 Evaluation by a speech-language/swallowing therapist is needed before and after treatment to help mitigate potential problems.271-273 Patients are also at risk for dental problems (see Principles of Dental Evaluation and Management in this Discussion and the NCCN Guidelines for Head and Neck Cancers).51

Oral mucositis, or tissue damage, is common in patients treated with RT for H&N cancers.274-279 It causes pain in the mouth and when swallowing, which may affect the ability to eat and drink.274,276,278,279 Oral mucositis is also associated with breaks and/or delays in treatment, as well as hospitalization.276,277,279 Oral mucositis may be worse in patients receiving concurrent systemic therapy/RT.279 The Multinational Association of Supportive Care in Cancer and the International Society of Oral Oncology have published clinical practice guidelines for treatment of oral mucositis, though there are few high-quality studies in this area.280 An RCT including 155 patients with H&N cancer undergoing treatment for pain related to oral mucositis showed that patients randomized to receive a doxepin oral rinse reported reduced throat and mouth pain, compared to patients randomized to receive a placebo (P < .001).281 Two small retrospective studies including patients with H&N cancer treated with RT or systemic therapy/RT showed that treatment with gabapentin for pain from oral
may be extrapolated from the management of squamous cell H&N cancers, with some NCCN Member Institutions using platinum-based regimens for these patients. With regard to unresectable salivary gland tumors, the NCCN Panel had less consensus about chemoradiation (which is reflected in the category 2B recommendations), because there are few published trials. Clinical trials are ongoing in this area (eg, NCT01220583, NCT02776163).

Systemic therapy may be used for palliation in advanced disease. Various agents alone or in combination (eg, cisplatin, cyclophosphamide, doxorubicin; epirubicin; mitoxantrone; carboplatin and vinorelbine) have been shown in small series to be active for some salivary gland malignant histologies.\(^{618,625}\) Although targeted therapy is associated with stable disease, it is minimally active and is generally not recommended outside of clinical trials.\(^{629,630}\) However, a significant number of advanced salivary gland tumors with distant metastases are androgen receptor-positive (AR+).\(^{627-631}\) Therefore, the panel recommends that patients with tumors that are AR+ receive androgen receptor therapy (eg, leuproline, bicalutamide).\(^{631-634}\) Two phase I/II studies including patients with advanced NTRK gene fusion-positive cancer (with 22%-33% being salivary gland tumors) showed promising objective response rates of 75% to 100% with the TRK Inhibitor larotrectinib.\(^{635,636}\) In 2018, the FDA approved larotrectinib for treatment of patients NTRK gene fusion-positive tumors, and the panel also recommends NTRK therapy options such as larotrectinib for patients with recurrent NTRK gene fusion-positive disease and distant metastases. Finally, HER2 positivity has also been found in some advanced salivary gland tumors.\(^{629,631,637}\) It is recommended that these patients receive a HER2-targeted treatment option such as trastuzumab,\(^{631,638}\) but this is a category 2B recommendation based on less consensus among the panel. AR and HER2 status should be checked in patients with distant metastases. NTRK status should be evaluated in mammary analogue secretory carcinoma of the salivary gland.\(^{639}\)

**Follow-up**

Recommendations for surveillance are in the algorithm (see Follow-up Recommendations in the NCCN Guidelines for Head and Neck Cancers).

**Mucosal Melanoma of the Head and Neck**

MM is a rare but highly aggressive neoplasm with a poor prognosis.\(^{640,641}\) It mainly occurs throughout the upper aerodigestive tract.\(^{642}\) Most MM (70%-80%) occurs in the nasal cavity or paranasal sinus region, and most of the remainder develops in the oral cavity.\(^{643}\) The incidence of nasal cavity MM appears to be increasing.\(^{640}\) Sinonasal MM is typically confined to the primary site at presentation.\(^{644}\) Oral cavity MM more frequently presents with clinically apparent lymph node metastasis.\(^{645}\) No etiologic risk factors are yet apparent.

**Workup and Staging**

Workup for MM should include clinical examination and CT and/or MRI with contrast for paranasal sinus disease and appropriate imaging for other mucosal sites. FDG PET/CT or chest/abdomen/pelvic CT and brain MRI may be considered to define distant disease in more advanced situations. The AJCC Cancer Staging Manual (8th edition) includes a staging system for MM (see Table 9).\(^{43}\) The AJCC staging recognizes 2 key factors specific to MM: 1) the poor prognosis of MM even with a limited primary burden of disease; and 2) there is still some gradation of survival based on the burden of disease as reflected in local, regional, and distant extent. Thus, the AJCC staging system for MM begins with T3, N0 disease as the most limited form of disease (similar to anaplastic thyroid carcinoma), and the staging reflects the local burden of disease, as well as regional and distant extent. In addition, the AJCC staging system reflects the fact that MM occurs at all mucosal sites in the H&N. Therefore, rules for classifying, staging, and surgical principles should be based on the appropriate anatomic site of origin.

\(^{43}\)
Treatment

Although limited data exist on treatment options, primary treatment should be surgical for T3, N0-1 and T4a, N0-1 disease; however, surgery is not recommended for T4b disease.646 Neck dissection with postoperative radiation is recommended for clinical nodal disease.647,648 Adjuvant radiation appears effective in improving local control and survival in most case series.649-651 Postoperative radiation is clearly indicated in more advanced cases.652 NCCN strongly encourages clinical trials for all patients with MM to better define treatment choices at all stages of the disease.

Radiation Therapy

The role of RT in MM has not been evaluated in prospective trials. However, results of a randomized trial in cutaneous melanoma are considered relevant to MM in the postoperative setting after neck dissection (see third paragraph in this section).653 Retrospective studies in MM have shown local recurrence to be common after surgery alone.654 After using postoperative radiation, lower rates of local and neck recurrence have been seen in historical comparison series.655-658 Reasonable local control outcomes using RT alone in unresectable or medically inoperable cases have been reported in small cohort series of MMs.659-661

Primary size or thickness is not used as a risk factor when considering RT to the primary site; all invasive primaries are considered at high risk for local recurrence. For sinonasal primary sites, target volumes may include the primary site without elective treatment of the neck (see the NCCN Guidelines for Mucosal Melanoma). Because oral cavity primary sites are felt to be at a higher risk for failure in the neck, elective management with neck dissection and RT may be applied (see the NCCN Guidelines for Mucosal Melanoma).

RT is often recommended in the postoperative management of MMs. Indications for postoperative radiation to the neck are generally extrapolated from cutaneous melanoma. An Australian-New Zealand consortium reported on a randomized trial (250 patients) of postoperative RT versus observation in patients with palpable adenopathy from cutaneous primaries. Postoperative RT was associated with a significant reduction in relapse in the nodal basin (19% vs. 31%) and a significant improvement in lymph node field control.653 Only 20 patients relapsed who received RT, whereas 34 patients relapsed who received observation only ($P = .04$). However, no significant differences in OS were reported.

Considering this trial and retrospective studies in MM, the NCCN Panel recommends postoperative RT for the following high-risk features: extranodal extension, involvement of 2 or more neck or intraparotid nodes, any node 3 cm or greater, neck dissection (alone) with no further basin dissection, or recurrence in the neck or soft tissue after initial surgical resection.662-664 Conventional fractionation is recommended (at 2 Gy per fraction to a total postoperative dose of 60–66 Gy). The Australian-New Zealand randomized trial used 48 Gy in 20 fractions (240 cGy/fraction) to the neck, axilla, or groin.653 However, the NCCN Panel prefers conventional fractionation to somewhat higher total doses (60–66 Gy) in the neck because of concerns about late effects from larger dose per fraction, which may not be fully expressed for many years after treatment. The following schedules may also be used: 1) 48 to 50 Gy (2.4–3 Gy/fraction); or 2) 30 to 36 Gy (6 Gy/fraction).653,655,663

IMRT may be very useful in helping to achieve homogenous dose distributions and to spare critical organs, especially in paranasal sinus sites.201,513,664 3D-CRT may also be used. Reports suggest that the use of hypofractionation in cutaneous melanomas (which is convenient) is associated with good outcomes but no clear advantage in cancer control. Little experience is available using large dose per fraction in mucosal
sites. Because of the close proximity of neural structures and risk of late effects, hypofractionation (if used) must be carefully planned and delivered.\textsuperscript{664} Care should be taken when RT is used in combination with BRAF inhibitors, as concurrent use has been found to be associated with grade ≥3 dermatologic reactions, and potentially lethal hemorrhaging in the liver, lung, and brain have all been reported.\textsuperscript{665}

**Systemic Therapy**

Systemic therapy used for cutaneous melanoma (eg, Interleukin-2) is recommended for MM (see Systemic Therapy for Metastatic or Unresectable Disease in the NCCN Guidelines for Cutaneous Melanoma, available at [www.NCCN.org]).\textsuperscript{644,666} Interferon and interleukin have been used to treat MM.\textsuperscript{666,667} Data suggest that c-KIT inhibitors (eg, imatinib) may be useful in selected patients with metastatic MM and specific mutations.\textsuperscript{668-671} Therefore, c-KIT inhibitors are reasonable to use in patients with MM who have c-KIT mutations (ie, exon 11 or 13 mutations).\textsuperscript{666,672,673} Although vemurafenib is recommended for patients with cutaneous melanoma who have the V600E mutation of the BRF gene, patients with MM rarely have this mutation.\textsuperscript{666,673,674}

**Follow-up**

Recommendations for surveillance are provided in the algorithm (see Follow-up Recommendations in the NCCN Guidelines for Head and Neck Cancers). Note that physical examination for MM should include endoscopic inspection for paranasal sinus disease.

**Recommended Reading List**


442. Lewis JS, Jr., Chernock RD. Human papillomavirus and Epstein Barr virus in head and neck carcinomas: suggestions for the new WHO...
APPENDIX 4
Central Nervous System Cancers

Version 1.2019 — March 5, 2019

NCCN.org

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**PCNS-3**

Treatment

- **Other systemic chemotherapy** has been added for No response or short duration (<12 mo) for the following arms: Prior high-dose methotrexate-based regimen without prior RT and Prior high-dose chemotherapy with stem cell rescue.

**FSCPT-2**

Footnotes


**LTD-2**

Footnotes

- Modified "g": If an active agent exists (e.g., cytotoxic, targeted, or immune modulating), trial of systemic therapy with good CNS penetration may be considered in select patients (e.g., for patients with small asymptomatic brain metastases from melanoma or ALK rearrangement positive NSCLC or EGFR mutated NSCLC); it is reasonable to hold on treating with radiation to see if systemic therapy can control the brain metastases. Close MRI surveillance is strongly recommended. There are no data from prospective clinical trials comparing the two strategies to assess what the impact of delayed radiation would be in terms of survival or in delay of neurologic deficit development. See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).

- SRS is preferred when safe, especially for low tumor volume, to both the resection cavity and any other non-resected brain metastases. WBRT is generally not recommended but may be appropriate in some rare clinical circumstances. (e.g., ventricle is violated, cerebellar lesions, risk of meningeal disease, need for complete CNS control before going on protocol, not good SRS candidate for technical reasons, poor PS, advanced age).

**LEPT-1**

Workup

- 3rd bullet modified: CSF analysis exam

**LEPT-2** and **LEPT-3**

- These pages have been extensively modified.

**SPINE-1**

- Symptomatic modified as follows: Severe, new, or progressive pain or neurologic symptoms or myelopathy

Footnotes

- Footnote for spinal MRI revised as follows: If the patient is unable to have an MRI, then a CT myelogram is recommended, which may also be useful for stereotactic radiotherapy planning.

**SPINE-2**

Treatment

- For patients with spinal cord compression, Surgery ± stabilization followed by RT

**SPINE-3**

Treatment for Recurrence or Progressive Disease

- For patients previously treated with chemotherapy, Consider surgery with or without RT

**BRAIN-A**

- Follow-up brain MRI should be performed at the frequency and intervals stated in the treatment algorithms. More frequent imaging may be done as clinically indicated by the treating physician, such as in the event of a clinical change such as development of seizures or neurologic deterioration is a new bullet under MRI of the brain and spine (with and without contrast).

**BRAIN-B**

Principles of Brain Tumor Surgery

- For patients with IDH1 mutations, there is evidence to suggest that a supramarginal resection is most appropriate, which would include not only enhancing areas but also T2/flair areas when appropriate in terms of a safe surgical approach, with the use of any and all surgical adjuncts possible is a new bullet under Factors.

- Carmustine polymer wafer may be placed in the tumor resection cavity of patients is a new bullet under Options, supporting references were added.

Footnotes

- A number of surgical adjuncts can be considered to facilitate safe brain tumor surgery including use of an intraoperative microscope, frameless stereotactic image guidance, preoperative functional MRI and/or DTI fiber tracking, awake craniotomy, motor and/or speech mapping, intraoperative MRI, and intraoperative fluorescence-guided surgery with 5-ALA, is a new footnote corresponding to the last bullet under "Factors" and the subheading "Options."
### Anaplastic Gliomas (See GLIO-3/GLIO-4 for Glioblastoma)

**Pathology**

<table>
<thead>
<tr>
<th>Anaplastic oligodendroglioma (1p19q codeleted)</th>
<th>Anaplastic astrocytoma, Anaplastic oligoastrocytoma, NOS</th>
<th>Anaplastic gliomasa</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADJUVANT TREATMENT</td>
<td>ADJUVANT TREATMENT</td>
<td>FOLLOW-UPb</td>
</tr>
<tr>
<td>Consider clinical trial (preferred for eligible patients)</td>
<td>Consider clinical trial (preferred for eligible patients)</td>
<td>Brain MRI 2–6 wks after RT, then every 2–4 mo for 3 y, then every 3–6 months indefinitely</td>
</tr>
<tr>
<td>or Fractionated external beam RT(^1) and neoadjuvant or adjuvant(^m) PCV (category 1)(^n)</td>
<td>or Fractionated external beam RT(^1) with concurrent and adjuvant temozolomide(^n)</td>
<td>See Recurrence (GLIO-5)</td>
</tr>
<tr>
<td>or Fractionated external beam RT(^1) and adjuvant temozolomide(^n)</td>
<td>or Fractionated external beam RT(^1) with concurrent and adjuvant temozolomide(^n)</td>
<td></td>
</tr>
<tr>
<td>Anaplastic astrocytoma, Anaplastic oligoastrocytoma, NOSk</td>
<td>Fractionated external beam RT(^1) with concurrent and adjuvant temozolomide(^n)</td>
<td></td>
</tr>
<tr>
<td>Anaplastic gliomasa</td>
<td>Fractionated external beam RT(^1) with concurrent and adjuvant temozolomide(^n)</td>
<td></td>
</tr>
<tr>
<td>Poor performance status (KPS &lt;60)</td>
<td>Fractionated external beam RT(^1) + neoadjuvant or adjuvant(^m) PCV</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fractionated external beam RT(^1) (hypofractionated [preferred] or standard)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>or Temozolomide (category 2B)(^n,(^o)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>or Palliative/best supportive care</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) This pathway includes the classification of mixed AOA, AA, AO, and other rare anaplastic gliomas.

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

\(^c\) See Principles of Brain Tumor Pathology (BRAIN-F).

\(^d\) The 2016 WHO Classification of Tumors of the CNS has deleted oligoastrocytoma as a category, although "anaplastic oligoastrocytoma, NOS" may continue to be used for 1) patients with mixed histology and no available molecular data (ie, no tissue available for analysis) for determining whether to classify as oligodendroglioma versus astrocytoma; or 2) rare instances in which the tumor has regions with histologic features of oligoastrocytoma with 1p19q-codeletion, and distinct regions with histologic features of astrocytoma without 1p19q-codeletion.

\(^e\) See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C).

\(^f\) The panel recommends that PCV be administered after RT (as per EORTC 26951) since the intensive PCV regimen given prior to RT (RTOG 9402) was not tolerated as well.

\(^g\) See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).

\(^h\) Consider temozolomide if tumor is MGMT promoter methylated.

\(^i\) Within the first 3 months after completion of RT and concomitant temozolomide, diagnosis of recurrence can be indistinguishable from pseudoprogression on neuroimaging.

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

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

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NCCN Guidelines Version 1.2019
Anaplastic Gliomas\textsuperscript{a}/Glioblastoma

**GLIOBLASTOMA PATHOLOGY\textsuperscript{d}**

<table>
<thead>
<tr>
<th>MGMT\textsuperscript{q} PROMOTER STATUS</th>
<th>ADJUVANT TREATMENT</th>
<th>FOLLOW-UP\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylated Good performance status (KPS ≥60)</td>
<td>Consider clinical trial (preferred for eligible patients) or Standard brain RT\textsuperscript{i} + concurrent temozolomide and adjuvant temozolomide + alternating electric field therapy (category 1)\textsuperscript{n,r,s,t} or Standard brain RT\textsuperscript{i} + concurrent temozolomide and adjuvant temozolomide (category 1)\textsuperscript{n,r,s}</td>
<td>Brain MRI 2–6 wks after RT,\textsuperscript{p} then every 2–4 mo for 3 y, then every 3–6 mo indefinitely</td>
</tr>
<tr>
<td>Unmethylated or indeterminate</td>
<td>Consider clinical trial (preferred for eligible patients) or Standard brain RT\textsuperscript{i} + concurrent temozolomide and adjuvant temozolomide\textsuperscript{u} + alternating electric field therapy (category 1)\textsuperscript{n,r,s,t} or Standard brain RT\textsuperscript{i} + concurrent temozolomide\textsuperscript{u} and adjuvant temozolomide (category 1)\textsuperscript{n,r,s,u} or Standard brain RT alone\textsuperscript{i}</td>
<td></td>
</tr>
<tr>
<td>Age ≤70 y Poor performance status (KPS &lt;60)</td>
<td>Hypofractionated brain RT\textsuperscript{i} (preferred) ± concurrent or adjuvant temozolomide\textsuperscript{n} or Temozolomide\textsuperscript{n,o} or Palliative/best supportive care</td>
<td>See Recurrence (GLIO-5)</td>
</tr>
<tr>
<td>Age &gt;70 y</td>
<td>See GLIO-4</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a}This pathway includes the classification of mixed AOA, AA, AO, and other rare anaplastic gliomas.
\textsuperscript{b}See Principles of Brain and Spine Tumor Imaging (BRAIN-A).
\textsuperscript{c}See Principles of Brain Tumor Pathology (BRAIN-F).
\textsuperscript{d}This pathway also includes gliosarcoma.
\textsuperscript{e}See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C).
\textsuperscript{f}See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).
\textsuperscript{g}Consider temozolomide if tumor is MGMT promoter methylated.
\textsuperscript{i}Within the first 3 months after completion of RT and concomitant temozolomide, diagnosis of recurrence can be indistinguishable from pseudoprogression on neuroimaging.
\textsuperscript{n}MGMT= O6-methylguanine-DNA methyltransferase.
\textsuperscript{r}Combination of agents may lead to increased toxicity or radiographic changes.
\textsuperscript{s}Benefit of treatment with temozolomide for glioblastomas beyond 6 months is unknown.
\textsuperscript{t}Alternating electric field therapy is only an option for patients with supratentorial disease.
\textsuperscript{u}Clinical benefit from temozolomide is likely to be lower in patients whose tumors lack MGMT promoter methylation.

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
NCCN Guidelines Version 1.2019
Anaplastic Gliomas\(^a\)/Glioblastoma

**GLIOBLASTOMA PATHOLOGY\(^d\)\(^a\)**

- Methylated
  - Good performance status (KPS ≥60)
  - Age ≥70 y Glioblastoma\(^l\)
- Unmethylated or indeterminate
  - Poor performance status (KPS <60)

**MGMT PROMOTER STATUS\(^q\)**

- Hypomethylated

**ADJUVANT TREATMENT**

Consider clinical trial (preferred for eligible patients)
- or Hypofractionated brain RT\(^l\)
- or Hypofractionated brain RT\(^l\) + concurrent and adjuvant temozolomide (category 1)\(^n,r,s\)
- or Standard RT\(^l\) + concurrent temozolomide and adjuvant temozolomide + alternating electric field therapy (category 1)\(^n,r,s,t\)
- or Standard RT\(^l\) + concurrent temozolomide and adjuvant temozolomide\(^n,r,s\)
- or Temozolomide\(^n\)
- or Hypofractionated brain RT alone\(^l\)

Consider clinical trial (preferred for eligible patients)
- or Hypofractionated brain RT\(^l\) + concurrent and adjuvant temozolomide\(^n,r,s\)
- or Standard RT\(^l\) + concurrent temozolomide\(^u\) and adjuvant temozolomide\(^u\) + alternating electric field therapy (category 1)\(^n,r,s,t\)
- or Standard RT\(^l\) + concurrent temozolomide\(^u\) and adjuvant temozolomide\(^n,r,s,u\)
- or Hypofractionated brain RT alone\(^l\)

**FOLLOW-UP\(^b\)**

- Hypofractionated brain RT alone\(^l\)
- or Temozolomide\(^n,o\)
- or Palliative/best supportive care

Within the first 3 months after completion of RT and concomitant temozolomide, diagnosis of recurrence can be indistinguishable from pseudoprogression on neuroimaging.

\(^a\)This pathway includes the classification of mixed AOA, AA, AO, and other rare anaplastic gliomas.

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

\(^c\)See Principles of Brain Tumor Pathology (BRAIN-F).

\(^d\)This pathway also includes gliosarcoma.

\(^e\)See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C).

\(^f\)See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).

\(^g\)Consider temozolomide if tumor is MGMT promoter methylated.

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Follow-Up

Recurrence Staging Workup

Treatment for Progression or Recurrence

- Imaging in the event of emergent signs or symptoms (brain and/or spine MRI)
- Imaging of tumor site (brain or spine MRI) every 3–4 mo for 1 yr, then every 4–6 mo for year 2, then every 6–12 mo for 5–10 yr, then as clinically indicated

If recurrent:

- Spine or brain recurrence
- MRI imaging of spine, brain, and CSF analysis

Resectable

- Gross total or subtotal resection; CSF cytology negative
  - Limited-field external beam RT
- Gross total or subtotal resection and evidence of metastasis (brain, spine, or CSF)
  - Craniospinal RT

Prior RT

- Gross total or subtotal resection; CSF cytology negative
  - Clinical trial or consider re-irradiation or chemotherapy

Localized recurrence

- Evidence of metastasis (brain, spine, or CSF)
  - Limited-field external beam RT
  - Craniospinal RT

Clinical trial or consider re-irradiation or chemotherapy

Unresectable

- Localized recurrence
  - Clinical trial or consider re-irradiation or chemotherapy
  - Chemotherapy

Evidence of metastasis (brain, spine, or CSF)

Clinical trial or chemotherapy

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

Lumbar puncture should be done after MRI of spine if performed to avoid a false-positive imaging result. Lumbar puncture for CSF should be delayed at least 2 weeks after surgery to avoid possible false-positive cytology. Lumbar puncture.

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

m Consider stereotactic radiosurgery (SRS) if geometrically favorable.

Chemotherapy should be reserved for patients who are refractory to surgery or radiation.

See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).
Brain MRI:
- every 3 mo for 2 y;
- then every 6–12 mo for 5–10 y;
- then as clinically indicated.

For patients with previous spine disease, concurrent spine imaging as clinically indicated.

**FOLLOW-UP**

**CLINICAL STAGING**

<table>
<thead>
<tr>
<th>Localized brain recurrence</th>
<th>Maximum safe resection</th>
<th>Brain and spine MRIa,g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent disease</td>
<td>Brain and spine MRIa,f</td>
<td>CSF analysis</td>
</tr>
<tr>
<td>Disseminated diseaseg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**SURGERY**

**TREATMENT FOR RECURRENTNESS**

Chemotherapy\(^\circ\) and/or Additional radiation,\(^u\) such as stereotactic radiosurgery (SRS), after resection or High-dose chemotherapy\(^\circ\) with autologous stem cell reinfusion\(^f\)

| Chemotherapy\(^\circ\) or Palliative/best supportive care, including focal radiation, if indicated\(^u\) |

---

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

\(^b\)Postoperative brain MRI within 48 hours after surgery.

\(^c\)Spine MRI should be delayed by at least 2–3 weeks post surgery to avoid postsurgical artifacts.

\(^d\)See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).

\(^f\)As clinically indicated, consider bone scan; contrast-enhanced CT scans of chest, abdomen, and pelvis; and/or bone marrow biopsy.

\(^u\)Consider resection for palliation of symptoms where indicated.

\(^g\)Only if the patient is without evidence of disease after surgery or conventional dose re-induction chemotherapy.

\(^\circ\)See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C).

---

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**FOLLOW-UP**

**RECURRENT**

**TREATMENT FOR RECURRENCE**

- **Low-grade tumors (I-II)**
  - Spine MRI every 3–6 mo until 5 y, then at least annually indefinitely

- **High-grade tumors (III-IV)**
  - Spine MRI 2–6 wk after treatment, then every 2–4 mo until 2–3 y, then every 3–6 mo until 5 y, then every 6–12 mo indefinitely

- **New/worsening symptoms or radiographic progression**
  - Re-resection or RT\(^9\) or re-irradiation (include stereotactic radiotherapy [SRT]), if surgery not possible or Chemotherapy\(^9\) if further surgery or RT not possible

---

\(^{9}\) See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D) for options according to disease histology.

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**PRESENTATION**

- Radiographic diagnosis by brain MRI:
  - Dural-based mass
  - Homogeneously contrast-enhancing
  - Dural tail
  - CSF cleft

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

---

**TREATMENT**

- Observe (preferred for small asymptomatic tumors; not generally recommended for symptomatic tumors)

  or

- Surgery (if accessible)

  or

- RT

---

Follow-up (See MENI-2)

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**Discussion**

*Multidisciplinary input for treatment planning if feasible.*

*Treatment selection should be based on assessment of a variety of inter-related factors, including patient features (e.g., age, performance score, comorbidities, treatment preferences), tumor features (e.g., size, grade, growth rate, location [proximity to critical structures]), potential for causing neurologic consequences if untreated, presence and severity of symptoms, and treatment-related factors (e.g., potential for neurologic consequences from surgery/RT, likelihood of complete resection and/or complete irradiation with SRS, treatability of tumor if it progresses, available surgical or radiation oncology expertise and resources). The decision to administer RT after surgery also depends on the extent of resection achieved. Multidisciplinary input for treatment planning is recommended.***

*For asymptomatic meningiomas, observation is preferred for small tumors, with a suggested cutoff of ≤3 cm. Active treatment with surgery and/or RT is recommended in cases with one or more tumor- and/or treatment-related risk factors, such as proximity to the optic nerve.*

*Postoperative brain MRI within 48 hours after surgery.*

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

*RT can be either external-beam or SRS.*

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

*WHO Grade I = Benign meningioma, WHO Grade II = Atypical meningioma, WHO Grade III = Malignant (anaplastic) meningioma.*

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

**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
NCCN Guidelines Version 1.2019
Limited Brain Metastases

CLINICAL PRESENTATION

WORKUP

No other readily accessible tumor for biopsy

Surgery to confirm diagnosis of CNS metastases:
- Resection for management of mass effect or symptoms
- Consider resection for treatment of patients with newly diagnosed or stable systemic disease or reasonable systemic treatment options
- Biopsy if resection not planned

Consider surgery for brain metastases:
- Resection for management of mass effect or symptoms
- Resection for treatment of patients with newly diagnosed or stable systemic disease or reasonable systemic treatment options
- Biopsy if concern exists about diagnosis of CNS lesions and resection is not planned

See Clinical Presentation and Treatment (LTD-2)

aSee Principles of Brain and Spine Tumor Imaging (BRaIN-A).
bConsider a multidisciplinary review in treatment planning, especially once pathology is available. See Principles of Brain and Spine Tumor Management (BRaIN-E).
c"Limited" brain metastases defines a group of patients for whom SRS is equally effective and offers significant cognitive protection compared with WBRT. The definition of "limited" brain metastases in terms of number of metastases or total intracranial disease volume is evolving and may depend on the specific clinical situation. (Yamamoto M, Serizawa T, Shuto T, et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. Lancet Oncol 2014;15:387-395.)
dSee Principles of Brain Tumor Surgery (BRaIN-B).

For secondary CNS lymphoma treatment may include systemic treatment, whole-brain or focal RT, or combination. The decision to resect a tumor may depend on the need to establish histologic diagnosis, the size of the lesion, its location, and institutional expertise. For example, smaller (<2 cm), deep, asymptomatic lesions may be considered for treatment with SRS versus larger (>2 cm), symptomatic lesions that may be more appropriate for surgery. (Ewens 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.)

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**Clinical Presentation**

<table>
<thead>
<tr>
<th>Disseminated systemic disease with poor systemic treatment options⁶</th>
<th>Consider palliative/best supportive care or WBRT⁷,⁸</th>
</tr>
</thead>
</table>

| Newly diagnosed or stable systemic disease or Reasonable systemic treatment options exist⁶ | SRS (preferred)⁹,⁷,¹ | WBRT⁷,¹ |

---

⁶For secondary CNS lymphoma treatment may include systemic treatment, whole-brain or focal RT, or combination.

⁷If an active agent exists (eg, cytotoxic, targeted, or immune modulating), trial of systemic therapy with good CNS penetration may be considered in select patients (eg, for patients with small asymptomatic brain metastases from melanoma or ALK rearrangement-positive NSCLC or EGFR-mutated NSCLC); it is reasonable to hold on treating with radiation to see if systemic therapy can control the brain metastases. Close MRI surveillance is strongly recommended. There are no data from prospective clinical trials comparing the two strategies to assess what the impact of delayed radiation would be in terms of survival or in delay of neurologic deficit development. See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).

⁸See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C).

⁹SRS is preferred when safe, especially for low tumor volume, to both the resection cavity and any other non-resected brain metastases. WBRT is generally not recommended but may be appropriate in some rare clinical circumstances.

¹For brain metastases not managed with resection, SRS + WBRT is generally not recommended but may be appropriate in some rare clinical circumstances. Brown 2016 showed that for tumors <3 cm, SRS + WBRT improved local control compared with SRS alone, but did not significantly improve survival, and was associated with greater cognitive decline and poorer quality of life. (Brown PD, Jaekle K, Ballman KV, et al. Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases: a randomized clinical trial. JAMA 2016;316:401-409.)

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**FOLLOW-UP**

<table>
<thead>
<tr>
<th>Brain MRI every 2–3 mo for 1 y, then every 4–6 mo indefinitely</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recurrent disease</strong></td>
</tr>
<tr>
<td><strong>Stable systemic disease or reasonable systemic treatment options</strong></td>
</tr>
</tbody>
</table>

**RECURRENT**

<table>
<thead>
<tr>
<th>Systemic disease progression, with limited systemic treatment options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Palliative/best supportive care</strong></td>
</tr>
</tbody>
</table>

**TREATMENT**

<table>
<thead>
<tr>
<th>Surgery or SRS or WBRT (if no prior WBRT)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brain MRI</strong></td>
</tr>
</tbody>
</table>

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**See Principles of Brain and Spinal Tumor Imaging (BRAIN-A).**
**See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C).**
**See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).**

*Imaging to evaluate emergent signs/symptoms is appropriate at any time.

*After SRS, recurrence on radiograph can be confounded by treatment effects; consider tumor tissue sampling if there is a high index of suspicion of recurrence.
Metastatic Spine Tumors

**Presentation**

Asymptomatic (Incidental finding)

Patient diagnosed with cancer or patient with newly discovered abnormality suspicious for spine metastasis

Symptomatic:
- Severe, new, or progressive pain or neurologic symptoms or myelopathy

**Workup**

- Systemic imaging (ie, contrast-enhanced chest/abdominal/pelvic CT or whole body PET/CT, bone scan as indicated for metastatic workup)
- Biopsy \(^a\) if it alters management

**Treatment**

- Observation
  - Spine MRI \(^d\) in 6–8 weeks, then every 2–3 months until the nature of the lesion is established
- Surgery/focal RT \(^f\) or chemotherapy \(^f\) are options for patients with asymptomatic epidural disease

- No tumor
  - Spinal MR \(^b,c,d\) (urgent in the event of neurologic symptoms)

- Spinal cord compression \(^d\)

- No spinal cord compression \(^d\)

---

\(^a\) Biopsy if remote history of cancer.

\(^b\) If the patient is unable to have an MRI, then a CT myelogram is recommended, which may also be useful for SRT planning.

\(^c\) 15%–20% of patients have additional lesions. Highly recommend complete spine imaging.

\(^d\) See Principles of Brain and Spine Tumor Imaging (BRAIN-A).

\(^e\) See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C).

\(^f\) See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).

\(^g\) Includes cauda equina syndrome.

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**NCCN Guidelines Version 1.2019**

**Metastatic Spine Tumors**

**PRESENTATION**

- **No tumor**
  - Evaluate for other causes of pain and/or neurologic symptoms
  - Surgery \( ^{k, l, m} \) ± stabilization followed by RT \( ^{n} \) (category 1)
  - or
  - Primary RT \( ^{n} \)
  - or
  - In the absence of clinical myelopathy, primary chemotherapy \( ^{f} \) if chemosensitive tumor (e.g., lymphoma, germ cell tumor, myeloma)

- **Spinal cord compression**
  - Steroids \( ^{h} \)
  - Fracture or spinal instability \( ^{i} \)
    - Surgical stabilization or Vertebral augmentation \( ^{o} \)
    - Followed by RT \( ^{n} \)

- **No spinal cord compression**
  - No fracture or spinal instability
    - RT \( ^{n} \) (preferred)
    - or
    - Chemotherapy \( ^{f} \) (if chemosensitive tumor)
    - or
    - Surgery \( ^{m} \) (selective cases) followed by RT
    - Consider surgery \( ^{m} \) or SRS \( ^{n} \) if:
      - Deterioration during RT
      - Intractable pain
      - Tumor progression

---

**ADJUVANT TREATMENT**

See Follow-up (SPINE-3)

---

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\( ^{f} \) See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).

\( ^{g} \) Includes cauda equina syndrome.

\( ^{h} \) The recommended minimum dose of steroids is 4 mg of dexamethasone every 6 hours, although dose of steroids may vary (10–100 mg). A randomized trial supported the use of high-dose steroids.

\( ^{i} \) Spinal instability is grossly defined as the presence of significant kyphosis or subluxation (deformity), or of significantly retropulsed bone fragment.

\( ^{j} \) Consider alternative diagnosis of leptomeningeal disease (See LEPT-1).

\( ^{k} \) Tumor resection with or without spinal stabilization. Surgery should be focused on anatomic pathology.

\( ^{l} \) Regarding surgery, note the following:
  - Category 1 evidence supports the role of surgery in patients with a solitary epidural spinal cord compression by a tumor not known to be radiosensitive and who are willing to undergo surgery.
  - For surgery, patients with hematologic tumors (e.g., lymphoma, myeloma, leukemia) should be excluded, life expectancy should be \( \geq 3 \) mo, and the patient should not be paraplegic for \( >24 \) h.
  - Surgery is especially indicated if the patient has any of the following: spinal instability, no history of cancer, rapid neurologic deterioration during RT, previous RT to site, and single-site spinal cord compression.

\( ^{m} \) Postoperative spine MRI should be delayed by at least 2–3 weeks to avoid post-surgical artifacts.

\( ^{n} \) Recommend SRS if oligometastases and radioresistant.

---

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**FOLLOW-UP**

**PRESENTATION**
(Symptom- or MRI-based)

**TREATMENT FOR RECURRENCE OR PROGRESSIVE DISEASE**

- Spine MRI/CT\(^d\)
  1–3 mo after treatment, then every 3–4 mo for 1 y, then as clinically indicated indefinitely

  - Progressive disease or Recurrent disease
    - If previously treated with:
      - RT
      - Surgery and RT
      - Consider surgery\(^m\) or SRS\(^n,p\)
    - Consider re-irradiation if recurrent

  - If previously treated with:
    - Chemotherapy
    - Consider surgery\(^m\) with or without RT\(^n\)

---

\(^d\)See *Principles of Brain and Spine Tumor Imaging (BRAIN-A)*.

\(^m\)Postoperative spine MRI should be delayed by at least 2–3 weeks to avoid post-surgical artifacts. See *Principles of Brain Tumor Surgery (BRAIN-E)*.

\(^n\)Recommend SRS if oligometastases and radioreistant. See *Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C)*.

PRINCIPLES OF RADIATION THERAPY FOR BRAIN AND SPINAL CORD

Adult Low-Grade (WHO Grade I or II) Glioma/Pilocytic and Infiltrative Supratentorial Astrocytoma/Oligodendroglioma

- Tumor volumes are best defined using pre- and postoperative MRI imaging, usually fluid-attenuated inversion recovery (FLAIR)/T2 and, occasionally, enhanced T1 sequences to define gross tumor volume (GTV). Clinical target volume (CTV) (GTV plus 1–2 cm margin) should receive 45–54 Gy in 1.8–2.0 Gy fractions. Consider RT dose escalation to 59.4–60 Gy for IDH-wild-type low-grade gliomas, as these patients have a more aggressive course of disease.

Anaplastic Gliomas/Glioblastoma High-Grade (Grades III/IV)

Simulation and Treatment Planning

- Tumor volumes are best defined using pre- and postoperative MRI imaging using enhanced T1 with/without FLAIR/T2 sequences to define GTV. To account for sub-diagnostic tumor infiltration, the GTV is expanded 1–2 cm (CTV) for grade III, and up to 2–2.5 cm (CTV) for grade IV. Although trials in glioblastoma have historically used CTV expansion in the range of 2 cm, smaller CTV expansions are supported in the literature and can be appropriate. A planning target volume (PTV) of margin of 3–5 mm is typically added to the CTV to account for daily setup errors and image registration. Daily image guidance is required if smaller PTV margins are used (3 mm or less). When edema assessed by T2/FLAIR is included in the initial phase of treatment, fields are usually reduced for the last phase of the treatment (boost). The boost target volume will typically encompass only the gross residual tumor and the resection cavity. A range of acceptable clinical target volume margins exists. Both strategies appear to produce similar outcomes.

RT Dosing Information

- The recommended dose is 60 Gy in 2.0 Gy fractions or 59.4 Gy in 1.8 Gy fractions.
- A slightly lower dose, such as 54–55.8 Gy in 1.8 Gy or 57 Gy in 1.9 Gy fractions, can be applied when the tumor volume is very large (gliomatosis), there is brainstem/spinal cord involvement, or for grade III astrocytoma.
- If a boost volume is used, the initial phase of the RT plan will receive 46 Gy in 2 Gy fractions or 45–50.4 Gy in 1.8 Gy fractions. The boost plan will typically then receive 14 Gy in 2 Gy fractions or 9–14.4 Gy in 1.8 Gy fractions.4
- In poorly performing patients or elderly patients, a hypofractionated accelerated course should be considered with the goal of completing the treatment in 2–4 weeks. Typical fractionation schedules are 34 Gy/10 fx, 40.05 Gy/15 fx, or 50 Gy/20 fx. Alternatively, a shorter fractionation schedule of 25 Gy/5 fx may be considered for elderly and/or frail patients with smaller tumors for whom a longer course of treatment would not be tolerable.

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PRINCIPLES OF RADIATION THERAPY FOR BRAIN AND SPINAL CORD

Adult Intracranial and Spinal Ependymoma

- Limited Fields:
  - Intracranial tumor volumes are best defined using pre- and postoperative MRI imaging, usually enhanced T1 and/or FLAIR/T2. GTV is defined as anatomic areas that are touched by preoperative tumor volume plus postoperative signal abnormality as seen on MRI.

- RT Dosing Information:
  - CTV (GTV plus 1–2 cm margin) should receive 54–59.4 Gy in 1.8–2.0 Gy fractions. PTV of margin of 3–5 mm is typically added to the CTV to account for daily setup errors and image registration.

- Craniospinal:
  - To reduce toxicity from craniospinal irradiation (CSI) in adults, consider the use of intensity-modulated radiotherapy or protons if available.

  - RT Dosing Information:
    - 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.
    - (Gross metastatic lesions below the conus could receive higher doses of 54–60 Gy).9
    - Primary intracranial site should receive total dose of 54–59.4 Gy in 1.8–2.0 Gy fractions.
    - Consider boosting any gross intracranial metastatic sites to a higher dose while respecting normal tissue tolerances.

- Spine Ependymoma:
  - For spine ependymomas, see section on primary spinal cord tumors (BRAIN-C 3 of 8).10,11
  - CTV margins of 1–2 cm in the superior and inferior directions are recommended.
  - PTV of margin of 3–5 mm is typically added to the CTV to account for daily setup errors and image registration.

Adult Medulloblastoma

- Standard Risk for Recurrence:
  - Conventional dose: 30–36 Gy CSI12,† and boosting the primary brain site to 54–55.8 Gy with or without adjuvant chemotherapy.
  - Reduced dose: May consider reduced dose radiation with adjuvant chemotherapy: 23.4 Gy CSI12,13,†† and boosting the primary brain site to 54–55.8 Gy.1

- High Risk for Recurrence:
  - 36 Gy CSI3,†† with boosting primary brain site to 54–55.8 Gy with adjuvant chemotherapy.

†To reduce toxicity from craniospinal irradiation in adults, consider the use of intensity-modulated radiotherapy or protons if available.

††Regimen supported by data from pediatric trials only.

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PRINCIPLES OF RADIATION THERAPY FOR BRAIN AND SPINAL CORD

Primary CNS Lymphoma

- WBRT may be withheld in the primary setting in patients treated with chemotherapy.

  ▶ RT Dosing:
    ◦ When used, low-dose WBRT should be limited to 23.4 Gy in 1.8 Gy fractions following a complete response (CR) to chemotherapy.\textsuperscript{14}
    ◦ For less than CR, consider WBRT to 30–36 Gy followed by a limited field to gross disease to 45 Gy or focal radiation to residual disease only.\textsuperscript{15-18}

  ▶ For patients who are not candidates for chemotherapy:
    ◦ WBRT doses of 24–36 Gy followed by a boost to gross disease for a total dose of 45 Gy.

Primary Spinal Cord Tumors

▶ RT Dosing:
  ◦ Doses of 45–54 Gy are recommended using fractions of 1.8 Gy.
  ◦ In tumors below the conus medullaris higher doses up to 60 Gy may be delivered.
  ◦ CTV margins of 1–2 cm in the superior and inferior directions are recommended.
  ◦ PTV margins of 3–5 mm are typically added to the CTV to account for daily setup errors and image registration.

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Meningiomas

- **General Treatment Information**
  - If appropriate, may be treated using SRS or fractionated SRS.
  - Highly conformal fractionated RT techniques (eg, 3D-CRT, IMRT, VMAT, proton therapy) are recommended to spare critical structures and uninvolved tissue.
  - Stereotactic or image-guided therapy is recommended when using tight margins or when close to critical structures.

- **WHO Grade I Meningiomas:**
  - **RT Dosing:**
    - 45–54 Gy.
    - WHO grade I meningiomas may also be treated with SRS doses of 12–16 Gy in a single fraction when appropriate, or consider hypofractionated SRT (25 Gy in 5 fractions) if near critical structures. Optimal dosing has not been determined.

- **WHO Grade II Meningiomas:**
  - **General Treatment Information**
    - Treatment should be directed to gross tumor (if present), surgical bed, and a margin (1–2 cm) to account for microscopic disease.
    - Limit margin expansion into the brain parenchyma if there is no evidence of brain invasion.
  - **RT Dosing:**
    - 54–60 Gy in 1.8–2.0 Gy fractions.

- **WHO Grade III Meningiomas:**
  - **General Treatment Information**
    - Treat as malignant tumors with treatment directed to gross tumor (if present), surgical bed, and a margin (2–3 cm).
  - **RT Dosing:**
    - 59.4–60 Gy in 1.8–2.0 Gy fractions.
PRINCIPLES OF RADIATION THERAPY FOR BRAIN AND SPINAL CORD

**Brain Metastases**

- **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 for patients with poor predicted prognosis.\(^{19}\)
  - For patients with a better prognosis, consider memantine during and after WBRT for a total of 6 months.\(^{20}\)
  - For patients with a better prognosis (4 months or greater), consider hippocampal-sparing WBRT.\(^{21,22}\)

- **SRS**: Maximum marginal doses from 15–24 Gy based on tumor volume is recommended.\(^{23–26}\)
  - Consider fractionated SRS for brain tumor >3 cm.
    - Most common fractionated SRT doses include: 27 Gy in 3 fx and 30 Gy in 5 fx.
  - Postoperative SRS or SRT: Local recurrence rates after brain metastasis resections remain high (in the range of 50% at 1–2 years) even in the setting of a radiographic GTR. Postoperative SRS or SRT to the surgical cavity is supported by randomized data to improve local control over observation and to offer similar overall survival and superior cognitive preservation to postoperative WBRT.\(^{27,28}\)
    - A consensus statement regarding radiation target delineation has been published.\(^{29}\)
    - Fractionated SRT may be preferred for larger cavities.\(^{30}\)
    - Common dose-fractionation schedules include 16–20 Gy in 1 fraction, 27 Gy in 3 fractions, and 30 Gy in 5 fractions.

- **SRS** is generally preferred over WBRT for limited brain metastases.

**Leptomeningeal Metastases**

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

- **General Treatment Information**
  - Doses to vertebral body metastases will depend on patient's PS, spine stability, location in relationship to spinal cord, primary histology, presence of epidural disease, and overall treatment intent (pain relief, long-term local control, or cure).
  - Stereotactic radiation approaches (SRS/stereotactic body radiotherapy [SBRT]) for spinal cases may be preferred for patients with oligometastatic disease where tumor ablation is a goal of treatment and in tumors considered radioresistant (eg, renal cell, melanoma, sarcoma, hepatocellular, and some colorectal and NSCLC cases). Stereotactic radiation approaches may also be preferred in the setting of tumor recurrence after prior radiation as a strategy to limit radiation dose to the spinal cord or other critical structures. Careful adherence to consensus guidelines for radiosurgery planning and delivery is recommended.\textsuperscript{31-33}

- **RT Dosing:**
  - Generally, conventional external beam radiation doses of 8 Gy/1 fx, 20 Gy/5 fx, or 30 Gy/10 fx can be used. It is critical to consider tolerance at the spine and/or nerve root. In selected cases, or recurrences after previous radiation, SBRT is appropriate.

- Common recommended doses for spine SRS/SBRT may include:
  - 16–24 Gy x 1 fx;
  - 24 Gy in 2 fx;
  - 24–27 Gy in 3 fx;
  - 30–35 Gy in 5 fx

- In patients with uncomplicated spine metastases that are treated primarily for pain relief, 8 Gy in 1 fraction has been shown to provide equivalent pain control to longer fractionation schedules. Single fraction treatment is more convenient for patients and an important consideration for patients with poor prognoses. This treatment may be associated with higher rates of retreatment, and a consideration for patients with a prognosis that exceeds 6 months or greater.

- When lower BED regimens are utilized upfront (ie, BED ≤60 Gy, which includes up to 20 Gy in 5 fractions but does not include 30 Gy in 10 fractions), retreatment with similar BED regimens, such as 20 Gy in 5 fractions or 8 Gy in 1 fraction, can safely be considered as early as 4 weeks from initial treatment for pain relief.

- In other cases of retreatment, doses ranging from 15 Gy in 1 fraction to 40 Gy in 20 fractions have been utilized for tumor control, with careful consideration of tolerance of the spinal cord and/or nerve roots. In these instances, it is generally recommended that 6 months or more of time between treatments is required.
PRINCIPLES OF BRAIN AND SPINAL CORD TUMOR RADIATION THERAPY

REFERENCES


PRINCIPLES OF BRAIN AND SPINAL CORD TUMOR RADIATION THERAPY
REFERENCES


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

#### BRAIN METASTASES

<table>
<thead>
<tr>
<th>Newly Diagnosed&lt;br&gt;**</th>
<th>** Recurrent Disease&lt;br&gt;**</th>
</tr>
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<tbody>
<tr>
<td><em>Treatment as per the regimens of the primary tumor</em>&lt;sup&gt;†&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td><em>Treatment as per the regimens of the primary tumor</em>&lt;sup&gt;†&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td><strong>Melanoma</strong></td>
<td></td>
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<tr>
<td>◦ Ipilimumab + nivolumab&lt;sup&gt;113,114&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>◦ Nivolumab&lt;sup&gt;114&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>◦ pembrolizumab&lt;sup&gt;115&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>◦ BRAF/MEK inhibitor combination:&lt;br&gt;  ◦ Dabrafenib&lt;sup&gt;116,118&lt;/sup&gt;/trametinib&lt;sup&gt;119&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>◦ Vemurafenib&lt;sup&gt;120&lt;/sup&gt;/cobimetinib&lt;sup&gt;8&lt;/sup&gt; (category 2B)</td>
<td></td>
</tr>
<tr>
<td><strong>Non-Small Cell Lung Cancer</strong></td>
<td></td>
</tr>
<tr>
<td>◦ pembrolizumab (PD-L1 positive)&lt;sup&gt;115&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>◦ Alectinib (ALK rearrangement-positive)&lt;sup&gt;121&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>◦ Osimertinib (EGFR mutation-positive)&lt;sup&gt;122&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>◦ Nivolumab (category 2B)&lt;sup&gt;123-125&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>◦ Brigatinib (ALK rearrangement-positive)&lt;sup&gt;126&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>◦ Ceritinib (ALK rearrangement-positive) (category 2B)&lt;sup&gt;127&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

| **Breast Cancer** |
| ◦ Capecitabine<sup>128-132</sup> |
| ◦ Capecitabine + lapatinib (HER2 positive)<sup>133,134</sup> |
| ◦ Capecitabine + neratinib (HER2 positive) (category 2B)<sup>135</sup> |
| ◦ Paclitaxel + neratinib (HER2 positive) (category 2B)<sup>136</sup> |
| ◦ Cisplatin<sup>137,138</sup> |
| ◦ Etoposide<sup>137,138</sup> |
| ◦ Cisplatin + etoposide (category 2B)<sup>138,139</sup> |
| ◦ High-dose methotrexate<sup>m,140</sup> |

| **Lymphoma** |
| ◦ High-dose methotrexate<sup>m,141</sup> |

| **Small Cell Lung Cancer** |
| ◦ Topotecan |

| **Melanoma** |
| ◦ Ipilimumab<sup>142</sup> |
| ◦ Nivolumab |
| ◦ Ipilimumab + nivolumab<sup>113,114,143</sup> |
| ◦ pembrolizumab<sup>115</sup> |
| ◦ BRAF/MEK inhibitor combination:<br>  ◦ Dabrafenib<sup>116,118</sup>/trametinib<sup>119</sup> |
| ◦ Vemurafenib<sup>120,144</sup>/cobimetinib<sup>8</sup> (category 2B) |

| **Non-Small Cell Lung Cancer** |
| ◦ Pembrolizumab (PD-L1 positive)<sup>115-145</sup> |
| ◦ Ceritinib<sup>127</sup>, alectinib, brigatinib<sup>147</sup> (ALK rearrangement-positive) |
| ◦ Erlotinib<sup>140,142</sup>, afatinib, gefitinib<sup>151,152</sup> (EGFR-sensitizing mutation-positive) |
| ◦ Osimertinib (EGFR T790M mutation-positive)<sup>153,154</sup> |
| ◦ Crizotinib (ALK rearrangement-positive or ROS1 positive)<sup>155</sup> |

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<sup>‡</sup> For patients with asymptomatic brain metastases, it is reasonable to treat with systemic therapy in lieu of upfront WBRT or SRS.

<sup>§</sup> See the appropriate NCCN treatment guidelines for systemic therapy recommendations for newly diagnosed brain metastases for any cancers not listed here.

<sup>‖</sup> Although there are no published prospective studies on the combination of vemurafenib and cobimetinib for melanoma patients with brain metastases, there is high-quality evidence that for melanoma with distant metastasis, combination therapy with vemurafenib and cobimetinib is associated with improved outcomes and safety compared with single-agent vemurafenib.

<sup>1</sup> Use agents active against primary tumor.

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

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

In the year 2018, an estimated 23,880 people in the United States will be diagnosed with a primary malignant brain tumor or other central nervous system (CNS) neoplasms. These tumors will be responsible for approximately 16,830 deaths. The incidence of primary brain tumors has been increasing over the last 30 years, especially in older adults.

Tumor Types

The NCCN Guidelines for CNS Cancers focus on management of the following adult CNS cancers: low-grade infiltrative supratentorial astrocytomas, oligodendrogliomas, anaplastic gliomas and glioblastoma, ependymomas, medulloblastoma, brain metastases, leptomeningeal metastases, non-AIDS-related primary CNS lymphomas (PCNSLs), metastatic spinal tumors, meningiomas, and primary spinal cord tumors. These guidelines are updated annually to include new information or treatment philosophies as they become available. However, because this field continually evolves, practitioners should use all of the available information to determine the best clinical options for their patients.

Principles of Management

Primary brain tumors are a heterogeneous group of neoplasms with varied outcomes and management strategies. Primary malignant brain tumors range from pilocytic astrocytomas, which are very uncommon, noninvasive, and surgically curable, to glioblastoma, 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 therapy (RT) or chemotherapy. Because of this marked heterogeneity, the prognostic features and treatment options for primary brain tumors must be carefully reviewed on an individual basis and sensitively communicated to each patient. In addition, these CNS tumors are associated with a range of symptoms and complications such as edema, seizures, endocrinopathy, fatigue, psychiatric disorders, and venous thromboembolism that can seriously impact patients’ quality of life. The involvement of an interdisciplinary team, including neurosurgeons, RT therapists, oncologists, neurologists, and neuroradiologists, is a key factor in the appropriate management of these patients. For any subtype of malignant brain tumors, the NCCN Panel encourages thorough multidisciplinary review of each patient’s case once the pathology is available. Further discussion of multidisciplinary care and allied services, as well as guidelines on medical management of various disease complications, can be found in the algorithm section, Principles of Brain and Spine Tumor Management. In 2016, the panel added a section describing guiding principles for CNS tumor pathology, given the recent addition of molecular parameters in the WHO classification of CNS tumors.

Treatment Principles

Several important principles guide surgical treatment and RT for adults with brain tumors. Regardless of tumor histology, neurosurgeons generally provide the best outcome for their patients if they remove as much tumor as safely possible (ideally achieving a gross total resection [GTR]) and thereby providing sufficient representative tumor tissue to ensure an accurate diagnosis. Decisions regarding aggressiveness of surgery for primary brain tumors are complex and depend on the: 1) age and performance status (PS) of the patient; 2) proximity to “eloquent” areas of the brain; 3) feasibility of decreasing the mass effect with aggressive surgery; 4) resectability of the tumor (including the number and location of lesions); and 5) time since last surgery in patients with recurrent disease.

The surgical options include stereotactic biopsy, open biopsy, subtotal resection (STR), or complete resection (GTR). The pathologic diagnosis is
critical and may be difficult to accurately determine without sufficient tumor tissue. Review by an experienced neuropathologist is highly recommended. In addition, a postoperative brain MRI scan should be obtained 24 to 72 hours after surgery to document the extent of residual disease after surgical intervention.

Radiation oncologists use several different treatment modalities in patients with primary brain tumors, including brachytherapy, fractionated stereotactic RT, and stereotactic radiosurgery (SRS). Standard fractionated external beam RT (EBRT) is the most common approach. Hypofractionated radiation is an appropriate option for select patients (ie, older adults and patients with a poor PS). RT for patients with primary brain tumors is administered within a limited field (tumor and surround), while whole brain RT (WBRT) and SRS are used primarily for brain metastases.

Enrollment in a clinical trial is the preferred treatment for eligible patients. Clinicians are advised to consult the algorithm sections, Principles of Brain and Spine Tumor Imaging, Principles of Brain Tumor Surgery, and Principles of Brain Tumor Pathology for further discussion of surgical management and diagnosis. The dose of RT administered varies depending on the pathology as seen in Principles of Brain and Spinal Cord Tumor Radiation Therapy. Appropriate chemotherapeutic and biologic regimens for each tumor subtype are listed under Principles of Brain and Spinal Cord Tumor Systemic Therapy.

Gliomas
The NCCN Guidelines for CNS Cancers include recommendations for management of grade II gliomas (ie, diffuse astrocytomas and oligodendrogliomas), grade III gliomas (ie, anaplastic astrocytoma and oligodendroglioma), and grade IV gliomas (ie, glioblastoma).

Molecular Profiling for Gliomas
In 2016, Principles of Brain Tumor Pathology was added to the NCCN Guidelines for CNS Cancers to provide guidance for histopathologic and molecular characterization of gliomas, which should now be standard practice. Molecular/genetic characterization complements standard histologic analysis, providing additional diagnostic and prognostic information that may improve diagnostic accuracy and aid in treatment selection.

Updated Classification of Gliomas Based on Histology and Molecular Features
Key changes to the WHO classification system for version 2016 for grade II–III gliomas are as follows: 1) oligodendrogliomas are defined as only tumors that have 1p19q codeletion and IDH mutation (unless molecular data are not available and cannot be obtained, in which case designation can be based on histology; 2) anaplastic gliomas are further subdivided according to IDH mutation status; and 3) oligoastrocytoma is no longer a valid designation unless molecular data (1p19q deletion and IDH mutation status) are not available and cannot be obtained, or there are phenotypic and genotypic evidence of spatially distinct oligodendroglioma (1p19q codeleted) and astrocytoma (1q19q intact or deletion of only 1p or 19q) components in the same tumor. It is important to note that correlations between the molecularly defined 2016 WHO categories and the histology-based 2007 WHO categories are limited and vary across studies. Thus, the change from 2007 WHO to 2016 WHO reclassifies a significant proportion of grade II–IV gliomas.

Multiple independent studies on glioma tissue removed from the brain have conducted genome-wide analyses evaluating an array of molecular features (eg, DNA copy number, DNA methylation, protein expression) in large populations of patients with grade II–IV disease. Unsupervised clustering analyses, an unbiased method for identifying molecularly similar
patients 60 years or older with a poor PS (KPS < 70) to 60 Gy given over 6 weeks versus 40 Gy given over 3 weeks and found no difference in survival between these two regimens.\textsuperscript{102} Subsequent studies in older adult patients have confirmed dose-fractionation regimens of 40 Gy in 15 fractions and 34 Gy in 10 fractions, all showing non-inferiority compared to the standard 60 Gy regimen.\textsuperscript{45} Interestingly, more recent data from Roa et al suggest that an even more hypofractionated regimen of 25 Gy in 5 fractions may be no less inferior to the previously mentioned hypofractionated regimen (40 Gy in 15 fractions) in a particularly poor prognosis subgroup of patients.\textsuperscript{103}

The EORTC 26062-22061/NCIC CTG randomized trial of hypofractionated RT with concurrent and adjuvant TMZ versus hypofractionated RT regimen alone in older adult patients showed an improvement in OS and PFS with the addition of concurrent and adjuvant TMZ.\textsuperscript{104} The largest benefit was noted in patients with MGMT promoter methylation. Ultimately, quality of life remains an important consideration in the optimal management of this patient population.

Systemic Therapy

Anaplastic Oligodendroglioma

Anaplastic oligodendrogliomas are relatively rare, they are characterized by high cellularity, nuclear pleomorphism, frequent mitosis, endothelial proliferation, and necrosis, and have a distinct molecular signature. While these tumors can be confused with glioblastoma histopathologically, if molecular analysis detects that the tumor is 1p19q codeleted and IDH 1 or 2 mutated, then the tumor is an anaplastic oligodendroglioma.\textsuperscript{3} This distinct subtype has a much better prognosis compared to other high-grade gliomas (anaplastic astrocytomas and glioblastomas). In the revised 2016 WHO Classification of Tumors of the CNS,\textsuperscript{3} oligoastrocytoma is no longer a valid diagnosis; however, “oligoastrocytoma, NOS” may continue to be used if a tumor has features of mixed histology and molecular testing is not possible or in the rare instance that the tumor has distinct histologic regions of oligodendroglioma that are 1p19q codeleted and astrocytoma that are not 1p19q codeleted.\textsuperscript{3}

The addition of PCV to RT for the treatment of newly diagnosed anaplastic oligodendrogliomas is supported by results from two phase III trials, one which tested RT followed by PCV for 6 cycles (EORTC 26951\textsuperscript{105,106}) and the other which assessed 4 cycles of dose-intensive PCV administered prior to RT (RTOG 9402\textsuperscript{107,108}). Both studies compared the combination therapy to RT alone, and found significant increases in median OS when PCV was added to RT for the upfront management of 1p19q codeleted tumors.

The EORTC 26951 trial showed that, among the entire group of 368 histopathologically diagnosed study patients with anaplastic oligodendroglioma or anaplastic oligoastrocytoma. RT followed by 6 cycles of PCV significantly improved median PFS and OS (42.3 vs. 30.6 months; HR, 0.75; 95% CI, 0.60–0.95; P = .018) compared with RT alone.\textsuperscript{106} Moreover, in an exploratory subgroup analysis of the 80 patients whose tumors were 1p19q codeleted, the benefit was even more pronounced (OS not reached in the RT + PCV group vs. 112 months in the RT group; HR, 0.56; 95% CI, 0.31–1.03)\textsuperscript{23,105,106}

RTOG 9402 randomized 291 patients with histopathologically diagnosed anaplastic oligodendroglioma or anaplastic oligoastrocytoma to PCV followed by immediate RT or RT alone.\textsuperscript{108} In contrast to the EORTC 26951 study, no difference in median OS was observed between the two arms (4.6 years vs. 4.7 years; HR, 0.79; 95% CI, 0.60–1.04; P = .10). However, an unplanned subgroup analysis of the 126 patients whose tumors were 1p19q co-deleted found a doubling in median OS (14.7 vs. 7.3 years; HR, 0.59; 95% CI, 0.37–0.95; P = .03) when PCV was added to RT as upfront treatment.
As would be predicted, in both studies, toxicity was higher in the treatment arms that included PCV. In EORTC 26951, 70% of patients in the RT followed by PCV arm did not complete the planned 6 cycles of treatment. In RTOG 9402, there was also a high rate of study treatment discontinuation and acute toxicities (mainly hematologic), including 2 early deaths attributed to PCV-induced neutropenia in the intense PCV arm followed by RT.

The phase III CODEL study was designed to assess the efficacy of TMZ for the treatment of newly diagnosed anaplastic oligodendrogliomas. The initial treatment arms were RT alone, RT + TMZ, and TMZ alone. However, when the results of RTOG 9402 and EORTC 26951 were reported showing significant improvement in median OS with RT + PCV upfront, the CODEL study was redesigned to compare RT + PCV to RT + TMZ in patients with anaplastic oligodendroglioma as well as low-grade oligodendroglioma. This study is ongoing.

**Anaplastic Astrocytoma**

The RTOG 9813 trial showed that RT with concurrent TMZ results in similar outcomes as RT with concurrent nitrosourea in patients with newly diagnosed anaplastic astrocytomas, with perhaps slightly better PFS with TMZ (HR, 0.70; 95% CI, 0.50–0.98; \textit{P} = .039). The toxicity of nitrosourea was far worse than for TMZ, and resulted in higher rates of discontinuation due to toxicity (79% vs. 40%, respectively; \textit{P} < .001). The ongoing CATNON phase 3 randomized trial is testing RT alone, as well as RT with adjuvant TMZ, concurrent TMZ, or both, in patients with anaplastic astrocytoma. A recently published interim analysis showed adjuvant TMZ significantly improved PFS (HR, 0.62; 95% CI, 0.50–0.76) and OS (HR, 0.67; 95% CI, 0.51–0.88). Median OS for the group of patients treated with post-RT TMZ had not been reached, but median OS at 5 years was 55.9% (95% CI, 47.2–63.8) with and 44.1% (36.3–51.6) without adjuvant TMZ. Further follow-up is needed to determine whether TMZ concurrent with RT provides any clinical benefit and which of the 3 RT + TMZ combination regimens provides the best outcomes.

**Glioblastoma**

TMZ is recommended in conjunction with postoperative RT for patients with glioblastoma and good PS. Stupp et al conducted the phase III, randomized EORTC-NCIC study that assessed the drug in 573 patients with glioblastoma with age ≤70 years with a WHO PS of 2 or less. Patients received either 1) daily TMZ administered concomitantly with postoperative RT followed by 6 cycles of adjuvant TMZ; or 2) RT alone. The chemoradiation arm resulted in a statistically better median survival (14.6 vs. 12.1 months) and 2-year survival (26.5% vs. 10.4%) when compared with RT. Final analysis confirmed the survival advantage at 5 years (10% vs. 2%). However, the study design does not shed light on which component is responsible for the improvement: TMZ administered with RT, TMZ following RT, or possibly both.

The TMZ dose used in the EORTC-NCIC trial is 75 mg/m² daily concurrent with RT, then 150 to 200 mg/m² post-irradiation on a 5-day schedule every 28 days. Alternate schedules such as a 21/28 dose-dense regimen or a 50 mg/m² continuous daily schedule have been explored in a phase II trial for newly diagnosed glioblastoma. However, a comparison of the dose-dense 21/28 and standard 5/28 schedules in the RTOG 0525 phase III study showed no difference in PFS, OS, or by MGMT methylation status with the post-radiation dose-dense TMZ, compared to the standard post-radiation TMZ dose. A pooled analysis of individual patient data from 4 randomized trials of patients with newly diagnosed glioblastoma determined that treating with post-radiation TMZ beyond 6 cycles does not improve OS, even for patients whose tumors are MGMT promoter methylated.

For older adults with newly diagnosed glioblastoma, building on the findings that hypofractionated RT alone has similar efficacy and is better...
tolerated compared to standard RT alone, a phase III randomized trial with 562 newly diagnosed patients 65 years of age or older compared hypofractionated RT with concurrent and adjuvant TMZ to hypofractionated radiation alone. Patients in the combination therapy arm had greater PFS (5.3 months vs. 3.9 months; HR, 0.50; 95% CI, 0.41–0.60; P < .001) and median OS (9.3 months vs. 7.6 months; HR, 0.67; 95% CI, 0.56–0.80; P < .001) compared to patients treated with hypofractionated RT alone.117 The greatest improvement in median OS was seen in patients with MGMT promoter-methylated tumors (13.5 months RT + TMZ vs. 7.7 months RT alone; HR, 0.63; 95% CI, 0.38–0.73; P < .001). The benefit of adding TMZ to RT was smaller in patients with MGMT promoter- unmethylated tumors and did not quite reach statistical significance (10.0 months vs. 7.9 months, respectively; HR, 0.75; 95% CI, 0.56–1.01; Z = 0.555; P = .08 for interaction).

Two phase III studies in elderly newly diagnosed glioblastoma patients assessed treatment with TMZ alone versus radiation.45,46 The Nordic trial randomized 291 patients aged 60 years and older with good PS across 3 treatment groups: TMZ, hypofractionated RT, or standard RT.46 Patients older than 70 years had better survival with TMZ or hypofractionated RT compared to standard RT, and patients whose tumors were MGMT promoter-methylated benefitted more from treatment with TMZ compared to patients with MGMT promoter- unmethylated tumors (median OS 9.7 vs. 6.8 months; HR, 0.56; 95% CI, 0.34–0.93; Z = 0.02). The NOA-08 study assessed the efficacy of TMZ alone compared to standard RT in 373 patients aged 65 years and older.40 TMZ was found to be non-inferior to standard RT: median OS was similar in both groups (8.6 months in the TMZ arm vs. 9.6 months in the standard RT arm; HR, 1.09; 95% CI, 0.84–1.42; Z = 0.033). For patients whose tumors were MGMT promoter methylated, event-free survival was longer with TMZ treatment compared to standard RT (8.4 months vs. 4.6 months). Although radiation in combination with TMZ may be recommended over single-modality therapy for newly diagnosed patients with glioblastoma who are older than 70 years of age and have good PS, the results of two phase III studies support the recommendation that TMZ alone as initial therapy may be a reasonable option for those elderly patients who have MGMT promoter-methylated tumors and would initially prefer to delay treatment with radiation.45,46

**Alternating Electric Field Therapy**

In 2015, the FDA approved alternating electric field therapy for the treatment of newly diagnosed glioblastoma based on the results of the phase 3 EF-14 clinical trial. This portable medical device generates low-intensity alternating electric fields to stop mitosis/cell division. In the EF-14 trial, 695 patients with newly diagnosed glioblastoma were randomized to TMZ alone on a 5/28 day schedule or the same TMZ and alternating electric field therapy, following completion of standard focal brain radiation and daily TMZ.118 The results of the study showed an improvement in median PFS (6.7 vs. 4.0 months, respectively; HR, 0.63; 95% CI, 0.52–0.76; P < .001) and OS (20.9 vs. 16.0 months, respectively; HR, 0.63; 95% CI, 0.53–0.76; P < .001) in patients who received TMZ plus alternating electric field therapy.119 The number of adverse events was not statistically different between the two treatment groups except for a greater frequency of mild to moderate local skin irritation/itchiness in the patients treated with the alternating electric fields.120 There was no increased frequency of seizures.121,122

**Therapy for Recurrence**

Patients with malignant gliomas eventually recur or progress. Unfortunately, there is no established second-line therapy for recurrent gliomas. If there has been a long interval of time between stopping temozolomide and tumor progression, it is reasonable to restart a patient on temozolomide,122 particularly if the patient’s tumor is MGMT methylated. Similarly, a nitrosourea, such as carmustine or lomustine,124-
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127 would be a reasonable second-line therapy, especially in a patient whose tumor is MGMT methylated. Although no studies of bevacizumab in patients with recurrent glioblastoma have demonstrated an improvement in survival, bevacizumab is FDA approved for the treatment of recurrent glioblastoma based on improvement in PFS.126,129 Of note, improvement in PFS may be due to bevacizumab’s ability to decrease BBB permeability (resulting in less contrast enhancement and vasogenic edema) rather than a true anti-tumor effect.130

Other routes of chemotherapy delivery have been evaluated. Local administration of carbamustine using a biodegradable polymer (wafer) placed intraoperatively in the surgical cavity has demonstrated a statistically significant improvement in survival with patients with recurrent high-grade gliomas (31 vs. 23 weeks; adjusted HR, 0.67; P = .006).131 Clinicians and patients should be aware that treatment with the carbamustine wafer may prevent participation in a clinical trial involving a locally delivered investigational agent.

Alternating electric field therapy is also FDA approved for treating recurrent glioblastoma based on the safety results of this medical device from the EF-11 clinical trial.132 This phase II study randomized 237 patients with recurrent glioblastoma to alternating electric field therapy or the treating oncologist’s choice of chemotherapy. The study did not meet its primary endpoint of demonstrating an improvement in survival in the cohort of patients treated with alternating electric field therapy. Although median OS was similar in both of the treatment arms (6.6 vs. 6 months), the study had not been powered for non-inferiority determination. Due to lack of clear efficacy data for alternating electric field therapy in EF-11, the panel is divided about recommending it for the treatment of recurrent glioblastoma.

To improve local control in patients with local recurrence, re-irradiation is an option.

NCCN Recommendations
Primary Treatment
When a patient presents with a clinical and radiologic picture suggestive of high-grade glioma, neurosurgical input is needed regarding the feasibility of maximal safe tumor resection. For first-line treatment of high-grade glioma, the NCCN Guidelines recommend maximal safe resection whenever possible. One exception is when CNS lymphoma is suspected; a biopsy should be performed first and management should follow the corresponding pathway if the diagnosis is confirmed. When maximal resection is performed, the extent of tumor debulking should be documented with a postoperative MRI scan with and without contrast performed within 72 hours after surgery. Multidisciplinary consultation is encouraged once the pathology is available.

Adjunctive Therapy
RT, unless PS precludes treatment, is uniformly indicated after maximal safe resection in the treatment of high-grade gliomas to improve local control and survival. For postoperative treatment of anaplastic gliomas in patients with good PS (KPS ≥ 60), combination therapy with fractionated EBRT combined with PCV or TMZ are among the recommended options. For patients with 1p/19q co-deleted anaplastic oligodendroglioma, fractionated EBRT plus PCV, given before or after RT, is a category 1 recommendation, based on the results of the RTOG 940234,108 and EORTC 26951 studies.105,106 The panel advises administering PCV after RT as per EORTC 26951 instead of the dose-intensive PCV used prior to RT in the RTOG 9402 study108 due to better patient tolerance. Fractionated RT plus concurrent and adjuvant TMZ is also recommended, particularly if it is predicted that the patient might have significant difficulty tolerating PCV due to age or coexisting medical conditions.

In the case of anaplastic astrocytoma and anaplastic oligoastrocytoma (not otherwise specified; NOS) with good PS, fractionated RT followed by
adjuvant TMZ is recommended based on the interim analysis results of the CATNON trial showing improvement in survival of RT followed by 12 cycles of TMZ compared to RT alone.\textsuperscript{110} Other acceptable treatment options include fractionated RT with concurrent and adjuvant temozolomide or fractionated RT and PCV.\textsuperscript{110}

For patients with anaplastic gliomas and a poor PS (KPS < 60), treatment options recommended in the NCCN Guidelines are limited to single-modality therapies due to concerns about the ability of these patients to tolerate the toxicity associated with combination regimens. Patients with a poor PS can be managed by RT (hypofractionation is preferred over standard fractionation), TMZ alone (considered for tumors that are MGMT promoter methylated), or palliative/best supportive care. TMZ alone is a category 2B option for these patients.

For patients diagnosed with glioblastoma, the adjuvant options mainly depend on the patient PS (as defined by KPS), age, and MGMT promoter methylation status.\textsuperscript{45,104,133,134} Category 1 recommendations for patients aged 70 years or younger with a good PS, regardless of the tumor's MGMT methylation status, include fractionated standard brain RT plus concurrent and adjuvant TMZ with or without alternating electric field therapy. Since patients with newly diagnosed glioblastoma whose MGMT promoter-unmethylated tumors are likely to experience less clinical benefit from treatment with TMZ, RT alone is included as a reasonable option, particularly if the patient is eligible to participate in a clinical trial, which omits the use of upfront TMZ.

Category 1 treatment recommendations for patients older than 70 years of age with newly diagnosed glioblastoma, a good PS, and MGMT promoter-methylated tumors include hypofractionated brain RT plus concurrent and adjuvant TMZ\textsuperscript{117} or standard brain RT plus concurrent and adjuvant TMZ and alternating electric field therapy. For those patients older than age 70 with newly diagnosed glioblastoma, a good PS, and with MGMT unmethylated or indeterminant tumors, standard brain RT plus concurrent and adjuvant TMZ and alternating electric field therapy is a category 1 option.\textsuperscript{118,119} The complete list of recommendations that the panel did not consider category 1 can be found in the treatment algorithms for patients with glioblastoma who are older than age 70.

Treatment recommendations for patients with newly diagnosed glioblastoma and KPS below 60 (regardless of age) include hypofractionated brain RT (preferred for patients who are age 70 or younger, possibly with concurrent and adjuvant TMZ), TMZ alone (for MGMT promoter-methylated tumors), or palliative/best supportive care.

**Follow-up and Recurrence**

Patients should be followed closely with serial brain MRI scans (at 2–6 weeks post-irradiation, then every 2–4 months for 3 years, then every 6 months indefinitely) after the completion of RT. Because RT can produce additional BBB dysfunction, scans may appear worse during the first 3 months after completion of RT even though there may be no actual tumor progression. Early MRI scans allow for appropriate titration of corticosteroid doses, based 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. Biopsy, MR spectroscopy, MR perfusion, or brain PET/CT can be considered to try to determine if the changes seen on brain MRI are due to RT-induced necrosis or "pseudoprogression" versus actual disease progression.\textsuperscript{135,136} Management of recurrent tumors depends on the extent of disease and patient condition. The efficacy of current treatment options for recurrent disease remains poor; therefore, enrollment in a clinical trial, whenever possible, is preferred for management of recurrent disease. A patient with a poor PS should receive palliative/best supportive care without further active treatment.
Intracranial and Spinal Ependymomas

Ependymomas constitute up to 4% of adult CNS tumors and 10% of pediatric CNS tumors.\(^{137}\) In adults, ependymomas occur more often in the spinal canal than in the intracranial compartment (two-thirds infratentorial). These tumors can cause hydrocephalus and increased intracranial pressure, mimic brainstem lesions, cause multiple cranial nerve palsies, produce localizing cerebellar deficits, and cause neck stiffness and head tilt if they infiltrate the upper portion of the cervical cord.\(^{138,139}\) This section focuses on adult intracranial and spinal grade II differentiated (termed ependymomas) and grade III (termed anaplastic ependymomas) ependymomas. Grade I ependymomas (subependymomas and myxopapillary) are non-infiltrative and can be cured by resection alone.

Treatment Overview

Surgery

There is a paucity of robust studies regarding this uncommon disease, but multiple case series have reported that patients with totally resected tumors tend to have the best survival for both low- and high-grade ependymomas.\(^{140-144}\) Supratentorial ependymomas generally have a poorer prognosis than their infratentorial counterparts, because a greater proportion of supratentorial lesions are of high grade and because large volumes of residual disease tend to be present after surgical resection at this location.

Radiation Therapy

The survival benefits of RT following surgical recovery have been established for anaplastic ependymomas and suboptimally resected tumors, although much of the data are derived from pediatric patients. Rodriguez et al\(^{145}\) reviewed over 2400 cases of ependymomas in the SEER database and reported the lack of RT to be a poor prognostic factor in partially resected patients (HR = 1.75; \(P = .024\)). The short-term and 10-year survival rate after RT reached over 70% and 50%, respectively.\(^{146-148}\)

The value of RT is more controversial for differentiated ependymomas,\(^{141,149}\) with data demonstrating improved survival mainly for subtotally resected tumors.\(^{142,145}\)

In the past, the standard practice was to irradiate the entire craniospinal axis or administer WBRT. However, studies have demonstrated that: 1) local recurrence is the primary pattern of failure; 2) spinal seeding is uncommon in the absence of local failure; 3) the patterns of failure are similar in patients with high-grade tumors who are treated with local fields or craniospinal axis irradiation; and 4) spinal metastases may not be prevented by prophylactic treatment.\(^{150-152}\) Prophylactic craniospinal or WBRT does not lead to improvement in survival compared to conformal regional RT with higher doses in modern studies of non-disseminated disease.\(^{143,149,150}\) Typical craniospinal irradiation scheme includes 36 Gy in 1.8 Gy fractions to the whole brain and spine, followed by limited field irradiation to spine lesions to 45 Gy. For intracranial ependymomas, the primary brain site should receive a total of 54 to 59.4 Gy in 1.8 to 2.0 Gy fractions. For spinal ependymomas, patients should receive 45 to 50.4 Gy in 1.8 Gy fractions. Higher doses up to 60 Gy are reasonable for spinal tumors below the conus medullaris. Proton beam craniospinal irradiation may be considered when toxicity is a concern.

SRS has been used as a boost after EBRT or to treat recurrence with some success, although long-term results are still lacking.\(^{154-158}\)

Systemic Therapy

Research on chemotherapeutic regimens has also centered on pediatric ependymomas, while the role of chemotherapy in the treatment of adult patients remains poorly defined. No study has demonstrated a survival advantage with the addition of chemotherapy to irradiation in newly diagnosed tumors. However, chemotherapy is sometimes considered as an alternative to palliative/best supportive care or RT in the recurrence setting. Possible options include platinum-based regimens (cisplatin or
carboplatin),\textsuperscript{157,158} etoposide,\textsuperscript{159} lomustine or carmustine,\textsuperscript{158} bevacizumab,\textsuperscript{160} and temozolomide.

**NCCN Recommendations**

**Primary and Adjuvant Treatment**

Whenever possible, maximal safe resection should be attempted with contrast-enhanced brain image verification within 24 to 72 hours. Spine MRI should be delayed by at least 2 to 3 weeks after surgery to avoid post-surgical artifacts. Due to the established relationship between the extent of resection and outcome, multidisciplinary review and re-resection (if possible) should be considered if MRI shows that initial resection is incomplete. If maximal resection is not feasible at diagnosis due to anatomic or other factors, biopsy (stereotactic or open) or STR should be performed. If feasible, reoperation should be considered to complete resection.

The adjuvant treatment algorithm revolves around the extent of surgical resection, histology, and staging by cranial spinal MRI and cerebrospinal fluid (CSF) cytology. For spinal ependymomas, brain MRI is necessary to determine if these are drop metastases from the brain. CSF dissemination develops in up to 15\% of intracranial ependymomas. Lumbar puncture for CSF cytology, delayed at least 2 weeks after surgery, should be performed for anaplastic ependymoma and/or if resection is suboptimal. CSF analysis is also indicated for grade II ependymomas following GTR if spine MRI is negative. However, lumbar puncture may be contraindicated in some cases (for example, posterior fossa mass). Patients who have undergone GTR and have negative findings for MRI and CSF may be observed if the tumor is supratentorial or spinal or consider adjuvant limited-field fractionated EBRT if the tumor is intracranial or myxopapillary. Patients with spinal ependymomas that have been totally resected usually do not require adjuvant RT as the recurrence rate is low. Limited-field fractionated EBRT is the appropriate postoperative management for patients with anaplastic ependymoma and/or STR, provided MRI (spine MRI for intracranial ependymoma and brain MRI for spinal ependymoma) and CSF findings are both negative. Craniospinal RT is mandatory when MRI spine or CSF results reveal metastatic disease, regardless of histology and extent of resection.

**Follow-up and Recurrence**

Follow-up of ependymoma depends on the extent and location of the disease. For localized disease, contrast-enhanced brain and spine MRI (if initially positive) should be done 2 to 3 weeks postoperatively and then every 3 to 4 months for one year. The interval can then be extended to every 4 to 6 months in the second year and then every 6 to 12 months, depending on the physician’s concern regarding the extent of disease, histology, and other relevant factors. If tumor recurrence in the brain or spine is noted on one of these scans, restaging by brain and spine MRI as well as CSF analysis is necessary. Resection is recommended if possible. RT should be administered (after surgery if performed) if not given originally; SRS may be considered in geographically favorable cases.

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

**Medulloblastoma and Supratentorial PNET**

Cranial PNETs are embryonal neoplasms showing varying degrees of differentiation. They are described by their location as infratentorial (medulloblastomas) and supratentorial (cerebral neuroblastoma, pineoblastoma, or esthesioneuroblastoma). The WHO classification system further divides these tumors into histologic variants.\textsuperscript{161} CNS PNETs are infrequent in children and very rare in adults, with an overall
incidence of 0.26 per 100,000 person-years reported by the Central Brain Tumor Registry of the United States (CBTRUS).\textsuperscript{162} Overall, it represents only 1.8\% of all brain tumors, although it is the most common type among pediatric brain malignancies.

About half of the affected patients will present with elevated intracranial pressure. Headache, ataxia, and nausea are commonly observed symptoms.\textsuperscript{163} All PNETs of the brain are WHO grade IV, as they are invasive and rapidly growing. They also have the tendency to disseminate through the CSF. Larger retrospective case series of adult patients reported a 10-year survival of 43\% to 55\% with frequent recurrence beyond 5 years, commonly in the posterior fossa.\textsuperscript{164,165}

Treatment Overview

\section*{Surgery}

Evidence in adult patients is meager for this rare disease and there are no randomized trial data, but there is general consensus that surgical resection should be the routine initial treatment to establish diagnosis, relieve symptoms, and maximize local control. Complete resection can be achieved in half of the patients\textsuperscript{163,166,167} and is associated with improved survival.\textsuperscript{166,168} In addition, surgical placement of a ventriculoperitoneal shunt can be used to treat hydrocephalus.

\section*{Radiation Therapy}

Adjuvant RT following surgery is the current standard of care, although most studies are based on the pediatric population. The conventional dose is 30 to 36 Gy of craniospinal irradiation and a boost to a total of 54 to 55.8 Gy to the primary brain site.\textsuperscript{166,168} A lower craniospinal dose of 23.4 Gy, combined with chemotherapy, has gained popularity for average-risk patients to lessen side effects while maintaining 54 to 55.8 Gy to the posterior fossa,\textsuperscript{164,168,170} although one randomized trial found an increased relapse risk with dose reduction.\textsuperscript{171} It is reasonable to consider proton beam for craniospinal irradiation where available as it is associated with less toxicity.\textsuperscript{172} SRS demonstrated safety and efficacy in a small series of 12 adult patients with residual or recurrent disease.\textsuperscript{173}

\section*{Systemic Therapy}

The use of post-irradiation chemotherapy to allow RT dose reduction is becoming increasingly common especially for children,\textsuperscript{169,170} but optimal use of adjuvant chemotherapy is still unclear for adult patients.\textsuperscript{163-165,174,175} A phase III study that enrolled more than 400 patients between ages 3 and 21 to receive post-irradiation cisplatin-based chemotherapy regimens recorded an encouraging 86\% 5-year survival.\textsuperscript{176}

Several regimens are in use in the recurrence setting, most of which include etoposide.\textsuperscript{177-179} Temozolomide has also been used in this setting.\textsuperscript{85} High-dose chemotherapy in combination with autologous stem cell transplantation is a feasible strategy for patients who have had good response with lower doses.\textsuperscript{179,180}

\section*{NCCN Recommendations}

\section*{Primary Treatment}

MRI scan is the gold standard in the assessment and diagnosis of PNET. The typical tumor shows enhancement and heterogeneity. Fourth ventricular floor infiltration is a common finding related to worse prognosis.\textsuperscript{164,165,175} Multidisciplinary consultation before treatment initiation is advised. Maximal safe resection is recommended wherever possible. Contrast-enhanced brain MRI should be performed within 24 to 72 hours following surgery, but spinal MRI should be delayed by 2 to 3 weeks. Because of the propensity of PNET to CSF seeding, CSF sampling after spine imaging via lumbar puncture is also necessary for staging. Medulloblastoma should be staged according to the modified Chang system using information from both imaging and surgery.\textsuperscript{181,182}
Adjuvant Therapy

Patients should be stratified according to recurrence risk for planning of adjuvant therapy (reviewed by Brandes et al\(^{183}\)). The NCCN Panel agrees that patients with large cell or anaplastic medulloblastoma, supratentorial PNET, disease dissemination, unresectable tumors, or residual tumors more than 1.5 cm\(^2\) postsurgery are at heightened risk. These patients should undergo irradiation of the neuraxis followed by chemotherapy. Collection of stem cells before RT may be considered on the condition that RT is not delayed for potential future autologous stem cell reinfusion at disease progression. For patients at average risk, craniospinal RT alone or craniospinal RT with chemotherapy followed by post-irradiation chemotherapy are both viable options.

Recurrence and Progression

There are no robust data supporting an optimal follow-up schedule for PNETs. General guidelines include brain/MRI every 3 months for the first 2 years, biannual brain MRI for the next 3 years, then yearly brain scans. If recurrent disease is detected on these scans, CSF sampling is also required. Concurrent spine imaging should be performed as clinically indicated for patients with previous spinal disease. Bone scans, CT scans, and bone marrow biopsies should be conducted as indicated.

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

Primary CNS Lymphomas

PCNSL accounts for approximately 3% of all primary CNS tumors. It is an aggressive form of non-Hodgkin's lymphoma that develops within the brain, spinal cord, eye, or leptomeninges without evidence of systemic involvement. Its age-adjusted incidence has seen a three-fold increase over the past 20 years from 0.15 to 0.48 per 100,000, in part due to the impact of HIV infections.\(^{184}\) Non-immunosuppressed patients have a better prognosis than AIDS-related cases,\(^{185}\) and survival of this group has improved over the years with treatment advances.\(^{186}\)

Pathologically, PCNSL is an angiocentric neoplasm composed of a dense monoclonal proliferation of lymphocytes, usually diffuse large B-cells.\(^{187}\) 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 BBB. The brain parenchyma is involved in more than 90% of all PCNSL patients, and the condition can be multifocal in more than 50% of cases. Leptomeningeal involvement may occur, either localized to adjacent parenchymal sites or in diffuse form (that is, positive cytology) in up to 30% of patients. Ocular involvement may develop independently in 10% to 20% of patients. Patients with PCNSL can present with various symptoms because of the multifocal nature of the disease. In a retrospective review of 248 immunocompetent patients, 43% had mental status changes, 33% showed signs of elevated intracranial pressure, 14% had seizures, and 4% suffered visual symptoms at diagnosis.\(^{188}\)

Treatment Overview

Steroid Administration

Steroids can rapidly alleviate signs and symptoms of PCNSL and improve PS. However, as these drugs are cytolytic, they can significantly decrease enhancement and size of tumors on CT and MRI scans as well as affect the histologic appearance. In the absence of significant mass effect, it is
recommended that steroids be withheld or used judiciously until diagnostic tissue can be obtained if PCNSL is suspected.

**Stereotactic Biopsy**

In contrast to the principles previously outlined for invasive astrocytomas and other gliomas, the surgical goals for PCNSL are more modest, with the goal of obtaining diagnostic tissue under minimal risk of morbidity. Currently, most authors recommend stereotactic biopsy as the surgical method of choice. This approach stems from the fact that data do not demonstrate a survival advantage for patients who have had a complete resection or extensive STR when compared with those who have had only a stereotactic biopsy. In addition, STR is associated with risk for postoperative neurologic deficits.

**Systemic Therapy**

Methotrexate is the most effective agent against PCNSL. It is commonly used in combination with other drugs such as vincristine, procarbazine, cytarabine, rituximab, and ifosfamide, but it may also be administered as monotherapy if toxicity tolerance is a concern. High doses of intravenous methotrexate are necessary (3.5 g/m² or higher) to overcome the BBB. Intrathecal methotrexate, when given as prophylaxis in addition to intravenous methotrexate in primary treatment, confers no clinical advantage and is not recommended, but can be useful where CSF cytology yields positive findings.

Renal dysfunction induced by high-dose methotrexate therapy is a potentially lethal medical emergency due to heightened toxicities resulting from a delay in methotrexate excretion. Early intervention with glucarpidase, a recombinant bacterial enzyme that provides an alternative route for methotrexate clearance, has shown efficacy in rapidly reducing plasma concentrations of methotrexate and preventing severe toxicity.

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

Because patients older than 60 years often suffer from significant and sometimes lethal neurotoxic effects from consolidation RT, a number of phase II trials have adopted the approach of chemotherapy with deferred RT. Complete response to chemotherapy ranged from 42% to 61%, with overall survival between 14 and 55 months. However, a high fraction of patients who have forgone initial RT—typically older or with significant comorbidities—will fail to achieve complete response to chemotherapy and later require WBRT.

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

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

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

Thiel and colleagues conducted a randomized, phase III, non-inferiority trial of high-dose methotrexate plus ifosfamide with or without WBRT in 318 patients with PCNSL. There was no difference in overall survival (HR, 1.06; 95% CI, 0.80–1.40; P = .71), but the primary hypothesis (0.9 non-inferiority margin) was not proven. Patients who received WBRT had a higher rate of neurotoxicity than those who did not (49% vs. 26%).

Although WBRT alone is seldom sufficient as primary treatment and is primarily reserved for patients who cannot tolerate multimodal treatment, it can be effective as second-line therapy following chemotherapy failure, with response rates reaching nearly 75%.

NCCN Recommendations

Initial Evaluation
Neuroradiologic evaluation is important in the diagnosis of PCNSL and to evaluate the effectiveness of subsequent therapy. With MRI, the tumor is often isointense or hypointense on T1- and T2-weighted images and enhances frequently. In addition, restricted diffusion can be seen in the area of the enhancing abnormality on diffusion-weighted imaging sequences. On a CT scan, PCNSL is usually isodense or hypodense compared to the brain and enhances in most cases. Hallmark features include a periventricular distribution, ring enhancement, multiple lesions, and a smaller amount of edema than might otherwise be expected from a similar-sized metastatic tumor or glioma. If enhanced-contrasted MRI (or contrast CT if MRI is contraindicated) suggests PCNSL, clinicians are advised to hold the use of steroids if possible before diagnosis is established, since the imaging and histologic features of PCNSL can be profoundly affected by these drugs.

A lumbar puncture with evaluation of CSF should be considered, if it can be done safely and without concern for herniation from increased intracranial pressure. The yield for a positive diagnostic test can be increased by the use of molecular markers of monoclonality, such as an immunoglobulin gene rearrangement. If the CSF is negative, consider an ophthalmologic evaluation including a slit-lamp examination to exclude an obvious malignant uveitis. Ocular biopsy should follow suspicious findings.
Despite CSF or uveal evaluation, the intracranial lesion often requires a brain biopsy for a definitive diagnosis.\(^{188}\) Because the role of maximal surgical resection is limited to alleviating symptoms of raised intracranial pressure or preventing hemiation,\(^{188}\) stereotactic biopsy is generally preferred to minimize invasiveness. Even with molecular marker testing, however, a biopsy can occasionally be falsely negative, particularly if the patient had been treated previously with steroids. Thus, if a biopsy is nondiagnostic, the panel recommended that the steroids be tapered and that the patient be followed closely, both clinically and radiographically. If and when the lesion recurs, the lesion should be promptly rebiopsied before the initiation of steroids. If, on the other hand, no definitive diagnosis of lymphoma is made from biopsy and the patient has not received steroid therapy, workup for other malignancies (for example, inflammatory processes) or rebiopsy is recommended.

**Staging Workup**

Once the diagnosis of PCNSL is established, the patient should undergo a thorough staging workup detailed by The International PCNSL Collaborative Group.\(^{189}\) This workup involves a complete CNS evaluation including imaging of the entire neuraxis (MRI of the spine with contrast). This should be done before CSF analysis is attempted to avoid post-lumbar puncture artifacts that can be mistaken for leptomeningeal disease on imaging. A slit-lamp eye examination, if not previously performed, should also be done, as well as a lumbar puncture for CSF flow cytometry. In addition, blood work (CBC and chemistry panel) and a CT of the chest, abdomen, and pelvis are required to rule out systemic involvement.

An HIV blood test should also be performed, because both prognosis and treatment of patients with HIV-related PCNSL may be different than that of patients who are otherwise immunocompetent. HIV-positive patients should consider highly active retroviral therapy.

More elaborate tests such as bone marrow biopsy, testicular ultrasound for older men, and body PET scan\(^{231}\) may be considered (category 2B), although their value in routine workup is still under debate.

**Primary Treatment**

Treatment should be initiated as soon as possible following confirmation of diagnosis. Given the dramatic effect of steroids on symptom relief, they are commonly administered concurrently with workup. Selection of primary therapy depends on the general health condition and age of the patient. For healthier patients with KPS 40 or higher, a high-dose methotrexate-containing regimen is recommended. In the case of methotrexate induced renal dysfunction, consider urgent glucarpidase to aid clearance.

Whether one performs WBRT after systemic chemotherapy depends on the responsiveness of the disease to chemotherapy and on the clinical judgment of the medical and radiation oncologists. WBRT may increase neurotoxicity, especially in patients older than 60 years, and may be withheld in the primary setting. If a patient is found to have malignant uveitis, RT 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.\(^{190}\) Therefore, with a PCNSL patient who has asymptomatic ocular involvement, a reasonable strategy is to delay RT to the globe in order to see if high-dose methotrexate is effective. Intraocular injection of chemotherapy (category 2B) is also an option. Additionally, if the patient is found to have a malignant pleocytosis in the CSF, direct intrathecal chemotherapy can be considered (category 2B).

Patients with KPS below 40 are too weak to undergo multi-modal treatment. However, these patients are potentially eligible for a change to more aggressive therapy if their PS improves following steroid therapy. If the health condition remains poor, it is recommended that treatment...
Primary spinal cord tumors are a histologically diverse set of disease that represents 2% to 4% of all primary CNS tumors. The overall incidence is 0.74 per 100,000 person-years with a 10-year survival rate of 64%. Extramedullary lesions, most commonly benign meningiomas, account for 70% to 80% of spinal cord tumors. Astrocytomas (more prevalent in children) and ependymomas (more prevalent in adults) are the most common intramedullary tumors. Clinicians are advised to refer to the corresponding sections in these guidelines for further details regarding these subtypes, as intracranial and spinal lesions are biologically similar.

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

Since 70% of primary spinal cord tumors are low-grade and slow-growing, it is common for patients to suffer from pain for months to years before diagnosis. Pain that worsens at night is a classic symptom for intramedullary lesions. Progressive motor weakness occurs in half of the patients, and patients may experience sensory loss with late autonomic dysfunction (incontinence).

**Treatment Overview**

**Observation**

Many asymptomatic primary tumors of the spinal cord, especially grade I meningiomas and peripheral nerve sheath tumors, follow an indolent course and can be followed by observation without immediate intervention.

**Surgery**

Surgery is the preferred treatment when the tumor is symptomatic. For lesions that are radiographically well defined, such as ependymoma, WHO grade I astrocytoma, hemangioblastoma, schwannoma, and WHO grade I meningioma, potentially curative, maximal, safe resection is the goal. En
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bloc total resection yielded excellent local control rates of more than 90%. GTR is seldom feasible with grade II or higher astrocytomas because they are infiltrative and poorly circumscribed. In a study of 202 patients with intramedullary tumors, over 80% of grade I astrocytomas were completely resected, while total resection was achieved in only 12% of grade II tumors. Nevertheless, Benes et al conducted a review of 38 studies on spinal astrocytomas and concluded that maximal safe resection should be attempted whenever possible based on reports of survival benefit.

Radiation Therapy
RT is not recommended as primary therapy because of limited response, unknown histology without surgery, and low RT tolerance of the spinal cord. It is also not advisable following GTR, as tumors that can be excised completely have a low local recurrence rate.

A large retrospective analysis including over 1700 patients with primary spinal gliomas found an association between RT and worse cause-specific and overall survival, although there may be a bias that patients who received RT had more adverse factors. The role of adjuvant RT following incomplete excision or biopsy remains controversial. One exception is primary spinal myxopapillary ependymoma, for which postoperative RT has been demonstrated to reduce the rate of tumor progression. On the other hand, EBRT is considered a viable option at disease progression or recurrence. SRS has also shown safety and efficacy in several patient series.

Systemic Therapy
Unfortunately, evidence on efficacious chemotherapeutic agents for primary spinal cord tumors is too scant for specific recommendations. The panel agrees that chemotherapy should be an option where surgery and RT fail, but there is no consensus on the best regimen. Chemotherapy is best given in the setting of a clinical trial.

NCCN Recommendations
MRI imaging is the gold standard for diagnosis of spinal cord lesions. Asymptomatic patients may be observed (especially for suspected low-grade) or resected, while all symptomatic patients should undergo some form of surgery. The surgical plan and outcome is influenced by whether a clear surgical plane is available. Whenever possible, maximal safe resection should be attempted. Postoperative adjuvant RT is appropriate if symptoms persist after incomplete resection or biopsy, or for patients with asymptomatic, intramedullary, low-grade glioma. Adjuvant RT may also be considered for patients with myxopapillary ependymoma that has been incompletely resected. Patients should be managed according to the pathology results (see Low-Grade Infiltrative Astrocytomas & Oligodendrogliomas, Anaplastic Gliomas and Glioblastomas, and Intracranial and Spinal Ependymomas). Those diagnosed with hemangioblastoma should consider screening for von Hippel-Lindau syndrome including neuraxis imaging.

All patients should be followed by sequential MRI scans. At progression or recurrence, re-resection is the first choice. If this is not feasible, conventional EBRT or SRS is the next option. Chemotherapy is reserved for cases where both surgery and RT are contraindicated.

Meningiomas
Meningiomas are extra-axial CNS tumors arising from the arachnoid cap cells in the meninges. They are most often discovered in middle-to-late adult life, and have a female predominance. The annual incidence for males and females reported by CBTRUS are 1.8 and 3.4 per 100,000 people, respectively. In a review of 319 cases using the WHO grading scale, 92% of meningiomas are grade I (benign), 6% are grade II
(atypical), and 2% are grade III (malignant).\textsuperscript{249} Small tumors are often asymptomatic, incidental findings.\textsuperscript{250} Seizure is a common presenting symptom occurring in 27% of patients.\textsuperscript{251}

**Imaging**

Brain imaging with contrast-enhanced CT or MRI is the most common method of diagnosing, monitoring, and evaluating response to treatment (review by Campbell et al.\textsuperscript{252}). The CT scan best reveals the chronic effects of slowly growing mass lesions on bone remodeling. Calcification in the tumor (seen in 25%) and hyperostosis of the surrounding skull are features of an intracranial meningioma that can be easily identified on a non-contrast CT scan. Nonetheless, MR imaging reveals a number of imaging characteristics highly suggestive of meningioma, and in stereotactic RT articles, MR has been used to operationally define pathology. These MR findings include a tumor that is dural-based and isointense with gray matter, demonstrates prominent and homogenous enhancement (>95%), has frequent CSF/vascular cleft(s), and often has an enhancing dural tail (60%). However, approximately 10% to 15% of meningiomas have an atypical MRI appearance mimicking metastases or malignant gliomas. In particular, secretory meningiomas may have a significant amount of peritumoral edema. Cerebral angiography is occasionally performed, often for surgical planning, as meningiomas are vascular tumors prone to intraoperative bleeding. In some instances preoperative embolization is helpful for operative hemostasis management. Angiographic findings consistent with a meningioma include a dual vascular supply with dural arteries supplying the central tumor and pial arteries supplying the tumor periphery. A “sunburst effect” may be seen due to enlarged and multiple dural arteries, and a prolonged vascular stain or so-called “blushing” can be seen, which results from intratumoral venous stasis and expanded intratumoral blood volume.

Meningiomas are also known to have high somatostatin receptor density, which allows for the use of octreotide brain scintigraphy to help delineate extent of disease and to pathologically define an extra-axial lesion.\textsuperscript{253-255} Octreotide imaging with radiolabeled indium or, more recently, gallium may be particularly useful in distinguishing residual tumor from postoperative scarring in subtotally resected/recurrent tumors.

**Treatment Overview**

**Observation**

Studies that examined the growth rate of incidental meningiomas in otherwise asymptomatic patients suggested that many asymptomatic meningiomas may be followed safely with serial brain imaging until either the tumor enlarges significantly or becomes symptomatic.\textsuperscript{256,257} These studies confirm the tenet that many meningiomas grow very slowly and that a decision not to operate is justified in selected asymptomatic patients. As the growth rate is unpredictable in any individual, repeat brain imaging is mandatory to monitor an incidental asymptomatic meningioma.

**Surgery**

The treatment of meningiomas is dependent upon both patient-related factors (i.e., age, PS, medical comorbidities) and treatment-related factors (i.e., reasons for symptoms, resectability, goals of surgery). Most patients diagnosed with surgically accessible symptomatic meningioma undergo surgical resection to relieve neurologic symptoms. Complete surgical resection may be curative and is therefore the treatment of choice. Both the tumor grade and the extent of resection impact the rate of recurrence. In a cohort of 581 patients, 10-year progression-free survival was 75% following GTR but dropped to 39% for patients receiving STR.\textsuperscript{258} Short-term recurrences reported for grade I, II, and III meningiomas were 1% to 16%, 20% to 41%, and 56% to 63%, respectively.\textsuperscript{259-261} The Simpson classification scheme that evaluates meningioma surgery based on extent of resection of the tumor and its dural attachment (grades I to V in
decreasing degree of completeness) correlates with local recurrence rates. First proposed in 1957, it is still being widely used by surgeons today.

**Radiation Therapy**

Safe GTR is sometimes not feasible due to tumor location. In this case, STR followed by adjuvant EBRT has been shown to result in long-term survival comparable to GTR (86% vs. 88%, respectively), compared to only 51% with incomplete resection alone. Of 92 patients with grade I tumors, Soyuer and colleagues found that RT following STR reduced progression compared to incomplete resection alone, but has no effect on overall survival.

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

Technical advances have enabled stereotactic administration of RT by linear accelerator (LINAC), Leksell Gamma Knife®, or CyberKnife™ radiosurgery. The use of stereotactic RT (either single fraction or fractionated) in the management of meningiomas continues to evolve. Advocates have suggested this therapy in lieu of EBRT for small (<35 mm), recurrent, or partially resected tumors. In addition, it has been used as primary therapy in surgically inaccessible tumors (ie, base-of-skull meningiomas) or in patients deemed poor surgical candidates because of advanced age or medical comorbidities. A study of about 200 patients compared surgery with SRS as primary treatment for small meningiomas. The SRS arm had similar 7-year progression-free survival compared to GTR and superior survival over incomplete resection. In another study, Kondziolka and colleagues followed a cohort of 972 meningioma patients managed by SRS over 18 years. Half of the patients have undergone previous surgery. SRS provided excellent tumor control (93%) in patients with grade I tumors. For grade II and III meningiomas, tumor control was 50% and 17%, respectively. Another smaller study of 72 patients also reported good 5-year overall and progression-free survival for grade 0 and I meningioma (79% and 95%, respectively). These results suggest that stereotactic RT is effective as primary and second-line treatment for meningiomas smaller than 3.5 cm.

**Systemic Therapy**

Targeted therapies that have shown partial efficacy in refractory meningiomas are somatostatin analogues and alpha interferon.

**NCCN Recommendations**

**Initial Treatment**

Meningiomas are typically diagnosed by CT or MRI imaging. Biopsy or octreotide scan may be considered for confirmation. For treatment planning, multidisciplinary panel consultation is encouraged. Patients are stratified by the presence or absence of symptoms and the tumor size. Most asymptomatic patients with small tumors (<30 mm) are best managed by observation. If neurologic impairment is imminent, surgery (if accessible) or RT (EBRT or SRS) is feasible. Asymptomatic tumors 30 mm or larger should be surgically resected or observed. Symptomatic disease requires active treatment by surgery whenever possible. Non-surgical candidates should undergo RT.

Regardless of tumor size and symptom status, all patients with surgically resected grade III meningioma (even after GTR) should receive adjuvant RT to enhance local control. Postoperative RT should be considered for the following: 1) asymptomatic grade II tumors; 2) large asymptomatic grade I tumors that have been incompletely resected; and 3) large
symptomatic grade I or II tumors that have been incompletely resected. SRS may be used in lieu of conventional RT as adjuvant or primary therapy in asymptomatic cases.

**Follow-up and Recurrence**

In the absence of data, panelists have varying opinions on the best surveillance scheme and clinicians should follow patients based on individual clinical conditions. Generally, malignant or recurrent meningiomas are followed more closely than grade I and II tumors. A typical schedule for low-grade tumors is MRI every 3 months in year 1, then every 6 to 12 months for another 5 years. Less frequent imaging is required beyond 5 to 10 years.

Upon detection of recurrence, the lesion should be resected whenever possible, followed by RT. Non-surgical candidates should receive RT. Chemotherapy is reserved for patients with an unresectable recurrence refractory to RT. Regimen options include somatostatin analogues (for somatostatin receptor-positive tumors only) and interferon alfa (category 2B). Observation is an option if there is no clinical indication for treatment at recurrence.

**Brain Metastases**

Metastases to the brain are the most common intracranial tumors in adults and may occur up to 10 times more frequently than primary brain tumors. Population-based data reported that about 8% to 10% of cancer patients are affected by symptomatic metastatic tumors in the brain. A much higher incidence based on autopsy has been reported. As a result of advances in the diagnosis and treatment, many patients improve with proper management and do not die of progression of these metastatic lesions. Primary lung cancers are the most common source, accounting for half of intracranial metastases, although melanoma has been documented to have the highest predilection to spread to the brain.

Diagnosis of CNS involvement is becoming more common in patients with breast cancer as therapy for metastatic disease is improving.

Nearly 80% of brain metastases occur in the cerebral hemispheres, an additional 15% occur in the cerebellum, and 5% occur in the brainstem. These lesions typically follow a pattern of hematogenous spread to the gray-white junction where the relatively narrow caliber of the blood vessels tends to trap tumor emboli. The majority of cases have multiple brain metastases evident on MRI scans. The presenting signs and symptoms of metastatic brain lesions are similar to those of other mass lesions in the brain, such as headache, seizures, and neurologic impairment.

**Treatment Overview**

**Surgery**

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

Patchell conducted a study that randomized 95 patients with single intracranial metastases to complete resection alone or surgery plus adjuvant WBRT. Postoperative RT was associated with dramatic reduction in tumor recurrence (18% vs. 70%; $P < .001$) and likelihood of neurologic deaths (14% vs. 44%; $P = .003$). Overall survival, a secondary endpoint, showed no difference between the arms. Comparison of surgery plus WBRT versus WBRT alone is discussed in the WBRT section.

In the case of multiple lesions, the role of surgery is more restricted to obtaining biopsy samples or relieving mass effect due to large symptomatic metastases. However, evidence from retrospective series...
suggested survival benefits from tumor resection for selected patients of good prognosis with up to three metastatic sites.\textsuperscript{280,281}

**Stereotactic Radiosurgery**

The advent of SRS offered a minimally invasive option as opposed to surgery. Patients undergoing SRS avoid the risk of surgery-related morbidity. Late side effects such as edema and RT necrosis are uncommon.\textsuperscript{282}

Accumulating evidence suggests that low disease volume is a better selection criterion for SRS than a low number of metastatic lesions. A multivariate analysis of 205 patients who received SRS for 4 or more brain metastases demonstrated total treatment volume to be the most significant prognostic factor of survival, while the number of metastases did not reach significance.\textsuperscript{283} The same group conducted another analysis that identified a favorable subgroup of patients with a total treatment volume less than 7 cc and less than 7 brain lesions. These patients had significantly prolonged median survival (13 months) than other patients (6 months, $P = .00005$).\textsuperscript{284} A cohort study revealed that patients with a total SRS-treated volume of less than 5 cc or 5 to 10 cc survived longer than those with a total treated volume greater than 10 cc.\textsuperscript{285} No survival difference was observed between patients with a single metastasis or multiple metastases. Another group analyzed patients divided by their number of brain lesions and found no difference in survival times or local control rates among the groups after SRS treatment.\textsuperscript{286} However, patients with more than 15 lesions had a higher risk of developing new lesions and distant disease progression.

Taken together, patients with multiple lesions but a low total volume of disease may be amenable to SRS. Additionally, patients with a favorable histology of the primary tumor (such as breast cancer) or controlled primary tumors can often benefit from SRS regardless of the number of brain metastases present.\textsuperscript{287,288} Some brain metastases of radio-resistant primary tumors such as melanoma and renal cell carcinoma have also been shown to achieve good local control with SRS.\textsuperscript{289} Other predictors of longer survival with SRS include younger age, good PS, and primary tumor control.\textsuperscript{283,287,288,290}

In a randomized Japanese study of 132 patients with 1 to 4 metastatic brain tumors smaller than 3 cm, addition of WBRT to SRS did not prolong median survival compared to SRS alone (7.5 months vs. 8.0 months, respectively).\textsuperscript{291} However, 1-year brain recurrence rate was lowered in the WBRT plus SRS arm (47\% vs. 76\%; $P < .001$). Another small randomized trial of 58 patients with 1 to 3 brain metastases was stopped early due to a significant decline in learning and memory function among the group receiving both SRS and WBRT compared to the SRS group (52\% vs. 24\%).\textsuperscript{283} Analysis showed that SRS plus WBRT was associated with better 1-year recurrence-free survival (73\%) than SRS alone (27\%). A third trial recruited 355 patients with 1 to 3 metastatic brain lesions who underwent surgery or SRS.\textsuperscript{285} They were randomized to either adjuvant WBRT or observation. Compared to the observation arm, intracranial relapse rates and neurologic mortality were lower in the WBRT arm, but overall survival and duration of functional independence were similar. A meta-analysis concluded no overall survival improvement with the addition of WBRT to SRS.\textsuperscript{284}

Retrospective comparative studies showed that SRS plus WBRT resulted in equivalent if not better survival compared with surgery and WBRT.\textsuperscript{295-297} SRS also conferred a significant improvement in local control, especially for patients with radiosensitive tumors or solitary brain lesions. A prospective observational study of 1194 patients reported no difference in overall survival between patients with 2 to 4 metastatic brain lesions and those with 5 to 10 lesions treated with SRS alone (HR, 0.97; 95\% CI, 0.81–1.18; $P$ non-inferiority < .0001).\textsuperscript{288} SRS alone compared to resection plus WBRT was evaluated in a randomized controlled trial by Muacevic et
The study was stopped prematurely due to poor accrual. In the final analysis based on 64 patients with solitary brain metastases, radiosurgery alone was less invasive and resulted in equivalent survival and local control, but it was associated with a higher rate of distant relapse.

Several patient series have demonstrated local control rates greater than 70% with SRS in the recurrence setting for patients with good PS and stable disease who have received prior WBRT.\(^{300-305}\)

**Whole Brain Radiation Therapy**

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

Three randomized trials investigated the effectiveness of WBRT with or without surgery in patients with single brain metastases. In a study of 48 patients, Patchell et al.\(^{306}\) demonstrated that surgery followed by WBRT lengthened overall survival (40 vs. 15 weeks in WBRT arm; \(P < .01\)) and functional dependence (38 vs. 8 weeks; \(P < .005\)), as well as decreased recurrence (20% vs. 52%; \(P < .02\)) compared to RT alone. Similarly, combined treatment led to longer survival and functional independence in another randomized study by Vecht and colleagues (n=63).\(^{307}\) The greatest difference was observed in patients with stable disease; median survival was 12 months versus 7 months, and functional independence was 9 months versus 4 months. A third study of 84 patients found no difference in survival between the two strategies; however, patients with extensive systemic disease and lower performance level were included, which likely resulted in poorer outcomes in the surgical arm.\(^{308}\)

The impact of SRS boost in addition to WBRT was evaluated in two published randomized controlled studies. A multi-institutional trial by RTOG (RTOG 9508) randomly assigned 333 patients with 1 to 3 brain metastases to WBRT plus SRS or WBRT only.\(^{309}\) Despite the inclusion of larger tumors (3–4 cm) that are not favorable to SRS, the authors found a significant survival benefit in the combined arm (6.5 vs. 4.9 months; \(P = .04\)) when treating a single metastases; this benefit was not observed in patients with multiple (2 or 3) lesions. A much smaller trial of 27 patients with 2 to 4 lesions found no significant difference in survival, although SRS did extend time to local failure (36 vs. 6 months; \(P = .0005\)).\(^{310}\) Overall, no difference in overall survival was reported between the 2 approaches in a meta-analysis of the 2 trials.\(^{311}\) However, the addition of SRS to WBRT significantly improved local control and PS. SRS plus WBRT also prolonged overall survival of patients with single brain metastasis compared to WBRT alone (6.5 vs. 4.9 months; \(P = .04\)).

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

No randomized data are available in the recurrent setting, but case series reported 31% to 70% of symptom-relieving response to irradiation.\(^{312-314}\)

**Systemic Therapy**

Systemic therapy is rarely used as primary therapy for brain metastases. In randomized studies, addition of carboplatin or temozolomide to WBRT did not improve overall survival compared to RT alone,\(^{315,316}\) although there have been reports of increase in progression-free survival or radiologic response with temozolomide.\(^{316,317}\) Many tumors that metastasize to the brain are not very chemoactive or have been already heavily pretreated with organ-specific effective agents. Poor penetration through the BBB is an additional concern. As such, chemotherapy is...
usually considered as a last line of therapy for recurrent disease when other options have been exhausted (ie, surgery, SRS, RT). The choice of agent depends on the histology of the primary tumor. Carmustine wafer implantation is a reasonable option at recurrence when resection is considered. 318

Among various agents, temozolomide may be useful in some patients with previously untreated brain metastases from metastatic melanoma. 319 Temozolomide given on a prolonged schedule in combination with thalidomide has been tested in a phase II study of patients with brain metastases, but the high toxicity and lack of response rendered the regimen inappropriate. 320

A study of high-dose methotrexate in patients mostly with breast cancer achieved disease control in 56% of patients. 321 Other agents shown to have activity in breast cancer include platinum plus etoposide 322, 323 and capecitabine with or without lapatinib. 324-326

A phase I/II study of topotecan plus WBRT has shown a 72% response rate in 75 patients with brain metastases. 327 Unfortunately, a follow-up phase III trial was closed early due to slow accrual. 328

Rapid advancements in melanoma have produced effective systemic options for metastatic disease. These immunotherapeutic agents (ipilimumab) and BRAF inhibitors (dabrafenib and vemurafenib) have demonstrated activity in melanoma that has metastasized to the brain. 329-331

**NCCN Recommendations**

**Workup**

Patients who present with a single mass or multiple lesions on MRI or CT imaging suggestive of metastatic cancer to the brain, and who 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 is more than one brain lesion and no primary has yet been found. If no other readily accessible tumor is available for biopsy, a stereotactic or open biopsy resection is indicated to establish a diagnosis. Among patients with a known history of cancer and if there are concerns regarding the diagnosis of CNS lesions, a stereotactic or open biopsy resection or STR is also needed. Because brain metastases are often managed by multiple modalities, the NCCN Panel encourages multidisciplinary consultation prior to treatment for optimal planning.

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

For patients with limited systemic disease or for whom reasonable systemic treatment options exist, aggressive management should be strongly considered. For surgical candidates, high-level evidence supports category 1 recommendations for surgical resection plus postoperative WBRT and for SRS plus WBRT if only one brain lesion is involved. Other options include SRS alone or SRS following resection (category 2B). Macroscopic total removal is the objective of surgery. The choice between open resection and SRS depends on multiple factors such as tumor size and location. The best outcome for SRS is achieved for small, deep lesions at institutions with experienced staff. If the tumor is unresectable, WBRT and/or radiosurgery can be used.

Patients with progressive extracranial disease whose survival is <3 months should consider best supportive care or be treated with WBRT alone, but surgery may be considered for symptom relief. In patients with systemic cancers and druggable targets (eg, epidermal growth factor receptor [EGFR] mutations in non-small cell lung cancer; BRAF mutations in metastatic melanoma), targeted therapy in neurologically asymptomatic patients with brain metastases is considered reasonable before administration of radiotherapy.
Patients should be followed with MRI every 2 to 3 months for 1 year and then as clinically indicated. Closer follow-up every 2 months is particularly helpful for patients treated with SRS alone. Recurrence on radiograph can be confounded by treatment effects of SRS. Consider tumor tissue sampling if there is a high index of suspicion of recurrence. Upon detection of recurrent disease, prior therapy clearly influences the choice of further therapies. Patients with recurrent CNS disease should be assessed for local versus systemic disease, because therapy will differ. For local recurrences, patients who were previously treated with surgery only can receive the following options: 1) surgery, 2) single-dose or fractionated SRS, 3) WBRT, or 4) chemotherapy. However, patients who previously received WBRT probably should not undergo WBRT at recurrence due to concern regarding neurotoxicity. If the patient had previous SRS with a durable response for >6 months, reconsider SRS if imaging supports active tumor and not necrosis. Repeat SRS to a prior location is a category 2B recommendation. The algorithm for distant brain recurrences branches depending on whether patients have either 1 to 3 lesions or more than 3 lesions. In both cases, patients may receive WBRT or consider local/systemic chemotherapy, but patients with 1 to 3 recurrent tumors have the additional options of surgery or SRS.

WBRT should be used (30–45 Gy, given in 1.8–3.0 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 and poor PS, palliative or best supportive care is the first option. WBRT may be administered if the patients have not been previously irradiated. For patients who have received prior WBRT, re-irradiation is an option only if they had a positive response to the first course of RT treatment.

Treatment for Multiple (>3) Metastatic Lesions
All patients diagnosed with more than three metastatic lesions should be treated with WBRT or SRS as primary therapy. The standard regimens for WBRT are 30 Gy in 10 fractions or 37.5 Gy in 15 fractions. For patients with poor neurologic performance, a more rapid course of RT can be considered (20 Gy, delivered in 5 fractions). SRS may be considered in patients with good PS and low overall tumor volume. Palliative neurosurgery should be considered if a lesion is causing a life-threatening mass effect, hemorrhage, or hydrocephalus.

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

Leptomeningeal Metastases
Leptomeningeal metastases or neoplastic meningitis refers to the multifocal seeding of the leptomeninges by malignant cells. It is known as leptomeningeal carcinomatosis or carcinomatous meningitis when these cells originate from a solid tumor. When it is related to a systemic lymphoma, it is called lymphomatous meningitis, and when associated with leukemia, it is termed leukemic meningitis. Leptomeningeal metastasis occurs in approximately 5% of patients with cancer. This disorder is being diagnosed with increasing frequency as patients live longer and as neuroimaging studies improve. Most cases arise from
breast and lung cancers; melanoma has the highest rate of leptomeningeal spread.\textsuperscript{334,335}

Tumor cells gain access to the leptomeninges by hematogenous dissemination, lymphatic spread, or direct extension. Once these cells reach the CSF, they are disseminated throughout the neuraxis by the constant flow of CSF. Infiltration of the leptomeninges by any malignancy is a serious complication that results in substantial morbidity and mortality. Cranial nerve palsies, headaches, cerebral disturbances, mental changes, and motor weakness are among the most common presenting symptoms.\textsuperscript{333} The median survival of patients diagnosed with this disorder is <3 months with death resulting from progressive neurologic dysfunction, but may be extended by early detection and intervention.\textsuperscript{333,335}

**Treatment Overview**

The goals of treatment in patients with leptomeningeal metastases are to improve or stabilize the neurologic status of the patient and to prolong survival. Unfortunately, there is a lack of standard treatments due to meager evidence in literature. Because treatment is palliative, aggressive chemotherapy should only be given to patients most likely to benefit (see Patient Stratification).

**Radiation Therapy**

RT is mainly given for symptom alleviation, CSF-flow correction, or for debulking to facilitate chemotherapy.\textsuperscript{335-337}

**Surgery**

The role of neurosurgery for leptomeningeal metastases is mainly to place an intraventricular catheter and subcutaneous reservoir for drug administration.\textsuperscript{338} This is preferred over lumbar punctures because of improved drug delivery, safety, superior pharmacokinetics, lower interpatient variability, and patient comfort.\textsuperscript{339}

**Systemic Therapy**

Chemotherapy can reach the whole neuraxis and can improve outcome of patients. Intrathecal (intra-CSF) chemotherapy is widely used, although drugs with good CNS penetration, particularly organ-specific targeted therapies, may be administered systemically in high doses. Intrathecal therapy can involve either administration via a lumbar puncture or intraventricular injections via an Ommaya reservoir. However, both intra-CSF therapy and high-dose systemic therapy are associated with significant toxicity or complications and are therefore restricted to patients with good PS.

Agents used for intra-CSF therapy are often organ-specific with good penetration capacity. The panel included options deemed appropriate based on moderate benefit: methotrexate for breast cancer, lymphoma, and leukemia\textsuperscript{340-342}; cytarabine and liposomal cytarabine for lymphoma and leukemia\textsuperscript{341}; thiotepa,\textsuperscript{342} ruxolitinib for lymphoma\textsuperscript{343}; topotecan\textsuperscript{344}; etoposide\textsuperscript{345}; trastuzumab for breast cancer\textsuperscript{346}; and interferon alfa.\textsuperscript{347} Interferon alfa received a category 2B designation due to concerns of its toxicity and limited evidence of efficacy.

Breast cancers\textsuperscript{348} and lymphomas\textsuperscript{348} are also particularly responsive to high-dose methotrexate. In addition, weekly pulse erlotinib has been used for metastatic non-small cell lung cancer with EGFR exon 19 or exon 21 deletions (category 2B).\textsuperscript{348}

**NCCN Recommendations**

**Patient Evaluation**

Patients present with signs and symptoms ranging from injury to nerves that traverse the subarachnoid space, direct tumor invasion of the brain or spinal cord, alter the local blood supply, obstruct normal CSF flow pathways leading to increased intracranial pressure, or interfere with normal brain function. Patients should have a physical examination with a...
careful neurologic evaluation and neuraxis imaging. MRI of the brain and spine should also be performed if intra-CSF chemotherapy is being considered. A definitive diagnosis is most commonly made by lumbar puncture if it is safe for the patient. The CSF protein is typically increased, and there may be a pleocytosis or decreased glucose levels. The CSF cytology is positive approximately 50% of the time with the first lumbar puncture, and 90% of the time after repeated CSF examinations in affected patients. Clinicians should be aware that lumbar punctures may be contraindicated in patients with anticoagulation, thrombocytopenia, or bulky intracranial disease. In these cases, suspicious CSF biochemical results combined with suggestive clinical and/or radiologic features should be taken into consideration. Although a positive CSF cytology in patients with solid tumors is virtually always diagnostic, reactive lymphocytes from infections (for example, herpes zoster infection) can often be mistaken for malignant lymphocytes.

**Patient Stratification**

Once the diagnosis has been established, the patient's overall status should be carefully assessed to determine how aggressively the carcinomatous or lymphomatous meningitis should be treated. Unfortunately, this disease is most common in patients with advanced, treatment-refractory systemic malignancies for whom treatment options are limited. In general, fixed neurologic deficits (such as cranial nerve palsies or paraplegia) do not resolve with therapy, although encephalopathies may improve dramatically. As a result, patients should be stratified into “poor-risk” and “good-risk” groups. The poor-risk group includes patients with KPS below 60; 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 KPS greater than or equal to 60, no major neurologic deficits, minimal systemic disease, and reasonable systemic treatment options. Many patients fall in between these 2 groups, and clinical judgment will dictate how aggressive their treatment should be.

**Treatment**

Patients in the poor-risk group are usually offered palliative/supportive care measures. Fractionated EBRT to symptomatic sites (eg, to the whole brain for increased intracranial pressure or to the lumbosacral spine for a developing cauda equina syndrome) can be considered.

Good-risk patients should receive fractionated EBRT to symptomatic sites and to areas of bulky disease identified on neuroimaging studies. If an intraventricular catheter was placed, a CSF flow scan should be strongly considered to ensure correct flow of chemotherapy.

For patients with a normal CSF flow scan and otherwise stable disease, surgical implantation of a subcutaneous reservoir and ventricular catheter (SRVC) should be considered for intrathecal chemotherapy administration. Induction intrathecal chemotherapy should be given for 4 to 6 weeks. Alternately, patients with breast cancer or lymphoma may receive high-dose methotrexate or craniospinal RT. Craniospinal RT is also an appropriate option for patients with leukemia. 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 lumbar spine. Neuraxis imaging can also be considered for sites that were previously positive on a radiograph.

If negative cytology is achieved after induction, continue the induction chemotherapy for another month before switching to maintenance intrathecal chemotherapy. The CSF cytology status should be followed every month. If the patient is clinically stable or improving after induction and there is no clinical or radiologic evidence of progressive leptomeningeal disease, the patient should receive another 4 weeks of
"induction" intrathecal chemotherapy or should consider switching intrathecal drugs for 4 weeks. This regimen should be followed by maintenance therapy and monthly cytology if the cytology has converted to negative or is improving (still positive) while the patient is clinically stable.

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, imaging of the brain and spine is performed immediately after injection, and then imaging is done again at 4 and 24 hours. If significant flow abnormalities are seen, fractionated EBRT can be administered to the sites of obstruction before repeating a CSF flow scan. High-dose methotrexate remains an option for patients with breast cancer or lymphoma, as normal CSF flow is not required to reach cytotoxic concentrations. Patients with breast cancer, leukemia, or lymphoma may receive craniospinal RT as an alternative. If CSF flow normalizes after RT, which occurs most commonly in radiosensitive neoplasms, intrathecal chemotherapy commences. If significant flow abnormalities remain, then the patient should be treated as a poor-risk patient (ie, with supportive measures or RT).

Progressive Disease
If the patient's clinical status is deteriorating from progressive leptomeningeal disease or if the cytology is persistently positive, the clinician has several options: 1) RT to symptom sites, 2) systemic chemotherapy, or 3) palliative or best supportive care.

Metastatic Spinal Tumors
Bone metastases are a growing problem among cancer patients due to increasing life expectancy, with the spine being the most frequently affected site. In a report of 832 patients who died of malignancies, vertebral involvement was found in 36% upon autopsy. Spinal metastases primarily arise from breast, lung, prostate, and renal cancers. Extratrad lesions account for about 95% of spinal tumores, mostly in the thoracic region.

Some patients are found to have vertebral involvement as an asymptomatic, incidental finding. However, for most affected patients, pain is the primary presenting symptom preceding neurologic dysfunction. Three types of pain have been classically defined. Local pain due to tumor growth is often described as a constant, deep aching that improves with steroid medications. Mechanical back pain varies with movement and position and is attributed to structural spinal instability. While seldom responsive to steroids, mechanical pain can be alleviated by surgical stabilization. Radicular pain is a sharp or stabbing sensation that occurs when nerve roots are compressed by the tumor. Patients may experience any one of a combination of these types of pain.

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

Treatment Overview

Dissemination to the spinal column is largely incurable. Therefore, the goals of treatment are palliation and improvement of quality of life through preservation of neurologic function, pain relief, and stabilization of mechanical structure. One exception is slow-growing cancers (mainly renal cell carcinoma) with solitary spinal metastasis, for which surgery may achieve possible cure.356

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

Surgery

There is general consensus that a patient should have a life expectancy of at least three months to be a surgical candidate. Paraplegia for over 24 hours is an exclusion criterion due to low chances of improvement when prolonged neurologic deficits exist before surgery.357 Patients with hematologic malignancies should also be excluded, as they are best managed by RT or chemotherapy. Because estimation of life expectancy can be difficult, several groups have developed prognostic scoring systems to help predict surgical outcomes.358-361

Posterior laminectomy has been widely used in the past but is now obsolete due to frequent complications and lack of benefit. Modern surgical techniques enable surgeons to achieve 360° decompression of the spinal cord, and stabilization can be performed concomitantly, if required. The development of a plethora of spinal implants composed of high-quality materials such as titanium greatly improve reconstruction outcome. The surgical approach—anterolateral, posterior, or combined/circumferential—is primarily determined by disease anatomy.362,363

Sundaresan and colleagues356 reported favorable results using a variety of surgical approaches on 80 patients with solitary spine metastases. Both pain and mobility were improved in the majority of patients. Overall survival reached 30 months, with 18% of patients surviving 5 years or more. The best outcome was observed in patients with kidney and breast cancers.

Surgery followed by adjuvant EBRT has emerged as a highly effective approach in relieving spinal cord compression and restoring function, especially for solid tumors. A meta-analysis including 24 surgery cohort studies and 4 RT studies found that patients are twice as likely to regain ambulatory function after surgery than RT alone.364 However, data also revealed significant surgery-related mortality (6.3%) and morbidity (23%).

In another review of literature from 1964 to 2005, anterior decompression with stabilization plus RT was associated with superior outcome over RT alone or laminectomy, achieving 75% mean improvement in neurologic function. However, high surgical mortality rate (mean 10%) was also reported.365

To date, only one relevant randomized trial has been reported.366 Approximately 100 patients with metastatic spinal compression were randomized to surgery plus postoperative RT or RT alone. Compared to the RT group, significantly more patients in the surgery group regained walking ability (84% vs. 57%; P = .001) and for a longer period of time (median 122 days vs. 13 days; P = .003). The impressive results were obtained with strict eligibility criteria. The study excluded patients with radiosensitive tumors, neurologic deficits for 24 hours, multiple spinal tumors, lesions only compressing spinal roots, and prior RT to the
vertebrae. Although studies demonstrated high efficacy of surgery, the formidable complications related to surgery cannot be overlooked. Using the Nationwide Inpatient Sample all-payer database, Patil et al.367 reviewed data of over 26,000 patients who had undergone surgery for spinal metastases. The in-hospital mortality and complication rates were 5.6% and 22%, respectively. The most common complications were pulmonary (6.7%) and hemorrhages or hematomas (5.9%). Clearly, careful individual patient selection based on life expectancy and overall health is warranted.

Radiation Therapy
Traditionally, EBRT has been the main form of treatment for spinal metastases. In the modern surgery era, RT alone is often not sufficient in achieving decompression or stabilization (see above), but it is routinely used as adjuvant therapy following surgery as it is difficult to obtain wide negative margins. Given the potential impact of RT on wound healing, most studies posed an interval of one to three weeks between resection and subsequent RT.368

An excellent response to RT alone for spinal compression was reported by Marazano and colleagues.369 Three hundred patients were randomized to a short-course (8 Gy x 2 days) or split-course (5 Gy x 3 days; 3 Gy x 5 days) schedule. After RT, 35% of nonambulatory patients regained walking ability, and pain relief was recorded in 57% of patients with a median survival of 4 months. Efficacy of RT was highly dependent on the histology; 70% of nonambulatory breast cancer patients recovered mobility compared to only 20% of hepatocellular carcinoma patients. In general, solid tumors are considered either moderately radiosensitive (eg, breast and prostate cancers) or radioresistant (eg, melanoma; osteosarcomas; cancers of the thyroid, colon, and kidney).370 On the other hand, hematologic malignancies such as lymphomas and multiple myelomas are highly responsive to RT. Hence, RT alone is routinely utilized as therapy for these cancers, even in the presence of cord compression.

Where there is no compression, fracture, or instability, EBRT is effective in achieving local control as primary treatment. A mean 77% local control rate from seven retrospective studies including 885 patients was found in a systematic review by Gerszten and colleagues.370 RT is also a mainstay of palliative treatment for patients with poor PS, significant comorbidities, and/or limited life expectancy (<3–4 months). Klimo’s meta-analysis, including 543 patients treated by RT, revealed pain control rates of 54% to 83%.364 Unlike surgery, RT has no immediate significant treatment-related complications and very few local recurrences. However, it increases surgical complications as it impairs wound healing.

The advent of SRS allowed precise high-dose targeting in one or two fractions while minimizing exposure of the surrounding cord. This is especially important in pre-irradiated patients. The largest prospective study involved a cohort of nearly 400 patients with 500 spinal metastases, 70% of which had previous conventional irradiation.371 At a median follow-up of 21 months, radiosurgery resulted in long-term pain improvement and tumor control in 85% and 90% of cases, respectively. Other single-institution reports also suggest that SRS is safe and offers more durable response than conventional therapy.370 An ongoing phase II/III trial (RTG 0631) is comparing single-dose stereotactic RT of 16 Gy to single-dose EBRT of 8 Gy in patients with 1 to 3 spinal metastases.

Vertebral Augmentation
Percutaneous vertebroplasty and kyphoplasty involve injection of cement (polymethyl methacrylate) into the vertebral body. Vertebroplasty is a direct injection, while kyphoplasty involves inserting a balloon that provides a cavity for the injection. These vertebral augmentation procedures immediately reinforce and stabilize the column, thereby relieving pain and preventing further fractures.372 They are suitable in poor surgical candidates with painful fractures, but are relatively contraindicated in the case of spinal cord compression because they do not achieve
decompression. Symptomatic complications occur in up to 8% of patients (mostly with vertebroplasty), including embolization of the cement and local metastasis along the needle tract.

**Systemic Therapy**
Corticosteroids remain a routine initial prescription for patients presenting with cord compression, with a number of theoretical benefits including anti-inflammation, reduction in edema, short-term neurologic function improvement, and enhanced blood flow. However, the preference between high-dose (96 mg daily) and low-dose (10-16 mg daily) is still unclear.\(^{373-375}\)

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

**NCCN Recommendations**

**Workup**
Initial workup depends on the presence or absence of symptoms. Patients with an incidental, asymptomatic, metastatic lesion confirmed by systemic imaging can be observed with MRI. However, biopsy and further treatment of an incidental lesion are indicated if treatment of the patient is altered as a result of treatment of the incidental lesion. In the absence of symptoms, it is not mandatory to obtain a spinal MRI for every incidental metastatic lesion seen on surveillance bone scans. The alternate category involves severe or new back pain. Increasing intensity, duration, and changes in the character of pain should trigger an evaluation with an MRI study, even in patients with pre-existing degenerative spine conditions. Immediate spinal MRI is warranted in the occurrence of neurologic symptoms including weakness, paresthesias, and bladder or bowel incontinence. Contrast can be used to highlight and further evaluate any focal abnormality. The MRI can be used to image the entire spine or a focal area of interest. If the patient is unable to have an MRI, then a CT myelogram is recommended.

A normal neurologic examination implies that there is no spinal radiculopathy or myelopathy correlating with the patient's symptoms. In this case, other causes should be considered (eg, leptomeningeal disease). An abnormal neurologic examination includes motor abnormalities, sphincter abnormalities, and/or sensory deficits attributable to a dysfunction of nerve root(s) and/or the spinal cord. Therefore, detection of radiculopathy, myelopathy, or cauda equina syndrome is indicative of an abnormal examination. However, reflex asymmetry and/or presence of pathologic reflexes, as well as sensory deficits of a stocking/glove distribution are excluded.

**Treatment**
Once metastatic vertebral involvement is diagnosed, treatment is based on whether the patient is suffering from spinal cord compression, fracture, or spinal instability. In the presence of multiple metastatic spinal tumors, the one causing the patient's main symptoms is addressed first. Additional tumors can be treated at a later point according to the algorithm.

Radiographic spinal cord compression implies deformation of the spinal cord because of epidural tumor, retropulsed bone fragment, or both. It should be noted that epidural tumor may occupy part of the spinal canal with or without partial obliteration of CSF around the spinal cord. Those cases are excluded because there is no cord deformation. For tumors occurring below L1, any canal compression of 50% or more should be considered of equal importance as spinal cord compression. Patients with radiographic cord compression should start on dexamethasone (10-100 mg) to alleviate symptoms. Decompressive surgery (concomitant stabilization if indicated) and adjuvant RT is the preferred treatment (category 1) where there is spinal instability and no surgical contraindication. Primary EBRT alone is appropriate for patients with...
Radiosensitive cancers (hematologic malignancies) and without evidence of spinal instability. Many fractionation schemes are available (15–40 Gy in 1–15 fractions over 1 day–3 weeks); the most common is a total of 30 Gy in 3-Gy daily fractions for 10 days.\textsuperscript{376,377} Tolerance at the spine and/or nerve route must be considered in determining dose. Primary chemotherapy is also an option for chemo-responsive tumors in the absence of clinical myelopathy. In general, a treatment interval of at least 6 months is recommended.

Metastases to the spine without cord compression include the presence of tumor in the vertebral body, pedicle(s), lamina, transverse, or spinous process. It can also include epidural disease without cord deformation. Patients in this category should be assessed for fractures and spinal instability. Because the criteria for spinal destabilization secondary to tumor remain unclear, consultation by a surgeon is recommended. \textit{Spinal instability} is grossly defined as the presence of significant kyphosis or subluxation (deformity) or of significantly retropulsed bone fragment. Not every pathologic fracture implies unstable structure. The degree of kyphosis or subluxation compatible with instability depends on the location of the tumor in the spine. The cross-sectional area of the vertebral body unaffected by the tumor and the patient’s bone mineral density are additional factors affecting stability. In addition, vertebral body involvement is more important than dorsal element involvement with regard to stability. Circumferential disease as well as junctional and contiguous tumor location should be taken into account when assessing spinal stability. If fracture or instability is detected, the patient should undergo surgical stabilization or minimally invasive vertebral augmentation to relieve pain. These procedures should be followed by adjuvant RT to obtain local control.

If no fracture or instability is found, EBRT is the treatment of choice. Stereotactic RT may be appropriate in select cases of limited disease. Other alternatives are chemotherapy for responsive tumors, or surgery plus adjuvant RT in select cases. Patients experiencing intractable pain or rapid neurologic decline during RT should consider surgery or SRS. Neurologic deterioration is apparent when the patient’s neurologic examination is becoming worse on a daily basis and the patient’s ambulatory status is threatened. Intractable pain means either that pain is not controlled with oral analgesics or that the patient cannot tolerate the medication due to side effects.

\textbf{Progression and Recurrence}

Follow-up involves MRI or CT imaging within one to three months post-treatment, then every three to six months as indicated. Upon detection of progression or recurrence on imaging scans, management strategy is based on previous treatment. Patients who underwent prior RT or surgery plus adjuvant RT may consider surgery or re-irradiation to the recurred area. Stereotactic RT may be appropriate for select patients. Clinicians should plan 6 months or more between treatments in consideration of tolerance of the spine and its nerve roots. Retreatment dose should be limited to no more than 10 Gy to the surface of the spinal cord. Patients previously treated by chemotherapy can consider RT.


