Mucosal Melanoma of the Head and Neck

Overview

Mucosal melanoma (MM) is a rare, very aggressive noncutaneous melanoma that affects the upper aerodigestive tract, genitourinary tract, and anal/rectal region. This portion of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Head and Neck (H&N) Cancers only describes MMs of the H&N, which constitute fewer than 10% of melanomas of the H&N. Note that a separate NCCN Guideline is available for cutaneous melanoma (see NCCN Guidelines for Melanoma, available in this issue and online at www.NCCN.org).

NCCN Clinical Practice Guidelines in Oncology for Mucosal Melanoma of the Head and Neck

Key Words
NCCN Clinical Practice Guidelines, NCCN Guidelines, mucosal melanoma, head and neck cancer, biopsy, neck dissection, adjuvant therapy, radiation therapy, chemotherapy, pathology (JNCCN 2012;10:320–338)

NCCN Categories of Evidence and Consensus
Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

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

Please Note

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Disclosures for the NCCN Mucosal Melanoma of the Head and Neck Panel

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

Individual disclosures for the NCCN Mucosal Melanoma of the Head and Neck Panel members can be found on page 338. (The most recent version of these guidelines and accompanying disclosures, including levels of compensation, are available on the NCCN Web site at www.NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit www.NCCN.org.
The full NCCN Guidelines for H&N Cancers address tumors arising in the upper aerodigestive tract (i.e., lip, oral cavity, pharynx, larynx, paranasal sinuses; see Figure 1). Occult primary cancer, salivary gland cancer, and MM are also addressed. Many of the approaches for managing H&N cancer are also applicable to MM (e.g., multidisciplinary team, surgical principles). To view the full NCCN Guidelines for H&N Cancers, visit the NCCN Web site at www.NCCN.org.

By definition, the NCCN Guidelines cannot incorporate all possible clinical variations and are not intended to replace good clinical judgment or individualization of treatments. Exceptions to the rule were discussed among the members of the NCCN H&N Cancers Panel while developing these guidelines.

Management Approaches

The staging system for MM begins with stage III disease, which is the most limited form of disease for MM (see Workup and Staging, page 333). Surgery (with or without radiation therapy [RT]) is the primary treatment for stage III MM, whereas surgery followed by RT or systemic therapy is the primary treatment for stage IV MM, depending on systemic involvement.

Multidisciplinary Team Involvement

The initial evaluation and development of a plan for treating patients with MM require a multidisciplinary team of health care providers with expertise in caring for these patients. Similarly, managing and preventing sequelae of radical surgery, RT, and...
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**PRESENTATION WORKUP**

- H&P including complete head and neck exam; mirror and fiberoptic examination as clinically indicated
- Verification of pathology using appropriate staining (HMB-45, S-100, Melan-A)
- CT and/or MRI to determine anatomic extent of disease, particularly for sinus disease
- Chest imaging as indicated
- Consider PET-CT scan to rule out metastatic disease

**PRIMARY TREATMENT**

- **Stage III**
  - T4a, N0: Wide surgical resection
  - T3-T4a, N1: Wide surgical resection + neck dissection of positive neck

- **Stage IVB**
  - Clinical trial (preferred)
  - Primary RT
  - Systemic therapy

- **Stage IVC**
  - Clinical trial (preferred)
  - Best supportive care
  - Primary RT
  - Systemic therapy

**ADJUVANT TREATMENT**

- Strongly consider postoperative RT to primary site
- Postoperative RT to primary site and neck
- Follow-up (see page 325)
- Recurrent or Persistent disease (see the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for [cutaneous] Melanoma, elsewhere in this issue and online at www.NCCN.org)

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*aSee Principles of Surgery (pages 326-329).
*bSee Principles of Radiation Therapy (page 330).
*cSee Systemic Therapy Options for Advanced or Metastatic Melanoma in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for [cutaneous] Melanoma, elsewhere in this issue and online at www.NCCN.org.

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**PRIMARY THERAPY FOR OCCULT PRIMARY-MELANOMA**

- **Level V, occipital node** → Posterior lateral node dissection
  - ± Adjuvant systemic therapy, per NCCN Guidelines for [cutaneous] Melanoma, elsewhere in this issue and online at www.NCCN.org

- **All other nodal sites** → Neck dissection
  - ± RT to nodal bed

**FOLLOW-UP RECOMMENDATIONS**

(based on risk of relapse, second primaries, treatment sequelae, and toxicities)

- History and physical exam:
  - Year 1, every 1-3 mo
  - Year 2, every 2-6 mo
  - Years 3-5, every 4-8 mo
  - > 5 years, every 12 mo
- Posttreatment baseline imaging of primary (and neck if treated) recommended within 6 mo of treatment (category 2B)
  - Further reimaging as indicated based on signs/symptoms; not routinely recommended for asymptomatic patients
- Chest imaging as clinically indicated
- Thyroid-stimulating hormone (TSH) every 6-12 mo if neck irradiated
- Speech/hearing and swallowing evaluation and rehabilitation as clinically indicated
- Smoking cessation and alcohol counseling as clinically indicated
- Dental evaluation
  - Recommended for oral cavity
  - As indicated for oropharynx, hypopharynx, and nasopharynx
  - As indicated for other sites, if significant intraoral radiation

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See Principles of Surgery (pages 326-329).


RT is indicated for satellitosis, positive nodes, or extracapsular spread.

For mucosal melanoma, physical exam should include endoscopic inspection for paranasal sinus disease.

For cancer of the oropharynx, hypopharynx, glottic larynx, supraglottic larynx, and nasopharynx: imaging recommended for T3-4 or N2-3 disease only.
**PRINCIPLES OF SURGERY**

**Evaluation**
All patients should be evaluated by a head and neck surgical oncologist before treatment to:

- Review the adequacy of biopsy material, review staging and imaging to determine the extent of disease, exclude the presence of a synchronous primary tumor, assess current functional status, and evaluate for potential surgical salvage if initial treatment is nonsurgical.
- 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, nutritional, and health behavior evaluation and intervention and any other ancillary evaluations that would provide for comprehensive rehabilitation.
- Develop and design the surgical procedure, margins, and reconstructive plan to resect all gross tumor with adequate tumor-free surgical margins for patients undergoing surgery. The surgical procedure should not be modified based on any response observed as a result of prior therapy except in instances of tumor progression that mandates a more extensive procedure to encompass the tumor at the time of definitive resection.

**Integration of Therapy**
- It is critical that multidisciplinary evaluation and treatment be coordinated by all modalities involved in patient care before the initiation of any treatment.

**Assessment of Resectability**
Tumor involvement of the following sites is associated with poor prognosis or function or with T4b cancer (i.e., unresectable based on technical ability to obtain clear margins):

- Involvement of the pterygoid muscles particularly when associated with severe trismus or pterygopalatine fossa involvement with cranial neuropathy
- Gross extension of tumor into the skull base (e.g., erosion of the pterygoid plates or sphenoid bone, widening of the foramen ovale)
- Direct extension to superior nasopharynx or deep extension into the eustachian tube and lateral nasopharyngeal walls
- Invasion (encasement) of the common or internal carotid artery. Encasement is usually assessed radiographically and defined as tumor surrounding the carotid artery ≥ 270°
- Direct extension of neck disease to involve the skin
- Direct extension to mediastinal structures, prevertebral fascia, or cervical vertebrae
- Presence of subdermal metastases

1 In selected cases, surgery might still be considered.
PRINCIPLES OF SURGERY (Cont.)

Primary Tumor Resection

The resection of advanced tumors of the oral cavity, oropharynx, hypopharynx, larynx, or paranasal sinus will vary in extent depending on the structures involved. The primary tumor should be considered surgically curable through appropriate resection using accepted criteria for adequate excision, depending on the region involved.

- En bloc resection of the primary tumor should be attempted whenever feasible.
- In continuity neck dissection is necessary when there is direct extension of the primary tumor into the neck.
- Surgical resection should be planned based on the extent of the primary tumor as ascertained by clinical examination and careful interpretation of appropriate radiographic images.
- For oral cavity cancers, as thickness of the lesion increases, so does the risk of regional metastases and the need for adjuvant elective neck dissection.
- Perineural invasion should be suspected when tumors are adjacent to motor or sensory nerves. When invasion is suspected, the nerve should be dissected both proximally and distally and should be resected to obtain clearance of disease. Frozen section determination of the proximal and distal nerve margins may prove helpful to facilitate tumor clearance.
- Partial or segmental resection of the mandible may be necessary to encompass adequately the cancer with adequate tumor-free margins. Adequate resection may require partial, horizontal, or sagittal resection of the mandible for tumors involving or adherent to mandibular periosteum. Segmental resection should be considered in tumors that grossly involve mandibular periosteum (as determined by tumor fixation to the mandible) or show evidence of direct tumor involvement of the bone at the time of operation or through preoperative imaging. The extent of mandibular resection will depend on the degree of involvement accessed clinically and in the operating room.
- For tumors of the larynx, the decision to perform either total laryngectomy or conservation laryngeal surgery (e.g., transoral resection, hemilaryngectomy, supraglottic laryngectomy) will be decided by the surgeon but should adhere to the principles of complete tumor extirpation with curative intent.
- For maxillary sinus tumors, note that "Ohngren's line" runs from the medial canthus of the eye to the angle of the mandible, helping to define a plane passing through the maxillary sinus. Tumors "below" or "before" this line involve the maxillary infrastructure. Those "above" or "behind" Ohngren's line involve the suprastructure.
Margins

Frozen section margin assessment is always at the discretion of the surgeon and should be considered when it will facilitate complete tumor removal. The achievement of adequate margins may require resection of an adjacent structure in the oral cavity or laryngopharynx (such as the base of tongue and/or anterior tongue, mandible, larynx, or portions of the cervical esophagus).

- Adequate resection is defined as clear resection margins with at least enough clearance from gross tumor to obtain clear frozen section and permanent margins (often 1.5-2 cm of visible and palpable normal mucosa). In general, frozen section examination of the margins will usually be undertaken intraoperatively and, importantly, when a line of resection has uncertain clearance because of indistinct tumor margins or there is suspected residual disease (e.g., soft tissue, cartilage, carotid artery, or mucosal irregularity).
- The details of resection margins should be included in the operative dictation. The margins may be assessed on the resected specimen or alternatively from the surgical bed with proper orientation.
- A clear margin is defined as the distance from the invasive tumor front that is ≥ 5 mm from the resected margin.
- A close margin is defined as the distance from the invasive tumor front to the resected margin that is < 5 mm.
- The primary tumor should be marked in a fashion adequate for orientation by the surgical pathologist.
- The neck dissection should be oriented or sectioned to identify levels of lymph nodes encompassed in the dissection.
- Reconstruction of surgical defects should be performed using conventional techniques at the discretion of the surgeon. Primary closure is recommended when appropriate but should not be pursued at the expense of obtaining wide, tumor-free margins. Reconstructive closure with local/regional flaps, free tissue transfer, or split-thickness skin or other grafts with or without mandibular reconstruction is performed at the discretion of the surgeon.

Surgical Management of Cranial Nerves VII, X (Including the Recurrent Laryngeal Nerve), XI, and XII

Operative management of the facial nerve and other major cranial nerves during primary or regional node resection is influenced by the preoperative clinical function of the nerve.

- When the nerve is functioning, thorough efforts should be made to preserve the structure and function of the nerve (main trunk and/or branches) even if otherwise adequate tumor margins are not achieved—recognizing that the surgeon should leave no gross residual disease.
- Adjuvant postoperative radiation or chemoradiation is generally prescribed when microscopic residual or gross residual tumor is suspected.
- Direct nerve invasion by tumor and/or preoperative paralysis of the nerve may warrant segmental resection (and sometimes nerve grafting) at the discretion of the surgeon if tumor-free margins are assured throughout the remainder of the procedure.
Neck Management
The surgical management of regional lymphatics is dictated by the extent of tumor at initial tumor staging. These guidelines apply to the performance of neck dissections as part of treatment of the primary tumor. In general, patients undergoing surgery for resection of the primary tumor will undergo dissection of the ipsilateral side of the neck that is at greatest risk for metastases.

- Tumor sites that frequently have bilateral lymphatic drainage (e.g., base of tongue, palate, supraglottic larynx, deep space pre-epiglottic involvement) should often have both sides of the neck dissected with the extent of dissection determined as suggested below. For patients with tumors at or approaching the midline, both sides of the neck are at risk for metastases, and bilateral neck dissections should be performed. Elective neck dissection may not be recommended if postoperative radiation is planned.

Patients with advanced lesions involving the anterior tongue or floor of mouth which approximate or cross the midline should undergo contralateral submandibular dissection as necessary to achieve adequate tumor resection.

- Elective neck dissection should be based on risk of occult metastasis in the appropriate nodal basin.
  - In general, elective neck dissections are not performed for mucosal melanoma, except for the oral cavity.
  - In mucosal melanoma, no evidence shows that the depth of invasion predicts occult metastatic disease, although the risk likely does increase with increasing depth.
- Elective dissections are generally selective, preserving all major structures, unless operative findings dictate otherwise.

Management of Recurrences
Surgically resectable primary cancers should be re-resected with curative intent if feasible, and recurrences in a previously treated neck should also undergo surgical salvage. Neck disease in an untreated neck should be addressed by formal neck dissection or modification depending on the clinical situation. Nonsurgical therapy may also be used as clinically appropriate.

Surveillance
All patients should have regular follow-up visits to assess for symptoms and possible tumor recurrence, health behaviors, nutrition, dental health, and speech and swallowing function.

- Tumor evaluations must be performed by specialists skilled in head and neck clinical examination.
- The frequency of evaluation is summarized in Follow-up Recommendations (page 325).

PRINCIPLES OF RADIATION THERAPY¹

RT for unresectable locally advanced melanoma:
- 66-74 Gy
- Palliative RT dose and schedule may be considered

Postoperative RT
- Primary site resection:
  - Paranasal sites:
    - RT to primary site + 2- to 3-cm margins or to anatomic compartment
  - Oral cavity, oropharynx, and hypopharynx sites:
    - RT to primary site (+ 2- to 3-cm margins or anatomic zone) and elective treatment to neck
    - (unless negative pathology findings of neck dissection)
    - Also strongly consider radiation to primary site for any locally recurrent disease after previous resection

- Neck/nodal basin dissection:
  - High-risk features:
    - ≥ 2 nodes
    - Single node ≥ 3 cm
    - Extracapsular nodal disease
    - Node resection (alone) with no further basin dissection
    - Recurrence in nodal basin after previous surgery

- Dose and fractionation:
  - Primary and neck (high-risk sites): 60-66 Gy (2.0 Gy/fx) or 70 Gy for gross disease
  - Low-risk, undissected, or uninvolved portions of neck: 50-60 Gy (2 Gy/fx)

¹See Radiation Techniques (facing page) and Discussion.
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. IMRT, 3D, and 2D conformal techniques 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, and chemotherapy options, resulting in a large number of combinations that may impact toxicity or tumor control. Close cooperation and interdisciplinary management are critical to treatment planning and radiation targeting, especially in the postoperative setting or after induction chemotherapy.

**Intensity-Modulated Radiotherapy (IMRT)**

IMRT has been shown to be useful in reducing long-term toxicity in oropharyngeal, paranasal sinus, and nasopharyngeal cancers by reducing the dose to salivary glands, temporal lobes, auditory structures (including cochlea), and optic structures. The application of IMRT to other sites (e.g., oral cavity, larynx, hypopharynx, salivary glands) is evolving and may be used at the discretion of treating physicians.

**IMRT and Fractionation**

Several ways exist to integrate IMRT, target volume dosing, and fractionation. The Simultaneous Integrated Boost (SIB) technique uses differential "dose painting" (66-74 Gy to gross disease; 50-60 Gy to subclinical disease) for each fraction of treatment throughout the entire course of radiation. SIB is commonly used in conventional (5 fractions/wk) and the "6 fractions/wk accelerated" schedule. The sequential (SEQ) IMRT 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 use 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.

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chemotherapy (e.g., pain, xerostomia, speech and swallowing problems, depression) require professionals familiar with the disease. Follow-up for these sequelae should include a comprehensive H&N examination. Adequate nutritional support can help to prevent severe weight loss in patients undergoing treatment for MM; therefore, patients should be encouraged to see a dietician.

Patients should also be encouraged to stop smoking and to modify alcohol consumption if excessive, because these habits may decrease the efficacy of treatment and adversely affect other health outcomes. Programs using behavioral counseling combined with medications that promote smoking cessation (approved by the FDA) can be very useful (http://www.ahrq.gov/clinic/tobacco/tobaqrg.htm). Specific components of patient support and follow-up are listed in the algorithm (see Team Approach, in the NCCN Guidelines for H&N Cancers, available online at www.NCCN.org [TEAM-1]). Notably, patients with MM require timely diagnosis and management of depression. The H&N Cancers Panel also recommends referring to the NCCN Guidelines for Palliative Care (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).

Comorbidity and Quality of Life

Comorbidity

Comorbidity refers to the presence of concomitant disease (in addition to MM) that may affect the diagnosis, treatment, and prognosis of the patient. Documentation of comorbidity is particularly important in oncology to facilitate optimal treatment selection and estimates of prognosis. Comorbidity is known to be a strong independent predictor of mortality in patients with H&N cancer, and comorbidity also influences costs of care, use of treatment, and quality of life. Traditional indices of comorbidity include the Charlson index and the Kaplan-Feinstein index and its modifications. The Adult Comorbidity Evaluation-27 (ACE-27) is specific for H&N cancer and has excellent emerging reliability and validity.

Quality of Life

Health-related quality-of-life issues are paramount in H&N cancer and MM. These tumors affect basic physiologic functions (e.g., ability to chew, swallow, and breathe), the senses (e.g., taste, smell, hearing), and uniquely human characteristics (e.g., appearance, voice). Health status describes an individual’s physical, emotional, and social capabilities and limitations. Function and performance refer to how well an individual is able to perform important roles, tasks, or activities. The definition of quality of life differs, because the central focus is on the value (determined by the patient alone) that individuals place on their health status and function.

Mucosal Melanoma of the Head and Neck

MM of the H&N is a rare but highly aggressive neoplasm with a poor prognosis. It may occur throughout the upper aerodigestive tract. Most MM of the H&N (~70%) occurs in the nasal cavity or paranasal sinus region, and approximately 25% develops in the oral cavity (see Figure 2). The remainder develops in other sites (e.g., oropharynx, hypopharynx, larynx). Sinonasal MM is typically confined to the primary site at presentation, and patients often present with symptoms (e.g., nasal obstruction). Oral cavity MM more frequently presents with clinically apparent lymph node metastasis and is often asymptomatic. No etiologic risk factors are yet apparent. MM occurs in a greater extent in Asians and less frequently in the Western population.
Workup and Staging

Diagnosis of MM of the H&N can be difficult. The differential diagnosis of sinonasal MM includes lymphoma, sarcoma, and olfactory neuroblastoma. Ideally, a combination of histology, immunohistochemistry, and clinical features is used for diagnosis. MM is immunoreactive for S-100 and HMB-45 (and to a lesser extent for melan-A); however, MM is negative for cytokeratin.

Workup for MM should include clinical examination and CT and/or MRI for paranasal sinus disease, and appropriate imaging for other mucosal sites. The physical examination should include endoscopic inspection for paranasal sinus disease. PET/CT scanning may be considered to define the presence of distant disease in more advanced situations.

The AJCC Staging Manual (7th edition) includes a staging system for MM (see Table 6 in the NCCN Guidelines for H&N, available online, at www.NCCN.org [ST-11]); previous editions did not have a classification for MM. The AJCC staging recognizes 2 key factors specific to MM: 1) the disease still has a poor prognosis 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 stage III disease as the most limited form of disease (similar to anaplastic thyroid carcinoma), and breaks the disease down into stages reflecting local burden of disease and regional and distant extent. Melanomas confined to the mucosa only are T3, those with moderately advanced lesions (involving underlying cartilage or bone) are T4a, and very advanced primary tumors are T4b. In addition, the AJCC staging system reflects the fact that MM occurs at all mucosal sites in the H&N. Therefore, rules for classifying and staging, and surgical principles should be based on the appropriate anatomic site of origin (see the NCCN Guidelines for H&N Cancers, available online at www.NCCN.org).

Treatment of the Primary

Although limited data are available on treatment options, surgery is the primary treatment for MM stage III through IVA (see Principles of Surgery on pages 326–329 and in the NCCN Guidelines for H&N Cancers, available online at www.NCCN.org [SURG-A]). However, surgery is not recommended for stage IVB or IVC disease. The panel strongly encourages clinical trials for all patients with MM to better define treatment choices at all stages of disease.

In most case series, adjuvant RT seems effective in improving local control and survival. RT is clearly indicated in more advanced cases as an adjunct to surgery (see the Principles of Radiation Therapy on page 330 and in the NCCN Guidelines for H&N Cancers, available online at www.NCCN.org [RAD-A]). The role of radiation in stage III disease is not clear, but it can be considered and should be determined on an individual basis by the treating clinicians. However, survival rates after surgery alone or surgery combined with radiation are better than those after radiation alone.

Treatment of the Neck

Neck dissection and postoperative radiation are recommended for clinical nodal disease. The role of elective neck treatment is unclear. The extension of elective treatment to the neck seems unwarranted in most cases of N0 paranasal sinus MM. However, for oral cavity disease, the likelihood of positive disease is significantly higher and the treatment can be better localized to the ipsilateral neck with both...
surgery and radiation (see Principles of Surgery on pages 326–329 and in the NCCN Guidelines for H&N Cancers, available online at www.NCCN.org [SURG-A]). Therefore, elective treatment to the neck for oral cavity MM seems justifiable.

**Radiation Therapy**

Prospective trials evaluating the role of RT in MM are lacking. However, recently reported results of a randomized trial in cutaneous melanoma are considered relevant to MM in the postoperative setting after neck dissection.\(^{37}\) Retrospective studies in MM have shown local recurrence to be common after surgery alone.\(^{30,38,39}\) After using postoperative radiation, lower rates of local and neck recurrence have been seen in historical comparison series.\(^{32,40}\) Reasonable local control outcomes using RT alone in unresectable or medically inoperable cases have been reported in small cohort series of MMs.\(^{30,41–44}\)

RT is often recommended in the postoperative management of MMs. 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. Because oral cavity primary sites are believed to be at a higher risk for failure in the neck, elective management with neck dissection and RT may be applied.

Indications for postoperative radiation to the neck are generally extrapolated from cutaneous melanoma. Recently, an Australian-New Zealand consortium reported on a randomized trial (N = 250) 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.\(^{37}\) Only 20 patients experienced disease relapse who underwent postoperative RT, compared with 34 patients who underwent observation only (P = .04).

Considering this trial and retrospective studies in MM, the panel recommends postoperative RT for the following high-risk features: extracapsular disease, involvement of 2 or more neck or intraparotid nodes, any node 3 cm or greater, neck excision (alone) with no further basin dissection, or recurrence in the neck or soft tissue after initial surgical resection.\(^{45,46}\) Conventional fractionation is recommended (at 2 Gy per fraction to a total postoperative dose of 60–66 Gy, or to 70 Gy for gross disease). Although the Australian-New Zealand randomized trial used 48 Gy in 20 fractions (240 cGy per fraction) to neck, axilla, or groin,\(^{37}\) the NCCN H&N Cancers 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.

Intensity modulated RT may be very helpful for achieving homogeneous dose distributions and sparing of critical organs, especially in paranasal sinus sites (see Radiation Techniques on page 331).\(^{47–49}\) Good outcomes have been reported with the use of hypofractionation in cutaneous melanomas, which has the advantage of convenience but no clear advantage in cancer control. There is little experience using large dose per fraction in mucosal sites. Because of the proximity of neural structures and risk of late effects, hypofractionation (if used) must be carefully planned and delivered.

**Systemic Therapy**

Systemic therapy used for cutaneous melanoma (e.g., interleukin-2) is recommended for MM (see Systemic Therapy Options for Advanced or Metastatic Melanoma in the NCCN Guidelines for Melanoma, available in this issue on pages 378–380 and online at www.NCCN.org [ME-E]). Interferon and interleukin have been used to treat MM.\(^{50}\) Data suggest that c-KIT inhibitors (e.g., imatinib) may be useful in patients with metastatic MM who have specific c-KIT mutations (i.e., exon 11 or 13 mutations).\(^{28,51}\) Therefore, imatinib is reasonable to use in patients with MM who have c-KIT mutations.\(^{52}\) Although vemurafenib is recommended for patients with cutaneous melanoma who have the V600E mutation of the BRAF gene, patients with MM rarely have this BRAF mutation.\(^{51}\)

**Follow-Up**

Recommendations for surveillance are provided in the algorithm (see Follow-Up Recommendations on page 325). Note that physical examination should include endoscopic inspection for paranasal sinus disease. Salvage surgery may be useful for patients with MM; therefore, surveillance is important.\(^{30}\)

**Recurrent or Persistent Disease**

For patients with MM who have recurrent or persistent disease, the NCCN H&N Cancers Panel recommends using the NCCN Guidelines for Melanoma (available in this issue and online at www.NCCN.org).
**Principles of Surgery**

All patients should be evaluated by an H&N surgical oncologist before being treated for MM. In addition, multidisciplinary evaluation and treatment must be well coordinated. Many surgical principles described in the NCCN Guidelines for H&N Cancers algorithm are applicable to MM (i.e., evaluation, integration of therapy, assessment of resectability, primary tumor resection, margins, management of recurrences, and surveillance; see Principles of Surgery on pages 326–329 and in the NCCN Guidelines for H&N Cancers, available online at www.NCCN.org [SURG-A]).

Resectable disease, neck dissection, and salvage surgery of high-risk disease are discussed in the following sections.

**Resectable Versus Unresectable Disease**

The term unresectable has resisted formal definition by H&N cancer specialists. The experience of the surgeon and the support available from reconstructive surgeons, physiatrists, and prosthetists often strongly influence recommendations, especially in institutions in which only a few patients with MM are treated. The NCCN Member Institutions have teams experienced in the treatment of H&N cancer and maintain the multidisciplinary infrastructure needed for reconstruction and rehabilitation. A patient’s cancer is deemed unresectable if H&N surgeons at NCCN Member Institutions do not think they can remove all gross tumor on anatomic grounds or if they are certain local control will not be achieved after surgery (even with the addition of RT to the treatment approach). Typically, these unresectable tumors densely involve the cervical vertebrae, brachial plexus, deep muscles of the neck, or carotid artery (see Principles of Surgery on pages 326–329 and in the NCCN Guidelines for H&N Cancers, available online at www.NCCN.org [SURG-A]). Tumor involvement of certain sites is associated with poor prognosis (e.g., direct extension of neck disease to involve the external skin or to mediastinal structures, prevertebral fascia, or cervical vertebrae).

Unresectable tumors (i.e., those that cannot be removed without causing unacceptable morbidity) should be distinguished from inoperable tumors in patients whose constitutional state precludes an operation (even if the cancer could be readily resected with few sequelae). Additionally, a subgroup of patients will refuse surgical management, but these tumors should not be deemed unresectable. Although local and regional disease may be surgically treatable, patients with distant metastases are usually treated as though the primary tumor was unresectable. This is balanced by the potential to mitigate suffering from local and regional disease. This may be particularly true in MM. Thus, patient choice or a physician’s expectations regarding cure and morbidity will influence or determine treatment.

**Neck Dissection**

Historically, cervical lymph node (i.e., neck) dissections have been classified as radical or modified radical procedures. The less-radical procedures preserve the sternocleidomastoid muscle, jugular vein, spinal accessory nerve, or selective lymph node levels. The NCCN H&N Cancers Panel prefers to classify cervical lymphadenectomy using contemporary nomenclature, thus classifying cervical lymph node dissections as either comprehensive or selective. A comprehensive neck dissection is one that removes all lymph node groups that would be included in a classic radical neck dissection. Whether the sternocleidomastoid muscle, jugular vein, or spinal accessory nerve is preserved does not affect whether the dissection is classified as comprehensive. Depending on the site, comprehensive neck dissection is often recommended for patients with positive nodal disease MM (see Neck Management in Principles of Surgery on pages 326–329 and in the NCCN Guidelines for H&N Cancers, available online at www.NCCN.org [SURG-A]). In general, elective neck dissections for melanoma are not performed, except for oral cavity. Currently, elective treatment of the neck tends to be reserved for when access to vessels is needed for microvascular anastomosis for free flaps and perhaps in oral cavity primary MM.

For a therapeutic dissection, whether the neck can be made more selective will depend on the primary location of the tumor. Level I disease may be cleared with a selective neck dissection encompassing levels I through IV, and pharyngeal disease may not require a level I dissection. For example, to remove the nodes most commonly involved with metastases from the oral cavity, a selective neck dissection is recommended, which includes the nodes found above the omohyoid muscle (levels I–III and sometimes the superior parts of level V). Similarly, to remove the nodes most commonly involved
with metastases from the pharynx and larynx, a selective neck dissection is recommended, which includes the nodes in levels II through IV and level VI when appropriate. Selective neck dissections may be used as treatment when neck tumor burden is low.

Salvage Surgery
Salvage surgery may be useful for patients with MM; therefore, surveillance is important. However, the NCCN H&N Cancers Panel emphasized the increased risk of complications when salvage surgery 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.

References
31. Meleti M, Leemans CR, de Bree R, et al. Head and neck mucosal melanoma: experience with 42 patients, with emphasis on the role
### Individual Disclosures for the NCCN Guidelines Panel for Mucosal Melanoma of the Head and Neck

<table>
<thead>
<tr>
<th>Panel Member</th>
<th>Clinical Research Support</th>
<th>Advisory Boards, Speakers Bureau, Expert Witnesses, or Patent, Equity or Royalty</th>
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