These guidelines are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no representations or warranties of any kind, regarding their content use or application and disclaims any responsibility for their application or use in any way. These guidelines are copyrighted by National Comprehensive Cancer Network. All rights reserved. These guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2007.
Summary of changes in the 1.2007 version of the Head and Neck Cancer guidelines from the 1.2006 version include:

Global Changes

- The risk categorization defining the indications for postoperative chemoradiation has been modified. Postoperative chemoradiation is indicated for "one or both major risk features or two or more minor risk features". Major risk features are positive margins and/or extracapsular spread. Minor risk features are pT3 or pT4 primary (excluding T3, N0 laryngeal cancer); N2 or N3 nodal disease, nodal disease in levels IV or V with oral cavity or oropharyngeal primary, perineural invasion, and vascular embolism.
- The terminology used to define nodal stations in the Principles of Radiation Therapy sections was changed to "involved" or "uninvolved".
- The qualifier of "selective versus comprehensive" was removed after the category 3 designation in the neck management after primary systemic therapy.

Ethmoid Sinus Tumors

- The treatment option of chemoradiation was added as a consideration for adjuvant therapy for patients with adverse characteristics (ETHM-2).

Cancer of the Hypopharynx

- Cisplatin is listed as the preferred agent if using the treatment option of concurrent systemic therapy/RT (HYPO-3).

Cancer of the Glottic Larynx

- Cisplatin is listed as the preferred agent if using the treatment option of concurrent systemic therapy/RT (GLOT-3).
- The recommendations for Definitive RT have been modified and are based on T and N classification and adenopathy (GLOT-A).

Cancer of the Supraglottic Larynx

- The category of "Adverse feature: positive margin" was separated out from extracapsular spread, with the treatment recommendations of "Further surgery or RT". The treatment option "RT" was added for "Adverse features: extracapsular nodal spread:" with a category 2B designation (SUPRA-2).
- Cisplatin is listed as the preferred agent if using the treatment option of concurrent systemic therapy/RT (SUPRA-3, SUPRA-6 SUPRA-7).

Unresectable Head and Neck Cancer

- A category 1 designation was added to the recommendation of "concurrent cisplatin- or carboplatin-based chemotherapy + RT". The recommendation for "induction chemotherapy followed by RT" was changed to "..followed by chemoradiation" (ADV-1).

Advanced Head and Neck Cancer

- The recommendation of Definitive RT + cetuximab was added for patients not able to tolerate cytotoxic chemotherapy. (ADV-A).

Principles of Systemic Therapy

- Cetuximab was added as a systemic therapy option with concurrent RT (CHEM-A).
The management of patients with head and neck cancers is complex. All patients need access to the full range of specialists and support services with expertise in the management of patients with head and neck cancer for optimal treatment and follow-up.

- Head and neck surgery
- Radiation oncology
- Medical oncology
- Plastic and reconstructive surgery
- Specialized nursing care
- Dentistry/prosthodontics
- Physical medicine and rehabilitation
- Speech and swallowing therapy
- Clinical Social work
- Nutrition support
- Pathology
- Diagnostic radiology
- Adjunctive services
  - Neurosurgery
  - Ophthalmology
  - Psychiatry
  - Addiction Services

Follow-up should be performed by a physician with expertise in the management and prevention of treatment sequelae. It should include a comprehensive head and neck exam. The management of head and neck cancer patients may involve the following:

- Pain and symptom management
- Nutritional support
  - Enteral feeding
  - Oral supplements
- Dental care for RT effects
- Xerostomia management
- Smoking cessation
- Tracheotomy care
- Social work and Case management
- Supportive Care (See NCCN Palliative Care Guideline)

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

**WORKUP**

Ethmoid sinus:
- Squamous cell carcinoma
- Undifferentiated carcinoma
- Adenocarcinoma
- Salivary gland tumor
- Esthesioneuroblastomas
- Sarcoma (non-rhabdomyosarcoma)

**Untreated**

- H&P
- CT and/or MRI
- Chest x-ray

**Biopsy** → **Malignant**

See Primary Treatment and Follow-up (ETHM-2)

**Lymphoma**

See NCCN Non-Hodgkin’s Lymphoma Guidelines

**Diagnosed with incomplete excision**

- H&P
- CT and/or MRI
- Pathology review
- Chest x-ray

See Primary Treatment and Follow-up (ETHM-2)

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

#### Ethmoid Sinus Tumors

### Clinical Presentation

<table>
<thead>
<tr>
<th>Newly diagnosed; T1, T2</th>
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<tbody>
<tr>
<td><strong>Complete surgical resection (preferred)</strong></td>
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<tr>
<td>or</td>
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<tr>
<td><strong>Definitive RT</strong></td>
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<table>
<thead>
<tr>
<th>Newly diagnosed; T3, T4a resectable</th>
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<tbody>
<tr>
<td><strong>Complete surgical resection</strong></td>
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<tr>
<td><strong>RT or Consider Chemo/RT</strong></td>
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<tr>
<td><strong>if adverse characteristics</strong></td>
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<table>
<thead>
<tr>
<th>Newly diagnosed, unresectable</th>
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<tbody>
<tr>
<td><strong>RT or Consider Chemo/RT</strong></td>
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<tr>
<td><strong>if adverse characteristics</strong></td>
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<tr>
<th>Diagnosed after incomplete excision (e.g., polypectomy, endoscopic procedure) and gross residual disease</th>
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<tbody>
<tr>
<td><strong>Surgery (preferred), if feasible</strong></td>
<td></td>
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<tr>
<td><strong>RT or Consider Chemo/RT</strong></td>
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<td><strong>if adverse characteristics</strong></td>
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<table>
<thead>
<tr>
<th>Diagnosed after incomplete excision (e.g., polypectomy, endoscopic procedure) and no disease on physical exam, imaging, and/or endoscopy</th>
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</thead>
<tbody>
<tr>
<td><strong>RT or Surgery, if feasible</strong></td>
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<tr>
<td><strong>RT</strong></td>
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</tbody>
</table>

### Primary Treatment

- Newly diagnosed, T1, T2: Complete surgical resection (preferred) or Definitive RT
- Newly diagnosed, T3, T4a resectable: Complete surgical resection or RT or Consider Chemo/RT if adverse characteristics
- Newly diagnosed, unresectable: RT or Consider Chemo/RT if adverse characteristics
- Diagnosed after incomplete excision (e.g., polypectomy, endoscopic procedure) and gross residual disease: Surgery (preferred), if feasible or RT or Consider Chemo/RT if adverse characteristics
- Diagnosed after incomplete excision (e.g., polypectomy, endoscopic procedure) and no disease on physical exam, imaging, and/or endoscopy: RT or Surgery, if feasible

### Follow-Up

- Year 1, every 1–3 mo
- Year 2, every 2–4 mo
- Years 3–5, every 4–6 mo
- > 5 years, every 6–12 mo
- Physical exam:
  - Year 1, every 1–3 mo
  - Year 2, every 2–4 mo
  - Years 3–5, every 4–6 mo
  - > 5 years, every 6–12 mo
- Chest imaging as clinically indicated
- TSH every 6–12 mo if neck irradiated
- CT scan/MRI- baseline (category 2B)

### Adverse Characteristics

- Positive margins and perineural invasion

### Recurrence

(see ADV-2)

---

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

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

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**See Principles of Systemic Therapy (CHEM-A).**

**Adverse characteristics include positive margins and perineural invasion.**
 WORKUP

- H&P
- Complete head and neck CT with contrast and/or MRI
- Dental/prosthetic consultation as indicated
- Chest x-ray

Biopsy

Biopsy:
- Preferred route is transnasal.
- Needle biopsy may be acceptable.
- Avoid canine fossa puncture or Caldwell-Luc approach.

PATHOLOGY

Lymphoma

See NCCN Non-Hodgkin’s Lymphoma Guidelines

Malignant
- Squamous cell carcinoma
- Undifferentiated carcinoma
- Adenocarcinoma
- Salivary gland tumor
- Esthesioneuroblastoma
- Sarcoma (non-rhabdomyosarcoma)

T1-2, N0
- All histologies

See Primary Treatment (MAXI-2)

T3-4, N0, Any T, N+
- All histologies

See Primary Treatment (MAXI-3)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
**Guidelines Index**  
Head and Neck Cancers TOC  
Staging, MS, References

**Head and Neck Cancers**  
Maxillary Sinus Tumors

<table>
<thead>
<tr>
<th>STAGING</th>
<th>PRIMARY TREATMENT</th>
<th>ADJUVANT TREATMENT</th>
<th>FOLLOW-UP</th>
</tr>
</thead>
</table>
| T1-2, N0 All histologies except adenoid cystic | Complete surgical resection | Consider RT\(^b\) or Consider chemo/RT (category 2B) | Physical exam:  
- Year 1, every 1–3 mo  
- Year 2, every 2–4 mo  
- Years 3–5, every 4–6 mo  
- > 5 years, every 6–12 mo  
- Chest imaging as clinically indicated  
- TSH every 6-12 mo, if neck irradiated  
- CT/MRI- baseline (category 2B) |
| Margin negative | Perineural invasion | Surgical resection, if possible | |
| Margin positive | | | |
| T1-2, N0 Adenoid cystic | Complete surgical resection | RT\(^b\) | |
| | | | |

\(^b\) See Principles of Radiation Therapy (MAXI-A).

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

**Maxillary Sinus Tumors**

### STAGING

- **T3, N0 Operable T4a, all histologies**
  - Complete surgical resection

- **T4b, N any, all histologies**
  - Clinical trial or Definitive RT or Chemo/RT

- **T any, N+, resectable**
  - Surgical excision + neck dissection

### PRIMARY TREATMENT

- **Adverse characteristics**
  - Chemo/RT to primary and neck (category 2B)

- **No adverse characteristics**
  - RT to primary + neck

### ADJUVANT TREATMENT

- Chemo/RT to primary and neck (category 2B)

### FOLLOW-UP

- Physical exam:
  - Year 1, every 1–3 mo
  - Year 2, every 2–4 mo
  - Years 3–5, every 4–6 mo
  - > 5 years, every 6–12 mo
- Chest imaging as clinically indicated
- TSH every 6-12 mo, if neck irradiated
- CT/MRI- baseline (category 2B)

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- **b** See Principles of Radiation Therapy (MAXI-A).
- **c** Adverse characteristics include positive margins, perineural invasion, or extracapsular nodal spread.

---

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

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

**Definitive RT**
- Primary and gross adenopathy:
  - ≥ 66 Gy (2.0 Gy/day)
- Neck
  - Uninvolved nodal stations:
    - ≥ 50 Gy (2.0 Gy/day)

**Postoperative RT**
- Primary: ≥ 60 Gy (2.0 Gy/day)
- Neck
  - Involved nodal stations:
    - ≥ 60 Gy (2.0 Gy/day)
  - Uninvolved nodal stations:
    - ≥ 50 Gy (2.0 Gy/day)

**Maxillary Sinus Tumors**

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

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

Untreated resectable

Previously treated incompletely resected

Not resectable

WORKUP

See Workup and Primary Treatment (SALI-2)

H&P
CT/MRI
Pathology review
Chest x-ray

Gross residual disease on physical exam or imaging

Surgical resection, if possible

No surgical resection possible

Fine-needle aspiration or Open biopsy

TREATMENT

Adjuvant RT<sup>b</sup>

Adjuvant RT<sup>b</sup>

Definitive RT<sup>b</sup> or Chemo/RT (category 2B)

Definitive RT<sup>b</sup> or Chemo/RT (category 2B)

SALI-1

<sup>a</sup>Site and stage determine therapeutic approaches.

<sup>b</sup>See Principles of Radiation Therapy (SALI-A).

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

Untreated resectable, clinically benign, < 4 cm (T1, T2)

Primary Treatment

Benign or low grade

Follow-up

Adenoid cystic; Indeterminate or high grade

RT (category 2B for T1)

WORKUP

Untreated resectable, clinically suspicious for cancer, > 4 cm or deep lobe

CT/MRI: base of skull to clavicle

Consider fine-needle aspiration

Lymphoma

Surgical resection

Benign

Follow-up

Cancer

Parotid superficial lobe

See Treatment (SALI-3)

Parotid deep lobe

See Treatment (SALI-3)

Other salivary gland tumors

See Treatment (SALI-3)

Characteristics of benign tumor include mobile superficial lobe, slow growth, painless, VII intact, and no neck nodes.

Surgical excision of clinically benign tumor: no enucleation of lateral lobe, intraoperative communication with pathologist if indicated.

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

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

**Parotid superficial lobe**
- **Clinical N0** → Parotidectomy
- **Clinical N+** → Parotidectomy + comprehensive neck dissection

**Parotid deep lobe**
- **Clinical N0** → Total parotidectomy
- **Clinical N+** → Total parotidectomy + comprehensive neck dissection

**Other salivary gland tumors**
- **Clinical N0** → Complete gland excision
- **Clinical N+** → Complete gland excision and lymph node dissection

**No adverse characteristics**
- See Follow-up (SALI-4)

- Intermediate or high grade or adenoidcystic
- Close or positive margins
- Neural/perineural invasion
- Lymph node metastases
- Lymphatic/vascular invasion

- Adjuvant RT
  - or Consider Chemo/RT (category 2B)

- Definitive RT
  - or Chemo/RT (category 2B)

Follow-up and Recurrence (see SALI-4)

---

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

*b* See Principles of Radiation Therapy (SALI-A).
**FOLLOW-UP**

- Physical exam:
  - Year 1, every 1–3 mo
  - Year 2, every 2–4 mo
  - Years 3–5, every 4–6 mo
  - > 5 yr, every 6–12 mo
- Chest imaging as clinically indicated
- TSH every 6-12 mo, if neck irradiated

**RECURRENT**

- Locoregional or distant disease; Resectable
  - Surgery or selected metastasectomy (category 3)
  - RT
- Locoregional disease; Not resectable
  - RT<sup>b</sup> or
    - Chemo/RT (category 2B)
    - Chemotherapy
    - Best supportive care

<sup>b</sup> See Principles of Radiation Therapy (SALI-A).

---

**Note:** All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Definitive RT
- Unresectable disease or gross residual disease
  - Photon/electron therapy or neutron therapy
  - Dose
    - Primary and gross adenopathy:
      - ≥ 70 Gy (1.8-2.0 Gy/day)\(^1\) or
      - 19.2 nGy (1.2 nGy/day)
    - Uninvolved nodal stations:
      - 45-54 Gy (1.8-2.0 Gy/day)\(^1\) or
      - 13.2 nGy (1.2 nGy/day)

Postoperative RT
- Photon/electron therapy or neutron therapy
- Dose
  - Primary: ≥ 60 Gy (1.8-2.0 Gy/day)\(^1\)
    - or 18 nGy (1.2 nGy/day)
  - Neck: 45-54 Gy (1.8-2.0 Gy/day)\(^1\)
    - or 13.2 nGy (1.2 nGy/day)

\(^1\)Range based on grade/natural history of disease (eg, 1.8 Gy fraction may be used for slower growing tumors).

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

**WORKUP**

- H&P
- Biopsy
- Chest x-ray
- As indicated for primary evaluation
  - Panorex
  - CT/MRI
- Preanesthesia studies
- Dental evaluation

Multidisciplinary consultation as indicated

**CLINICAL STAGING**

- **T1-2, N0**
  - Resectable
    - T3, T4a, N0
    - Any T, N1-3
  - Poor surgical risk
  - Definitive RT\(^a\) to primary and nodes or Chemo/RT\(^b\)
- Unresectable

Follow-up

See Treatment of Primary and Neck (LIP-2)

See Treatment of Primary and Neck (LIP-3)

See Treatment of Head and Neck Cancer (ADV-1)

---

\(^a\) See Principles of Radiation Therapy (LIP-A).
\(^b\) 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 cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
**CLINICAL STAGING**

**TREATMENT OF PRIMARY AND NECK**

**ADJUVANT TREATMENT**

**FOLLOW-UP**

---

**T1–2, N0**

Surgical excision

or

External-beam RT $\geq$ 50 Gy + brachytherapy

or

Brachytherapy alone

or

External-beam RT $\geq$ 66 Gy

Positive margins

- Reexcision or RT$^a$
  - or
  - Chemo/RT$^b$
    - (category 3)

Perineural/vascular/lymphatic invasion

- RT$^a$
  - or
  - Chemo/RT$^b$
    - (category 3)

No adverse pathologic findings

- Residual or recurrent tumor post-RT

- Surgery/reconstruction

---

**Follow-up**

- Physical exam:
  - Year 1, every 1–3 mo
  - Year 2, every 2–4 mo
  - Years 3–5, every 4–6 mo
  - > 5 yr, every 6–12 mo

---

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

---

**References**

- See Principles of Radiation Therapy (LIP-A).
- See Principles of Systemic Therapy (CHEM-A).
**CLINICAL STAGING:**
RESECTABLE T3, T4a, N0; Any T, N1-3

**TREATMENT OF PRIMARY AND NECK**

**Surgical candidate**

- **Surgery**
  - N0
  - N1, N2a–b, N3
  - N2c (bilateral)

- **External RT\(^a\) ± brachytherapy**

- **Excision of primary ± unilateral or bilateral selective neck dissection (reconstruction as indicated)**

- **Excision of primary, ipsilateral comprehensive neck dissection ± contralateral selective neck dissection (reconstruction as indicated)**

- **Excision of primary and bilateral comprehensive neck dissection (reconstruction as indicated)**

**ADJUVANT TREATMENT**

**FOLLOW-UP**

- **One positive node without adverse features\(^c,d\)**
  - RT\(^a\) optional

- **Major risk features\(^c\)**
  - Chemo/RT\(^b\)

- **Minor risk features\(^d\)**
  - RT\(^a\) or Chemo/RT\(^b\)

- **Extracapsular nodal spread and/or positive margins.**

- **Minor risk features: multiple positive nodes (without extracapsular nodal spread) or perineural/lymphatic/vascular invasion.**

- **Physical exam:**
  - Year 1, every 1–3 mo
  - Year 2, every 2–4 mo
  - Years 3–5, every 4–6 mo
  - > 5 yr, every 6–12 mo

**Residual tumor**

- **Primary site: Complete response**
  - Complete response of neck

- **N1 (initial stage)**
  - Observe

- **N2-3 (initial stage)**
  - Observe or Neck dissection (category 3)

- **Primary site: < complete response**
  - Salvage surgery + neck dissection as indicated

**ADJUVANT TREATMENT**

- **RT\(^a\) or Chemo/RT\(^b\)**

**FOLLOW-UP**

- **Recurrence (see ADV-2)**

---

\(^a\) See Principles of Radiation Therapy (LIP-A).
\(^b\) See Principles of Systemic Therapy (CHEM-A).
\(^c\) Extracapsular nodal spread and/or positive margins.
\(^d\) Minor risk features: multiple positive nodes (without extracapsular nodal spread) or perineural/lymphatic/vascular invasion.
PRINCIPLES OF RADIATION THERAPY

Definitive RT

- Primary and gross adenopathy:
  \[ \geq 66 \text{ Gy (2.0 Gy/day)} \]
- External-beam RT \[ \geq 50 \text{ Gy} \]
- Neck
- Uninvolved nodal stations:
  \[ \geq 50 \text{ Gy (2.0 Gy/day)} \]

Postoperative RT

- Primary: \[ \geq 60 \text{ Gy (2.0 Gy/day)} \]
- Neck
  - Involved nodal stations:
    \[ \geq 60 \text{ Gy (2.0 Gy/day)} \]
  - Uninvolved nodal stations:
    \[ \geq 50 \text{ Gy (2.0 Gy/day)} \]
Buccal mucosa, floor of mouth, anterior tongue, alveolar ridge, retromolar trigone, hard palate

WORKUP

• H&P
• Biopsy
• Chest x-ray or Chest CT
  - As indicated for evaluation
    - Panorex
    - CT/MRI
• Examination under anesthesia, if indicated
• Preanesthesia studies
• Dental evaluation

Multidisciplinary consultation as indicated

CLINICAL STAGING

T1–2, N0 → See Treatment of Primary and Neck (OR-2)

T3, N0 → See Treatment of Primary and Neck (OR-2)

T1–3, N1–3 → See Treatment of Primary and Neck (OR-3)

T4a, any N → See Treatment of Primary and Neck (OR-4)

Unresectable → See Treatment of Head and Neck Cancer (ADV-1)

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\(^a\) Chest CT should be considered for patients at high risk for thoracic metastases.

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Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Buccal mucosa, floor of mouth, anterior tongue, alveolar ridge, retromolar trigone, hard palate

**CLINICAL STAGING**

<table>
<thead>
<tr>
<th>T1–2, N0</th>
<th>Excision of primary (preferred) ± unilateral or bilateral selective neck dissection</th>
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<tr>
<td></td>
<td>or</td>
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<tr>
<td></td>
<td>External-beam RT ± brachytherapy ≥ 70 Gy to primary ≥ 50 Gy to neck at risk</td>
</tr>
</tbody>
</table>

| T3, N0  | Excision of primary and reconstruction as indicated and unilateral or bilateral selective neck dissection |

**TREATMENT OF PRIMARY AND NECK**

- **No adverse features**
  - RT (optional)
  - Chemo/RT (category 1)

- **One positive node without adverse features**
  - RT optional

- **One or both major risk features or ≥ 2 minor risk features**
  - Chemo/RT (category 1)

- **< 2 minor risk features**
  - RT

**ADJUVANT TREATMENT**

- Physical exam:
  - Year 1, every 1-3 mo
  - Year 2, every 2-4 mo
  - Years 3-5, every 4-6 mo
  - > 5 yr, every 6-12 mo

- Chest imaging as clinically indicated
- TSH every 6-12 mo, if neck irradiated
- Speech and swallowing evaluation and rehabilitation as indicated

**FOLLOW-UP**

- Physical exam:
  - Year 1, every 1-3 mo
  - Year 2, every 2-4 mo
  - Years 3-5, every 4-6 mo
  - > 5 yr, every 6-12 mo

- TSH every 6-12 mo, if neck irradiated
- Speech and swallowing evaluation and rehabilitation as indicated

- Year 1, every 1-3 mo
- Year 2, every 2-4 mo
- Years 3-5, every 4-6 mo
- > 5 yr, every 6-12 mo

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

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

Recurrence (see ADV-2)

---

*b* Major risk features: positive margins and/or extracapsular nodal spread.

*c* Minor risk features: pT3 or pT4 primary; N2 or N3 nodal disease, nodal disease in levels IV or V, perineural invasion, vascular embolism.

*d* See Principles of Radiation Therapy (OR-A).

*e* See Principles of Systemic Therapy (CHEM-A).
**Buccal mucosa, floor of mouth, anterior tongue, alveolar ridge, retromolar trigone, hard palate**

### CLINICAL STAGING

<table>
<thead>
<tr>
<th>T1-3, N1-3</th>
<th>Surgery</th>
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<tbody>
<tr>
<td>N1, N2a-b, N3</td>
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<tr>
<td>N1</td>
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<td>N2c (bilateral)</td>
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</tbody>
</table>

### TREATMENT OF PRIMARY AND NECK

| Excision of primary, ipsilateral comprehensive neck dissection ± contralateral selective neck dissection (reconstruction as indicated) |
| Excision of primary and bilateral comprehensive neck dissection (reconstruction as indicated) |
| No adverse features \(b, c\) |
| One or both major risk features or \(\geq 2\) minor risk features \(b, c\) |
| \(< 2\) minor risk features \(c\) |
| RT\(d\) optional |
| RT\(d\) |
| Chemo/RT\(d, e\) (category 1) |

### ADJUVANT TREATMENT

- RT\(d\)
- Chemo/RT\(d, e\)

### FOLLOW-UP

- **Physical exam:**
  - Year 1, every 1-3 mo
  - Year 2, every 2-4 mo
  - Years 3-5, every 4-6 mo
  - > 5 yr, every 6-12 mo
- **Chest imaging as clinically indicated**
- **TSH every 6-12 mo, if neck irradiated**
- **Speech and swallowing evaluation and rehabilitation as indicated**

### ADVERSE FEATURES

\(b\): Major risk features: positive margins and/or extracapsular nodal spread.

\(c\): Minor risk features: pT3 or pT4 primary; N2 or N3 nodal disease, nodal disease in levels IV or V, perineural invasion, vascular embolism.

\(d\): See Principles of Radiation Therapy (OR-A).

\(e\): See Principles of Systemic Therapy (CHEM-A).

**Recurrence (see ADV-2)**

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**Note:** All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Buccal mucosa, floor of mouth, anterior tongue, alveolar ridge, retromolar trigone, hard palate

**CLINICAL STAGING**

<table>
<thead>
<tr>
<th>T4a, Any N</th>
<th>Surgery (preferred for bone invasion)</th>
<th>Chemotherapy/RT&lt;sup&gt;d,e&lt;/sup&gt; (category 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>or</td>
<td>Concurrent systemic therapy/RT&lt;sup&gt;e&lt;/sup&gt; (category 3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Residual tumor</td>
<td>Complete response of neck</td>
</tr>
<tr>
<td></td>
<td>Primary site: Complete response</td>
<td>Neck dissection (category 3)</td>
</tr>
<tr>
<td></td>
<td>Primary site: residual tumor</td>
<td>Salvage surgery + neck dissection as indicated</td>
</tr>
</tbody>
</table>

- Physical exam:
  - Year 1, every 1-3 mo
  - Year 2, every 2-4 mo
  - Years 3-5, every 4-6 mo
  - > 5 yr, every 6-12 mo
- Chest imaging as clinically indicated
- TSH every 6-12 mo, if neck irradiated
- Speech and swallowing evaluation and rehabilitation as indicated

**FOLLOW-UP**

Recurrence (see ADV-2)

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<sup>d</sup> See Principles of Radiation Therapy (OR-A).
<sup>e</sup> 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 cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
PRINCIPLES OF RADIATION THERAPY

**Definitive RT**
- Primary and gross adenopathy:
  - ≥ 70 Gy (2.0 Gy/day)
  - External-beam RT ≥ 50 Gy ± brachytherapy
- Neck
  - Uninvolved nodal stations:
    - ≥ 50 Gy (2.0 Gy/day)

**Postoperative RT**
- Primary: ≥ 60 Gy (2.0 Gy/day)
- Neck
  - Involved nodal stations:
    - ≥ 60 Gy (2.0 Gy/day)
  - Uninvolved nodal stations:
    - ≥ 50 Gy (2.0 Gy/day)

Any one minor risk feature: pT3 or pT4 primary; N2 or N3 nodal disease, nodal disease in levels IV or V, perineural invasion, vascular embolism.

**Postoperative chemoradiation for high pathologic risk features**
- One or both major risk features or two or more minor risk features.
- Concurrent single agent cisplatin at 100 mg/m^2 every 3 wks is recommended.

---


**Note:** All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Base of tongue/tonsil/posterior pharyngeal wall/soft palate

WORKUP

- H&P
- Biopsy
- Chest x-ray or Chest CT
- CT with contrast or MRI recommended for primary and neck
- Panorex as indicated
- Dental evaluation as indicated
- Speech & swallowing evaluation as indicated
- Examination under anesthesia with laryngoscopy
- Preanesthesia studies

Multidisciplinary consultation as indicated

CLINICAL STAGING

- T1-2, N0-1
  - See Treatment of Primary and Neck (ORPH-2)
- T3-4a, N0
  - See Treatment of Primary and Neck (ORPH-3)
- Any T, N2-3
  - See Treatment of Primary and Neck (ORPH-4)
- T3-4a, N+
  - See Treatment of Primary and Neck (ORPH-4)
- Unresectable
  - See Treatment of Head and Neck Cancer (ADV-1)

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

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

*aChest CT should be considered for patients at high risk for thoracic metastases.*
Base of tongue/tonsil/posterior pharyngeal wall/soft palate

**CLINICAL STAGING**

**TREATMENT OF PRIMARY AND NECK**

- **Definitive RT**\(^b\) preferred (category 2B)

  - **Primary controlled**
  - **Residual disease**

- **Excision of primary ± unilateral or bilateral neck dissection**

  - **No adverse features**\(^c,d\)
    - **One positive node without adverse features**\(^c,d\)
      - **Consider RT**\(^b\)
    - **Adverse features**
      - **One or both major risk features or ≥ 2 minor risk features**\(^c,d\)
      - **< 2 minor risk features**\(^d\)
        - **RT**\(^b\)
  - **Primary controlled**
  - **Residual disease**
    - **Salvage surgery**

**ADJUVANT TREATMENT**

**FOLLOW-UP**

- Physical exam:
  - Year 1, every 1-3 mo
  - Year 2, every 2-4 mo
  - Years 3-5, every 4-6 mo
  - > 5 yr, every 6-12 mo
- Chest imaging as clinically indicated
- TSH every 6-12 mo, if neck irradiated
- Speech and swallowing evaluation and rehabilitation as indicated

**Recurrence (see ADV-2)**

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\(^b\) **See Principles of Radiation Therapy (ORPH-A).**

\(^c\) Major risk features: positive margins and/or extracapsular nodal spread.

\(^d\) Minor risk features: pT3 or pT4 primary; N2 or N3 nodal disease, nodal disease in levels IV or V, perineural invasion, vascular embolism.

\(^e\) **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 cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.*
Base of tongue/tonsil/posterior pharyngeal wall/soft palate

**CLINICAL STAGING**

**TREATMENT OF PRIMARY AND NECK**

**ADJUVANT TREATMENT**

**FOLLOW-UP**

Concurrent systemic therapy/RT$^b,e$

- Primary controlled
- Residual disease

or

Surgery

No adverse features$^c,d$

- Primary controlled
- Residual disease

or

Adverse features

One or both major risk features or $\geq$ 2 minor risk features$^c,d$

- Chemo/RT$^b,e$
  - (category 1)

< 2 minor risk features$^d$

- RT$^b$

- Salvage surgery

**T3-4a, N0**

- Physical exam:
  - Year 1, every 1-3 mo
  - Year 2, every 2-4 mo
  - Years 3-5, every 4-6 mo
  - > 5 yr, every 6-12 mo

- Chest imaging as clinically indicated
- TSH every 6-12 mo, if neck irradiated
- Speech and swallowing evaluation and rehabilitation as indicated

Induction chemotherapy followed by chemo/RT off protocol (category 3)

- Primary controlled
- Residual disease

Multimodality clinical trials that include function evaluation

$^b$See Principles of Radiation Therapy (ORPH-A).

$^c$Major risk features: positive margins and/or extracapsular nodal spread.

$^d$Minor risk features: pT3 or pT4 primary; N2 or N3 nodal disease, nodal disease in levels IV or V, perineural invasion, vascular embolism.

$^e$See Principles of Systemic Therapy (CHEM-A).

**Recurrence (see ADV-2)**

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

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Base of tongue/tonsil/posterior pharyngeal wall/soft palate

**CLINICAL STAGING**

**TREATMENT OF PRIMARY AND NECK**

- Concurrent systemic therapy/RT\textsuperscript{b,e} cisplatin (category 1) preferred
- Induction chemotherapy followed by chemo/RT off protocol (category 3)
- Surgery: primary and neck
- Multimodality clinical trials that include function evaluation

**ADJUVANT TREATMENT**

- Residual tumor
- Complete response of neck
- N1 (initial stage) → Observe
- N2-3 (initial stage) → Observe or Neck dissection (category 3)
- Excision of primary, ipsilateral comprehensive neck dissection (reconstruction as indicated)
- Excision of primary and bilateral comprehensive neck dissection (bilateral is category 3 if neck nodes contralateral only) (reconstruction as indicated)
- RT\textsuperscript{b} or Chemo/RT\textsuperscript{b,e} (category 1)

**FOLLOW-UP**

- Year 1, every 1-3 mo
- Year 2, every 2-4 mo
- Years 3-5, every 4-6 mo
- > 5 yr, every 6-12 mo
- Physical exam:
- Chest imaging as clinically indicated
- TSH every 6-12 mo, if neck irradiated
- Speech and swallowing evaluation and rehabilitation as indicated

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

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

\textsuperscript{b} See Principles of Radiation Therapy (ORPH-A).
\textsuperscript{e} See Principles of Systemic Therapy (CHEM-A).

Recurrence (see ADV-2)
### PRINCIPLES OF RADIATION THERAPY

**Selected T1-2, N0**
- Conventional fractionation:
  - 70 Gy (2.0 Gy/day)

**Selected T1, N1; T2, N0-1**
- Altered fractionation (preferred):
  - 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)
  - Hyperfractionation:
    - 81.6 Gy/7 weeks (1.2 Gy/fraction BID)

**Postoperative RT**
- Primary: ≥ 60 Gy (2.0 Gy/day)
- Neck
  - Involved nodal stations:
    - ≥ 60 Gy (2.0 Gy/day)
  - Uninvolved nodal stations:
    - ≥ 50 Gy (2.0 Gy/day)

Any one minor risk feature: pT3 or pT4 primary; N2 or N3 nodal disease, nodal disease in levels IV or V, perineural invasion, vascular embolism.

**T2-4a, N0-3**
- Concurrent chemoradiation
  - Conventional fractionation:
    - Primary and gross adenopathy
      - ≥ 70 Gy (2.0 Gy/day)
    - Neck
      - Uninvolved nodal stations:
        - 44-50 Gy (2.0 Gy/day)

**Postoperative chemoradiation for high pathologic risk features**
- One or both major risk features, or two or more minor risk features.
- Concurrent single agent cisplatin at 100 mg/m\(^2\) every 3 wks is recommended.

**Radiation Techniques**
3D conformal techniques may be used depending on the stage, tumor location, physician training/experience and available physics support. IMRT techniques are an area of active development among the NCCN institutions and others. Target delineation and optimal dose distribution require special training in head and neck imaging, a thorough understanding of patterns of disease spread, and special training in IMRT techniques. Standards for target definition, dose specification, fractionation (with and without concurrent chemotherapy), and normal tissue constraints should emerge within the next few years.

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1 The majority of the published experience with concurrent chemoradiation has utilized conventional fractionation at 2.0 g per fraction to ≥ 70 Gy in 7 wks with single agent cisplatin given every 3 wks at 100 mg/m\(^2\). Use of other fraction sizes (eg, 1.8 Gy, conventional), multiagent chemotherapy, or altered fractionation with chemotherapy has been evaluated with 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 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 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 cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
WORKUP

- H&P
- Biopsy
- Chest x-ray or Chest CT
- CT with contrast or MRI of primary and neck recommended
- Examination under anesthesia with laryngoscopy and esophagoscopy
- Preanesthesia studies
- Dental evaluation

Multidisciplinary consultation as indicated

CLINICAL STAGING

Early T stage not requiring total laryngectomy
- Most T1, N0-1; small T2, N0

See Treatment of Primary and Neck (HYPO-2)

Resectable advanced cancer requiring total laryngectomy
- T1, N2-3; T2-4a, Any N (Participation in clinical trials preferred)

See Treatment of Primary and Neck (HYPO-3)

T4a, Any N

See Treatment of Primary and Neck (HYPO-5)

Unresectable

See Treatment of Head and Neck Cancer (ADV-1)

\(^a\)Chest CT should be considered for patients at high risk for thoracic metastases.

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

Primary site: complete response

Definitive RT

or

Primary site: residual tumor

Surgery: Partial laryngopharyngectomy (open or endoscopic) + ipsilateral or bilateral selective neck dissection (N0); Comprehensive neck dissection levels 1-5 (N1)

Residual tumor

Complete response of neck

Salvage surgery + neck dissection as indicated

Neck dissection (category 3)

Observe

Physical exam:
- Year 1, every 1-3 mo
- Year 2, every 2-4 mo
- Years 3-5, every 4-6 mo
- > 5 yr, every 6-12 mo

• Chest imaging as clinically indicated

Follow-up

HYPO-2

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

HYPO-A

See Principles of Radiation Therapy (HYPO-A).

Major risk features: positive margins and/or extracapsular nodal spread.

Minor risk features: pT3 or pT4 primary; N2 or N3 nodal disease, perineural invasion, vascular embolism.

See Principles of Systemic Therapy (CHEM-A).
Induction chemotherapy x 2 cycles (category 1)

or

Laryngopharyngectomy + selective (N0) or comprehensive (N+) neck dissection

or

Concurrent systemic therapy/RT\textsuperscript{b,e} cisplatin preferred (category 2B)

or

Multimodality clinical trials that include function evaluation

No adverse features\textsuperscript{c,d}

\textbf{See Response After Induction Chemotherapy (HYPO-4)}

One or both major risk features or \geq 2 minor risk features\textsuperscript{c,d}

Chemo/RT\textsuperscript{b,e} (category 1)

\textsuperscript{b}See Principles of Radiation Therapy (HYPO-A).
\textsuperscript{c}Major risk features: positive margins and/or extracapsular nodal spread.
\textsuperscript{d}Minor risk features: pT3 or pT4 primary; N2 or N3 nodal disease, perineural invasion, vascular embolism.
\textsuperscript{e}See Principles of Systemic Therapy (CHEM-A).

\textbf{Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.}
RESPONSE AFTER INDUCTION CHEMOTHERAPY FOR T1, N2-3; T2-3, ANY N TUMORS

**Primary site:**
- **Complete response**
  - Definitive RT<sup>b</sup>

**Primary site:**
- **Partial response (evaluation may require endoscopy)**
  - Chemotherapy x 1 cycle
  - Primary site: Complete response

**Primary site:**
- **< Partial response**
  - Surgery

**Residual tumor**
- Complete response of neck
- Observe
- Neck dissection (category 3)
- Observe or Neck dissection (category 3)

**Chemotherapy x 1 cycle**
- Salvage surgery
- No adverse features<sup>c,d</sup>
- RT<sup>b</sup>
- One or both major risk features or ≥ 2 minor risk features<sup>c,d</sup>
- Chemo/RT<sup>b,e</sup>

**Definitive RT<sup>b</sup>**
- N1 (initial stage)
- Observe
- N2-3 (initial stage)
- Observe or Neck dissection (category 3)

**Salvage surgery**
- Adverse features
- < 2 minor risk features<sup>d</sup>
- RT<sup>b</sup>

**Surgery**
- Physical exam:
  - Year 1, every 1-3 mo
  - Year 2, every 2-4 mo
  - Years 3-5, every 4-6 mo
  - > 5 yr, every 6-12 mo
- Chest imaging as clinically indicated
- TSH every 6-12 mo, if neck irradiated

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<sup>b</sup>See Principles of Radiation Therapy (HYPO-A).

<sup>c</sup>Major risk features: positive margins and/or extracapsular nodal spread.

<sup>d</sup>Minor risk features: pT3 or pT4 primary; N2 or N3 nodal disease, perineural invasion, vascular embolism.

<sup>e</sup>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 cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Head and Neck Cancers

Cancer of the Hypopharynx

CLINICAL STAGING

TREATMENT OF PRIMARY AND NECK

ADJUVANT TREATMENT

FOLLOW-UP

Surgery + comprehensive neck dissection (preferred)

Chemo/RT\textsuperscript{b,e} (category 1)

Concurrent systemic therapy/RT\textsuperscript{b,e} (category 3)

Residual tumor

Complete response of neck

Primary site: complete response

T4a, any N

Multimodality clinical trials that include function evaluation

Primary site: residual tumor

Salvage surgery + neck dissection as indicated

N1 (initial stage)

N2-3 (initial stage)

Observe

Observe or Neck dissection (category 3)

Neck dissection (category 3)

Physical exam:
- Year 1, every 1-3 mo
- Year 2, every 2-4 mo
- Years 3-5, every 4-6 mo
- > 5 yr, every 6-12 mo

Chest imaging as clinically indicated

TSH every 6-12 mo, if neck irradiated

\textsuperscript{b} See Principles of Radiation Therapy (HYPO-A).

\textsuperscript{e} 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 cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
PRINCIPLES OF RADIATION THERAPY

Definitive RT
- Primary and gross adenopathy: 
  \( \geq 70 \text{ Gy (2.0 Gy/day)} \)
- Neck
  Uninvolved nodal stations: 
  \( \geq 50 \text{ Gy (2.0 Gy/day)} \)

Postoperative RT
- Primary: \( \geq 60 \text{ Gy (2.0 Gy/day)} \)
- Neck
  » Involved nodal stations: 
    \( \geq 60 \text{ Gy (2.0 Gy/day)} \)
  » Uninvolved nodal stations: 
    \( \geq 50 \text{ Gy (2.0 Gy/day)} \)

Any one minor risk feature: pT3 or pT4 primary; N2 or N3 nodal disease, perineural invasion, vascular embolism.

Postoperative chemoradiation for high pathologic risk features\(^1,2,3\)
- One or both major risk features or two or more minor risk features.
- Concurrent single agent cisplatin at 100 mg/m\(^2\) every 3 wks is recommended.

---


Preparation of the patient for neck dissection at time of biopsy, if necessary.
PATHOLOGIC FINDINGS

Primary found

- Treat as appropriate (See Guidelines Index)

Node level I, II, III, upper V

- Examination under anesthesia
- Palpation and inspection
- Biopsy of areas of clinical concern, including tonsillectomy
- Direct laryngoscopy and nasopharynx survey

Node level IV, lower V

- Direct laryngoscopy, bronchoscopy, esophagoscopy
- Chest/abdominal/pelvic CT

WORKUP

- Adenocarcinoma (levels I–III)
- Squamous cell carcinoma
- Poorly differentiated or Nonkeratinizing squamous cell or NOS or Anaplastic (Not thyroid)

PRIMARY TREATMENT

- Comprehensive neck dissection + parotidectomy, if indicated
- Surgery → Comprehensive neck dissection (levels I–V)
- RT\(^c\) (category 3) → No residual tumor
- Chemotherapy/RT\(^d\) (category 3) → Residual tumor

- RT to neck ± parotid bed
- N1 with FNA → Consider RT as per OCC-3
- See N1 with open biopsy (OCC-3)
- Extracapsular spread or N2, N3 (OCC-4)
- Observe or Consider neck dissection for initial stage N3

- Comprehensiveneck dissection (levels I–V)
- Comprehensiveneck dissection + parotidectomy, if indicated

\(^c\) See Principles of Radiation Therapy (OCC-A)
\(^d\) 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 cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
POSTSURGICAL TREATMENT FOR SQUAMOUS CELL CARCINOMA; NOS OR ANAPLASTIC

N1 with open biopsy

Level I only

Level II, III, upper level V

Level IV only

Lower level V

RT<sup>c</sup> to neck only (category 3) or
RT<sup>c</sup> to oral cavity, Waldeyer’s ring, oropharynx, both sides of the neck (block RT to the larynx)

RT<sup>c</sup> to neck only (category 3) or
RT<sup>c</sup> to nasopharynx, both sides of the neck, hypopharynx, larynx, oropharynx

RT<sup>c</sup> to neck only (category 3) or
RT<sup>c</sup> to Waldeyer’s ring, larynx, hypopharynx, both sides of the neck

RT<sup>c</sup> to neck only (category 3) or
RT<sup>c</sup> to larynx, hypopharynx, both sides of the neck

<sup>c</sup>See Principles of Radiation Therapy (OCC-A).

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
POSTSURGICAL TREATMENT FOR SQUAMOUS CELL CARCINOMA; NOS OR ANAPLASTIC

Level I only
- RT to neck only (category 3)
- RT to oral cavity, Waldeyer’s ring, oropharynx, both sides of the neck (block RT to the larynx)
- Chemotherapy/RT (category 2B)

Level II, III, upper level V
- RT to neck only (category 3)
- RT to nasopharynx, both sides of the neck, hypopharynx, larynx, oropharynx
- Chemotherapy/RT (category 2B)

Level IV only
- RT to neck only (category 3)
- RT to Waldeyer’s ring, larynx, hypopharynx, both sides of the neck
- Chemotherapy/RT (category 2B)

Lower level V
- RT to neck only (category 3)
- RT to larynx, hypopharynx, both sides of the neck
- Chemotherapy/RT (category 2B)

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

See Principles of Radiation Therapy (OCC-A).
See Principles of Systemic Therapy (CHEM-A).
PRIMARY THERAPY FOR OCCULT PRIMARY - MELANOMA

Level V, occipital node → Posterior lateral node dissection

All other nodal sites → Comprehensive neck dissection

± RT to nodal bed\(^d\) → ± Adjuvant systemic therapy, per NCCN Melanoma Guidelines

\(^d\)Adjuvant radiotherapy: 30 Gy/5 fx over 2.5 weeks (6.0 Gy/fx). Careful attention to dosimetry is necessary.


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

Mucosal sites:
• 50-60 Gy (2.0 Gy/day) to mucosa, depending on field size and use of chemotherapy. Consider boost to 60-64 Gy to particularly suspicious areas

Neck
• Uninvolved nodal stations:
  ≥ 50 Gy (2.0 Gy/day)
• Involved nodal station(s):
  60-66 Gy* (2.0 Gy/day)

*Up to 70 Gy in case of excision only for N1 neck.
**WORKUP**

- H&P
- Biopsy
- Chest x-ray or Chest CT
- CT with contrast and thin cuts through larynx, or MRI of primary and neck recommended
- Examination under anesthesia with laryngoscopy
- Preanesthesia studies
- Dental evaluation as indicated
- Speech & swallowing evaluation as indicated
- Multidisciplinary consultation as indicated

**CLINICAL STAGING**

- Severe dysplasia/carcinoma in situ
  - Total laryngectomy not required
  - Most T1-2, any N
- Resectable
  - Requiring total laryngectomy
  - Most T3, any N
- T4a disease
- Unresectable
  - See Treatment and Follow-up (GLOT-2)
  - See Treatment and Follow-up (GLOT-3)
  - See Treatment and Follow-up (GLOT-4)
  - See Treatment of Head and Neck Cancer (ADV-1)

**TREATMENT OF PRIMARY AND NECK**

- See Treatment and Follow-up (GLOT-2)
- See Treatment and Follow-up (GLOT-3)
- See Treatment and Follow-up (GLOT-4)
- See Treatment of Head and Neck Cancer (ADV-1)

---

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

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

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GLOT-1
**CLINICAL STAGING**

- Severe dysplasia/carcinoma in situ
  - Clinical trial or endoscopic removal (stripping/laser) or RT<sup>c</sup>

**TREATMENT OF PRIMARY AND NECK**

- Total laryngectomy not required
  - Most T1-2, any N
  - RT<sup>c</sup> or partial laryngectomy/ endoscopic resection (selected superficial lesions) or open partial laryngectomy

**FOLLOW-UP**

- Physical exam:
  - Year 1, every 1-3 mo
  - Year 2, every 2-4 mo
  - Years 3-5, every 4-6 mo
  - > 5 years, every 6-12 mo
- Chest imaging as clinically indicated
- TSH every 6-12 mo, if neck irradiated
- Speech and swallowing evaluation and rehabilitation as indicated

---

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

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

---

<sup>c</sup>See Principles of Radiation Therapy (GLOT-A).

**Recurrence (see ADV-2)**
CLINICAL STAGING

TREATMENT OF PRIMARY AND NECK

Residual tumor

Primary site: Complete response

Complete response of neck

N1 (initial stage)

N2-3 (initial stage)

Resectable

Requiring total laryngectomy

Most T3, any N

Surgery → N1 → N2-3

Primary site: residual tumor

Salvage surgery + neck dissection as indicated

Laryngectomy with ipsilateral thyroidectomy ± unilateral or bilateral selective neck dissection (reconstruction as indicated)

Laryngectomy with ipsilateral thyroidectomy, ipsilateral comprehensive neck dissection ± contralateral selective neck dissection (reconstruction as indicated)

Laryngectomy with ipsilateral thyroidectomy, ipsilateral or bilateral comprehensive neck dissection (reconstruction as indicated)

No adverse features\(^{e,f}\)

Adverse features

One or both major risk features or \(\geq 2\) minor risk features\(^{e,f}\)

\(< 2\) minor risk features\(^f\)

Neck dissection (category 3)

Observe

Observe or Neck dissection (category 3 for selective vs comprehensive)

ADJUVANT TREATMENT

FOLLOW-UP

• Physical exam:
  ▶ Year 1, every 1-3 mo
  ▶ Year 2, every 2-4 mo
  ▶ Years 3-5, every 4-6 mo
  ▶ > 5 years, every 6-12 mo

• Chest imaging as clinically indicated

• TSH every 6-12 mo, if neck irradiated

• Speech and swallowing evaluation and rehabilitation as indicated

See Principles of Radiation Therapy (GLOT-A)
See Principles of Systemic Therapy (CHEM-A)

Major risk features: positive margins and/or extracapsular nodal spread.

Minor risk features: pT4 primary; N2 or N3 nodal disease, perineural invasion, vascular embolism.

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

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

\(^c\) See Principles of Radiation Therapy (GLOT-A).
\(^d\) See Principles of Systemic Therapy (CHEM-A).
\(^e\) Major risk features: positive margins and/or extracapsular nodal spread.
\(^f\) Minor risk features: pT4 primary; N2 or N3 nodal disease, perineural invasion, vascular embolism.
CLINICAL STAGING

TREATMENT OF PRIMARY AND NECK

ADJUVANT TREATMENT

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

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

See Principles of Radiation Therapy (GLOT-A).

See Principles of Systemic Therapy (CHEM-A).

**CLINICAL STAGING**

**TREATMENT OF PRIMARY AND NECK**

- **Selected T4a**
  - Consider concurrent chemoradiation or Clinical trial for function preserving surgical or nonsurgical management

- **T4a disease**
  - Primary site: Residual tumor

- **T4a, Any N**
  - **N0**
    - Laryngectomy with ipsilateral thyroidectomy ± unilateral or bilateral selective neck dissection (reconstruction as indicated)
  - **N1**
    - Laryngectomy with ipsilateral thyroidectomy, ipsilateral comprehensive neck dissection ± contralateral selective neck dissection (reconstruction as indicated)
  - **N2-3**
    - Laryngectomy with ipsilateral thyroidectomy, ipsilateral or bilateral comprehensive neck dissection (reconstruction as indicated)

- **Residual tumor**
  - Complete response of neck

- **N1 (initial stage)**
  - Observe

- **N2-3 (initial stage)**
  - Neck dissection (category 3 for selective vs comprehensive)

- **Observe or Neck dissection (category 3)**
  - **Chemo/RT (category 1)**

- **Recurrence (see ADV-2)**

- **Physical exam:**
  - Year 1, every 1-3 mo
  - Year 2, every 2-4 mo
  - Years 3-5, every 4-6 mo
  - > 5 years, every 6-12 mo

- **Chest imaging as clinically indicated**

- **TSH every 6-12 mo, if neck irradiated**

- **Speech and swallowing evaluation and rehabilitation as indicated**
Definitive RT
- T1, N0: 63-66 Gy in 2.25-2.0 Gy/day
- ≥ T2 and gross adenopathy:
  - 70 Gy (2.0 Gy/day) in 7 weeks
  - 72 Gy in 6 weeks (1.8 Gy/fraction, large field; 1.5 Gy boost as second daily fraction during last 12 treatment days)
  - 79.2 - 81.6 Gy in 7 weeks (1.2 Gy/fraction, twice daily)
- Elective nodal RT
  - ≥ 50 Gy (2.0 Gy/day)

Postoperative RT
- Primary: ≥ 60 Gy (2.0 Gy/day)
- Neck
  - Involved nodal stations: ≥ 60 Gy (2.0 Gy/day)
  - Uninvolved nodal stations: ≥ 50 Gy (2.0 Gy/day)

Any one minor risk feature: pT4 primary; N2 or N3 nodal disease, perineural invasion, vascular embolism.

Postoperative chemoradiation for high pathologic risk features¹,²,³
- One or both major risk features or two or more minor risk features.
- Concurrent single agent cisplatin at 100 mg/m² every 3 wks is recommended.


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

- H&P
- Biopsy
- Chest x-ray or Chest CT
- CT with contrast and thin cuts through larynx or MRI of primary and neck recommended
- Examination under anesthesia with laryngoscopy
- Preanesthesia studies
- Dental evaluation as indicated
- Speech & swallowing evaluation as indicated
- Multidisciplinary consultation as indicated

CLINICAL STAGING

- Not requiring total laryngectomy
  - Most T1–2, N0
  - See Treatment of Primary and Neck (SUPRA-2)

- Requiring laryngectomy
  - T3, N0
  - T4a, N0
    - No cartilage destruction
    - Low-volume base-of-tongue involvement
  - See Treatment of Primary and Neck (SUPRA-3)

- T4a, N0
  - Cartilage destruction
  - Skin involvement
  - High-volume invasion of base of tongue
  - See Treatment of Primary and Neck (SUPRA-4)

Node positive disease
- See Workup and Clinical Staging (SUPRA-5)

Unresectable
- See Treatment of Head and Neck Cancer (ADV-1)

---

*a Chest CT should be considered for patients at high risk for thoracic metastases.

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

**Cancer of the Supraglottic Larynx**

### CLINICAL STAGING
- Not requiring total laryngectomy
- Most T1–2, N0

### TREATMENT OF PRIMARY AND NECK
- Endoscopic resection ± selective neck dissection or Open partial supraglottic laryngectomy ± selective neck dissection or Definitive RT

### ADJUVANT TREATMENT
- One positive node without other adverse features → Consider RT
- Adverse features: positive margins → Further surgery or RT
- Adverse features: extracapsular nodal spread → Chemo/RT (category 2B) or RT (category 2B)

### FOLLOW-UP
- Physical exam:
  - Year 1, every 1-3 mo
  - Year 2, every 2-4 mo
  - Years 3-5, every 4-6 mo
  - > 5 years, every 6-12 mo
- Chest imaging as clinically indicated
- TSH every 6-12 mo, if neck irradiated
- Speech and swallowing rehabilitation and therapy as indicated

---

**b** See Principles of Radiation Therapy (SUPRA-A).

**c** 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 cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

**Recurrence (see ADV-2)**
CLINICAL STAGING

- Requiring laryngectomy
- T3, N0
- T4a, N0
  - No cartilage destruction
  - Low-volume base-of-tongue involvement

TREATMENT OF PRIMARY AND NECK

Laryngectomy, ipsilateral thyroidectomy with ipsilateral or bilateral selective neck dissection

or

Concurrent systemic therapy/RT\(^b\),\(^c\) cisplatin (category 1) preferred

Primary site:

- Complete response

- Residual tumor

ADVERSE FEATURES

N0 or one positive node without adverse features\(^d\),\(^e\)

One or both major risk features or \(\geq 2\) minor risk features\(^d\),\(^e\)

< 2 minor risk features\(^e\)

ADJUVANT TREATMENT

RT\(^b\) optional

Chemo/RT\(^b\),\(^c\) (category 1)

RT\(^b\)

FOLLOW-UP

Physical exam:

- Year 1, every 1-3 mo
- Year 2, every 2-4 mo
- Years 3-5, every 4-6 mo
- > 5 years, every 6-12 mo

- Chest imaging as clinically indicated
- TSH every 6-12 mo, if neck irradiated
- Speech and swallowing evaluation and rehabilitation as indicated

Recurrence (see ADV-2)

\(^b\) See Principles of Radiation Therapy (SUPRA-A).
\(^c\) See Principles of Systemic Therapy (CHEM-A).
\(^d\) Major risk features: positive margins and/or extracapsular nodal spread.
\(^e\) Minor risk features: pT4 primary; N2 or N3 nodal disease, perineural invasion, vascular embolism.

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

• T4a, N0
  ➤ Cartilage destruction
  ➤ Skin involvement
  ➤ High-volume invasion of base of tongue

TREATMENT OF PRIMARY AND NECK

Laryngectomy, ipsilateral thyroidectomy with ipsilateral or bilateral selective neck dissection or Clinical trial

ADJUVANT TREATMENT

RT\textsuperscript{b}
or Chemo/RT\textsuperscript{b,c} (category 1)

FOLLOW-UP

• Physical exam:
  ➤ Year 1, every 1-3 mo
  ➤ Year 2, every 2-4 mo
  ➤ Years 3-5, every 4-6 mo
  ➤ > 5 years, every 6-12 mo
• Chest imaging as clinically indicated
• TSH every 6-12 mo, if neck irradiated
• Speech and swallowing evaluation and rehabilitation as indicated

\textsuperscript{b}See Principles of Radiation Therapy (SUPRA-A).
\textsuperscript{c}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 cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
**WORKUP**

- H&P
- Biopsy
- Chest x-ray or Chest CT
- CT with contrast and thin cuts through larynx
- MRI of primary and neck recommended
- Examination under anesthesia with laryngoscopy
- Preanesthesia studies
- Dental evaluation as indicated
- Speech & swallowing evaluation as indicated
- Multidisciplinary consultation as indicated

**CLINICAL STAGING**

- Not requiring total laryngectomy
  - T1–2, N+ and selected T3–4a
  
  → See Treatment of Primary and Neck (SUPRA-6)

- Requiring total laryngectomy
  - Most T3–4a, N+
    - No cartilage destruction
    - Low-volume base-of-tongue involvement
  
  → See Treatment of Primary and Neck (SUPRA-7)

- T4a, N+
  - Cartilage destruction
  - Skin involvement
  - High-volume invasion of base of tongue

  → See Treatment of Primary and Neck (SUPRA-8)

**Node positive disease**

- Unresectable (T4b)
  
  → See Treatment of Head and Neck Cancer (ADV-1)

---

*a*Chest CT should be considered for patients at high risk for thoracic metastases.

_Note: All recommendations are category 2A unless otherwise indicated._

_Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged._
**CANCER OF THE SUPRAGLOTTIC LARYNX**

**CLINICAL STAGING**

- Not requiring total laryngectomy
- T1–2, N+ and selected T3–4a

**TREATMENT OF PRIMARY AND NECK**

- Definitive RT
  - or
  - Concurrent systemic therapy/RT cisplatin (category 1) preferred

- Partial supraglottic laryngectomy and comprehensive neck dissection(s)

**ADJUVANT TREATMENT**

- Residual tumor
  - Primary site: Complete response
    - Complete response of neck
      - N1 (initial stage)
        - Observe
      - N2–3 (initial stage)
        - Observe or neck dissection (category 3)
  - Primary site: residual tumor
    - Salvage surgery + neck dissection as indicated
    - No adverse features
      - One or both major risk features or ≥ 2 minor risk features
        - Chemo/RT (category 1)
      - < 2 minor risk features
        - RT
  - Adverse features

**FOLLOW-UP**

- Physical exam:
  - Year 1, every 1-3 mo
  - Year 2, every 2-4 mo
  - Years 3-5, every 4-6 mo
  - > 5 years, every 6-12 mo
- Chest imaging as clinically indicated
- TSH every 6-12 mo, if neck irradiated
- Speech and swallowing evaluation and rehabilitation as indicated

**Recurrence (see ADV-2)**

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

---

[c]See Principles of Systemic Therapy (CHEM-A).
[d]Major risk features: positive margins and/or extracapsular nodal spread.
[e]Minor risk features: pT4 primary; N2 or N3 nodal disease, perineural invasion, vascular embolism.
**CLINICAL STAGING**

- **Requiring total laryngectomy**
  - **Most T3–4a, N+**
  - **No cartilage destruction**

**TREATMENT OF PRIMARY AND NECK**

- **Primary site:** Complete response
  - **Residual tumor**
    - **Complete response of neck**
      - **N1 (initial stage)**
        - Observe
      - **N2-3 (initial stage)**
        - Observe or Neck dissection (category 3)
    - **Salvage surgery + neck dissection as indicated**

- **Concurrent systemic therapy/RT\textsuperscript{b,c} (category 1)** preferred
  - **cisplatin** preferred

- **Primary site:** residual tumor
  - **Laryngectomy, ipsilateral thyroidectomy with comprehensive neck dissection**
    - **No adverse features\textsuperscript{d,e}**
      - **One or both major risk features or ≥ 2 minor risk features\textsuperscript{d,e}**
        - RT
      - **< 2 minor risk features\textsuperscript{e}**
        - RT\textsuperscript{b}

**ADJUVANT TREATMENT**

- **Neck dissection (category 3)**

**FOLLOW-UP**

- **Physical exam:**
  - Year 1, every 1-3 mo
  - Year 2, every 2-4 mo
  - Years 3-5, every 4-6 mo
  - > 5 years, every 6-12 mo
- **Chest imaging as clinically indicated**
- **TSH every 6-12 mo, if neck irradiated**
- **Speech and swallowing evaluation and rehabilitation as indicated**

**ADJUVANT TREATMENT**

- **Cancer of the Supraglottic Larynx**
  - **Head and Neck Cancers**
  - **Induction chemotherapy followed by chemo/RT (category 3) in selected N2, N3 patients**

**Recurrence (see ADV-2)**

\textsuperscript{b}See Principles of Radiation Therapy (SUPRA-A).
\textsuperscript{c}See Principles of Systemic Therapy (CHEM-A).
\textsuperscript{d}Major risk features: positive margins and/or extracapsular nodal spread.
\textsuperscript{e}Minor risk features: pT4 primary; N2 or N3 nodal disease, perineural invasion, vascular embolism.

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

**Cancer of the Supraglottic Larynx**

---

**CLINICAL STAGING**

- T4a, N+
  - Cartilage destruction
  - Skin involvement

**TREATMENT OF PRIMARY AND NECK**

- Laryngectomy, ipsilateral thyroidectomy with ipsilateral or bilateral neck dissection or Clinical trial

**ADJUVANT TREATMENT**

- Chemo/RT\(b,c\) (category 1)

**FOLLOW-UP**

- Physical exam:
  - Year 1, every 1-3 mo
  - Year 2, every 2-4 mo
  - Years 3-5, every 4-6 mo
  - > 5 years, every 6-12 mo

- Chest imaging as clinically indicated
- TSH every 6-12 mo, if neck irradiated
- Speech and swallowing evaluation and rehabilitation as indicated

---

\(b\) See Principles of Radiation Therapy (SUPRA-A).
\(c\) 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 cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
PRINCIPLES OF RADIATION THERAPY

Definitive RT
- Primary and gross adenopathy:
  ≥ 70 Gy (2.0 Gy/day)
- Neck
  ▷ Uninvolved nodal stations:
    ≥ 50 Gy (2.0 Gy/day)

Postoperative RT
- Primary: ≥ 60 Gy (2.0 Gy/day)
- Neck
  ▷ Involved nodal stations:
    ≥ 60 Gy (2.0 Gy/day)
  ▷ Uninvolved nodal stations:
    ≥ 50 Gy (2.0 Gy/day)

Any one minor risk feature: pT4 primary; N2 or N3 nodal disease, perineural invasion, vascular embolism.

Postoperative chemoradiation for high pathologic risk features\textsuperscript{1,2,3}
- One or both major risk features or two or more minor risk features.
- Concurrent single agent cisplatin at 100 mg/m\textsuperscript{2} every 3 wks is recommended.

WORKUP

- H&P
- Nasopharyngeal exam and biopsy
- Chest x-ray or Chest CT
- MRI with gadolinium of nasopharynx and base of skull to clavicles and/or CT with contrast
- Dental evaluation as indicated
- Speech & swallowing evaluation as indicated
- Imaging for distant metastases (chest, liver, bone) for WHO class 2-3/N2-3 disease (may include PET scan and/or CT)

Multidisciplinary consultation

CLINICAL STAGING

T1, N0, M0 and T2a, N0, M0

T1-T2a, N1-3; T2b-T4a, Any N

Any T, Any N, M1

See Treatment of Primary and Neck (NASO-2)

See Treatment of Primary and Neck (NASO-2)

See Treatment of Primary and Neck (NASO-2)

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

aChest CT should be considered for patients at high risk for thoracic metastases.
**CLINICAL STAGING**

- **T1, N0, M0 and T2a, N0, M0**
  - Definitive RT\(^b\) to nasopharynx and elective RT to neck

- **T1-T2a, N1-3; T2b-T4a, any N**
  - Cisplatin, 100 mg/m\(^2\) on days 1, 22, 43, + RT (≥ 70 Gy) to primary and gross nodal disease (category 1) and bilateral neck: ≥ 50 Gy
  - Neck: complete response
  - Neck dissection
  - Observe

- **Any T, any N, M1**
  - Platinum-based combination chemotherapy
  - If complete response
  - Definitive RT\(^b\) to primary and neck

---

**TREATMENT OF PRIMARY AND NECK**

- **Definitive RT\(^b\) to nasopharynx and elective RT to neck**

**FOLLOW-UP**

- Physical exam:
  - Year 1, every 1–3 mo
  - Year 2, every 2–4 mo
  - Year 3–5, every 4–6 mo
  - > 5 years, 6–12 mo
- **TSH every 6-12 mo, if neck irradiated**
- **Speech and swallowing evaluation and rehabilitation as indicated**

---

\(^b\)See Principles of Radiation Therapy (NASO-A).

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

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

Definitive RT
- Primary and gross adenopathy:
  \[ \geq 70 \text{ Gy} (2.0 \text{ Gy/day}) \]
- Neck
  - Uninvolved nodal stations:
    \[ \geq 50 \text{ Gy} (2.0 \text{ Gy/day}) \]

Radiation Techniques
Radiation technique may play a critical role in reducing toxicity and enhancing tumor control in nasopharyngeal cancers. 3D conformal techniques and IMRT techniques should be strongly considered, though consensus on optimal technique has not yet emerged. IMRT techniques are an area of active development among the NCCN institutions and others. Target delineation and optimal dose distribution require special training in head and neck imaging, a thorough understanding of patterns of disease spread, and special training in IMRT techniques. Standards for target definition, dose specification, fractionation (with and without concurrent chemotherapy), and normal tissue constraints should emerge within the next few years.
**TREATMENT OF HEAD AND NECK CANCER**

Newly diagnosed Unresectable (M0); T4b, N any, or unresectable N+

- **Clinical trial preferred**
  - Concurrent cisplatin or carboplatin-based chemotherapy\(^a\) + RT\(^b\) (category 1)
  - Induction chemotherapy\(^c\) followed by chemoradiation (category 3)

- **Standard therapy**
  - Induction chemotherapy\(^c\) followed by RT (category 3)
  - Definitive RT\(^b\) ± concurrent systemic therapy

- **PS 0-1**
  - Definitive RT\(^b\)
  - Best supportive care

- **PS 2**
  - Residual neck disease: Neck dissection, if feasible + primary site controlled

- **PS 3**

---

\(^a\) The single-agent cisplatin or carboplatin-based chemoradiotherapy regimens have not been compared in randomized trials. Therefore, no optimal standard regimen is defined. Combination chemotherapy regimens are more toxic and have not been directly compared to single-agent regimens.

\(^b\) See Principles of Radiation Therapy (ADV-A).

\(^c\) Cisplatin 100 mg/m\(^2\) day 1 + 5-FU 1000mg/m\(^2\)/24 hrs continuous IV infusion for 120 hours for 3 cycles.

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

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

**Concurrent chemoradiation (preferred)**

Conventional fractionation:¹

- Primary and gross adenopathy
  
  - ≥ 70 Gy (2.0 Gy/day)

- Neck
  
  Uninvolved nodal stations:
  
  - 44-50 Gy (2.0 Gy/day)

**Definitive RT without chemotherapy (for medically unfit or those who refuse chemotherapy)**

Altered fractionation (hyperfractionation or concomitant boost) regimens preferred for RT alone.

- Hyperfractionation:
  
  - 81.6 Gy/7 wks (1.2 Gy/fraction BID)

- Concomitant boost accelerated RT:
  
  - 72 Gy/6 wks (1.8 Gy/fraction, large field; 1.5 Gy boost as second daily fraction during last 12 treatment days)

**Definitive RT + cetuximab (for patients not able to tolerate cytotoxic therapy)**

**Radiation Techniques**

3D conformal techniques may be used depending on the stage, tumor location, physician training/experience and available physics support. IMRT techniques are an area of active development among the NCCN institutions and others. Target delineation and optimal dose distribution require special training in head and neck imaging, a thorough understanding of patterns of disease spread, and special training in IMRT techniques. Standards for target definition, dose specification, fractionation (with and without concurrent chemotherapy), and normal tissue constraints should emerge within the next few years.

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¹The majority of the published experience with concurrent chemoradiation has utilized conventional fractionation at 2.0 g per fraction to ≥ 70 Gy in 7 wks with single agent cisplatin given every 3 wks at 100 mg/m². Use of other fraction sizes (eg, 1.8 Gy, conventional), multiagent chemotherapy or altered fractionation with chemotherapy has been evaluated with 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 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 include substantial supportive care.

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

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
### PRINCIPLES OF SYSTEMIC THERAPY (Page 1 of 2)

The choice of chemotherapy should be individualized based on patient characteristics (performance status, goals of therapy).

#### Squamous Cell Cancers

- **Maxillary Sinus, Ethmoid Sinus, Lip, Oral Cavity, Oropharynx, Hypopharynx, Glottic larynx, Supraglottic larynx, Occult Primary**

  **Primary Systemic Therapy + concurrent RT**
  - Cisplatin alone\(^1,2\) (preferred)
  - 5-FU/hydroxyurea\(^3\)
  - Cisplatin/paclitaxel\(^3\)
  - Cisplatin/infusional 5-FU\(^3,4\)
  - Carboplatin/infusional 5-FU\(^5\)
  - Cetuximab\(^6\)

  **Postoperative Chemoradiation**
  - Cisplatin alone\(^7-9\)

  **Induction chemotherapy (followed by chemoradiation)**
  - Docetaxel/cisplatin/5-FU\(^10,11\)

#### Nasopharynx

Chemoradiation followed by adjuvant chemotherapy
- Cisplatin + RT followed by Cisplatin/5-FU\(^12\)

#### Unresectable Recurrent Head and Neck Cancers

**Combination therapy**
- Cisplatin or carboplatin + 5-FU\(^4,13\)
- Cisplatin or carboplatin + taxane\(^4\)
- Cisplatin/cetuximab\(^14\)

**Single agent**
- Carboplatin
- Paclitaxel
- Docetaxel
- 5-FU
- Methotrexate
- Cetuximab\(^15\)
- Ifosfamide
- Bleomycin
- Gemcitabine (nasopharyngeal)

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**See References on page CHEM-A 2 of 2**
REFERENCES


# Staging

## Table 1

**2002 American Joint Committee on Cancer (AJCC)**
**TNM Staging System for the Lip and Oral Cavity**

### Primary Tumor (T)
- **TX**: Primary tumor cannot be assessed
- **T0**: No evidence of primary tumor
- **Tis**: Carcinoma *in situ*
- **T1**: Tumor 2 cm or less in greatest dimension
- **T2**: Tumor more than 2 cm but not more than 4 cm in greatest dimension
- **T3**: Tumor more than 4 cm in greatest dimension
- **T4a** *(oral cavity)*: Tumor invades adjacent structures *(eg, through cortical bone, into deep [extrinsic] muscle of tongue [genioglossus, hyoglossus, palatoglossus, and styloglossus], maxillary sinus, skin of face)*
- **T4b**: Tumor invades masticator space, pterygoid plates, or skull base and/or encases internal carotid artery

*Note: Superficial erosion alone of bone/tooth socket by gingival primary is not sufficient to classify as T4.*

### Regional Lymph Nodes (N)
- **NX**: Regional nodes cannot be assessed
- **N0**: No regional lymph node metastasis
- **N1**: Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
- **N2**: Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
- **N2a**: Metastasis in single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension
- **N2b**: Metastasis in multiple ipsilateral lymph nodes, none

### Distant Metastasis (M)
- **MX**: Distant metastasis cannot be assessed
- **M0**: No distant metastasis
- **M1**: Distant metastasis

### Stage Grouping

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</tr>
</tbody>
</table>

### Histologic Grade (G)
- **GX**: Grade cannot be assessed
- **G1**: Well differentiated
- **G2**: Moderately differentiated
- **G3**: Poorly differentiated

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### Table 2

2002 American Joint Committee on Cancer (AJCC)
TNM Staging System for the Pharynx (Including Base of Tongue, Soft Palate, and Uvula)

#### Primary Tumor (T)
- **TX**: Primary tumor cannot be assessed
- **T0**: No evidence of primary tumor
- **Tis**: Carcinoma in situ

#### Nasopharynx
- **T1**: Tumor confined to the nasopharynx
- **T2**: Tumor extends to soft tissues
- **T2a**: Tumor extends to the oropharynx and/or nasal cavity without parapharyngeal extension*
- **T2b**: Any tumor with parapharyngeal extension*
- **T3**: Tumor invades bony structures and/or paranasal sinuses
- **T4**: Tumor with intracranial extension and/or involvement of cranial nerves, infratemporal fossa, hypopharynx, orbit, or masticator space

*Note: Parapharyngeal extension denotes posterolateral infiltration of tumor beyond the pharyngobasilar fascia.

#### Oropharynx
- **T1**: Tumor 2 cm or less in greatest dimension
- **T2**: Tumor more than 2 cm but not more than 4 cm in greatest dimension
- **T3**: Tumor more than 4 cm in greatest dimension
- **T4a**: Tumor invades the larynx, deep/extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible
- **T4b**: Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery

#### Hypopharynx
- **T1**: Tumor limited to one subsite of hypopharynx and 2 cm or less in greatest dimension
- **T2**: Tumor invades more than one subsite of hypopharynx or an adjacent site, or measures more than 2 cm but not more than 4 cm in greatest diameter without fixation of hemilarynx
- **T3**: Tumor more than 4 cm in greatest dimension or with fixation of hemilarynx
- **T4a**: Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, esophagus, or central compartment soft tissue*
- **T4b**: Tumor invades prevertebral fascia, encases carotid artery, or involves mediastinal structures

*Note: Central compartment soft tissue includes prelaryngeal strap muscles and subcutaneous fat.

#### Regional Lymph Nodes (N)

#### Nasopharynx
The distribution and the prognostic impact of regional lymph node spread from nasopharynx cancer, particularly of the undifferentiated type, are different from those of other head and neck mucosal cancers and justify the use of a different N classification system.

- **NX**: Regional lymph nodes cannot be assessed
- **N0**: No regional lymph node metastasis
- **N1**: Unilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa*
- **N2**: Bilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa*
- **N3**: Metastasis in a lymph node(s)* more than 6 cm and/or to supraclavicular fossa
- **N3a**: More than 6 cm in dimension
- **N3b**: Extension to the supraclavicular fossa**

*Note: Midline nodes are considered ipsilateral nodes.

**Supraclavicular zone or fossa is relevant to the staging of nasopharyngeal carcinoma and is the triangular region originally described by Ho. It is defined by three points: (1) the superior margin of the sternal end of the clavicle; (2) the superior margin of the lateral end of the clavicle, and (3) the point where the neck meets the shoulder. Note that this would include caudal portions of levels IV and V. All cases with lymph nodes (whole or part) in the fossa are considered N3b.

Continued...
## Table 2 - Continued

### Oropharynx and Hypopharynx

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<thead>
<tr>
<th>NX</th>
<th>Regional lymph nodes cannot be assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
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<tr>
<td>N1</td>
<td>Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N2a</td>
<td>Metastasis in a single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N2b</td>
<td>Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N2c</td>
<td>Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in a lymph node more than 6 cm in greatest dimension</td>
</tr>
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### Distant Metastasis (M)

<table>
<thead>
<tr>
<th>MX</th>
<th>Distant metastasis cannot be assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
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### Stage Grouping: Nasopharynx

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<th>M0</th>
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<tr>
<td>Stage IIB</td>
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<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2a</td>
<td>N1</td>
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<tr>
<td></td>
<td>T2b</td>
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<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2b</td>
<td>N1</td>
<td>M0</td>
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<tr>
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<td>N2</td>
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<td></td>
<td>T2a</td>
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<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2b</td>
<td>N2</td>
<td>M0</td>
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</table>

### Stage Grouping: Oropharynx, Hypopharynx

<table>
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<th>N0</th>
<th>M0</th>
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<td>M0</td>
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<td>N1</td>
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<tr>
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</tr>
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<td>T4a</td>
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<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
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<td>T2</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
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### Histologic Grade (G)

- **Oropharynx**
- **Hypopharynx**

<table>
<thead>
<tr>
<th>Grade</th>
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<tbody>
<tr>
<td>G1</td>
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<tr>
<td>G2</td>
<td>Moderately differentiated</td>
</tr>
<tr>
<td>G3</td>
<td>Poorly differentiated</td>
</tr>
</tbody>
</table>

---

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### Table 3

**2002 American Joint Committee on Cancer (AJCC) TNM Staging System for the Larynx**

<table>
<thead>
<tr>
<th>Primary Tumor (T)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma <em>in situ</em></td>
</tr>
</tbody>
</table>

#### Supraglottis

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>Tumor limited to one subsite of supraglottis with normal vocal cord mobility</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (eg, mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, pre-epiglottic tissues, paraglottic space, and/or minor thyroid cartilage erosion (eg, inner cortex)</td>
</tr>
<tr>
<td>T4a</td>
<td>Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)</td>
</tr>
<tr>
<td>T4b</td>
<td>Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures</td>
</tr>
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</table>

#### Glottis

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumor involves both vocal cords</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor involves both vocal cords</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor limited to the larynx with vocal cord fixation and/or invades paraglottic space, and/or minor thyroid cartilage erosion (eg, inner cortex)</td>
</tr>
<tr>
<td>T4a</td>
<td>Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)</td>
</tr>
</tbody>
</table>

#### Subglottis

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>Tumor limited to the subglottis</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor extends to vocal cord(s) with normal or impaired mobility</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor limited to larynx with vocal cord fixation</td>
</tr>
<tr>
<td>T4a</td>
<td>Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)</td>
</tr>
<tr>
<td>T4b</td>
<td>Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures</td>
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#### Regional Lymph Nodes (N)

<table>
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<th>Stage</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N2a</td>
<td>Metastasis in single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N2b</td>
<td>Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension</td>
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<tr>
<td>N2c</td>
<td>Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in a lymph node, more than 6 cm in greatest dimension</td>
</tr>
</tbody>
</table>

#### Distant Metastasis (M)

<table>
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<th>Description</th>
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</thead>
<tbody>
<tr>
<td>MX</td>
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<tr>
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<td>No distant metastasis</td>
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<tr>
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<td>Distant metastasis</td>
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*Continued...*
### Table 3 - Continued

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<thead>
<tr>
<th>Stage Grouping</th>
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<th>M0</th>
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<td>M0</td>
<td><strong>G2</strong></td>
<td>Moderately differentiated</td>
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<td><strong>Stage III</strong></td>
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<td>M0</td>
<td><strong>G3</strong></td>
<td>Poorly differentiated</td>
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<td></td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
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<tr>
<td></td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
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<td>T3</td>
<td>N1</td>
<td>M0</td>
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<td><strong>Stage IVA</strong></td>
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### Table 4

2002 American Joint Committee on Cancer (AJCC)
TNM Staging System for the Major Salivary Glands (Parotid, Submandibular, and Sublingual)

<table>
<thead>
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<th>Primary Tumor (T)</th>
<th>Stage Grouping</th>
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<tbody>
<tr>
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<td>T1 N0 M0</td>
</tr>
<tr>
<td>T0</td>
<td>T2 N0 M0</td>
</tr>
<tr>
<td>T1</td>
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</tr>
<tr>
<td>T2</td>
<td>T4a N0 M0</td>
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<tr>
<td>T3</td>
<td>T4a N1 M0</td>
</tr>
<tr>
<td>T4a</td>
<td>T1 N2 M0</td>
</tr>
<tr>
<td>T4b</td>
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<td></td>
<td>T3 N2 M0</td>
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<tr>
<td></td>
<td>T4a N2 M0</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Regional Lymph Nodes (N)</th>
<th>Stage Grouping</th>
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</thead>
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<tr>
<td>NX</td>
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<td>Any T N3 M0</td>
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<tr>
<td>N1</td>
<td>Any T Any N M1</td>
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<tr>
<td>N2</td>
<td>Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N2a</td>
<td>Metastasis in a lymph node, more than 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N2b</td>
<td>Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in a lymph node, more than 6 cm in greatest dimension</td>
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</table>

*Distant Metastasis (M)*

<table>
<thead>
<tr>
<th>Stage IVA</th>
<th>Stage IVB</th>
<th>Stage IVC</th>
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<tbody>
<tr>
<td>T4a</td>
<td>T4b</td>
<td>Any T</td>
</tr>
<tr>
<td>N0</td>
<td>Any N</td>
<td>N3</td>
</tr>
<tr>
<td>M0</td>
<td>M0</td>
<td>M1</td>
</tr>
</tbody>
</table>

*Note: Extraparenchymal extension is clinical or macroscopic evidence of invasion of soft tissues. Microscopic evidence alone does not constitute extraparenchymal extension for classification purposes.*

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### Table 5

2002 American Joint Committee on Cancer (AJCC) TNM Staging System for the Nasal Cavity and Paranasal Sinuses

#### Primary Tumor (T)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor limited to maxillary sinus mucosa with no erosion or destruction of bone</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor causing bone erosion or destruction including extension into the hard palate and/or middle nasal meatus, except extension to posterior wall of maxillary sinus and pterygoid plates</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor invades any of the following: bone of the posterior wall of maxillary sinus, subcutaneous tissues, floor or medial wall of orbit, pterygoid fossa, ethmoid sinuses</td>
</tr>
<tr>
<td>T4a</td>
<td>Tumor invades anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribiform plate, sphenoid or frontal sinuses</td>
</tr>
<tr>
<td>T4b</td>
<td>Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve (V₂), nasopharynx, or clivus</td>
</tr>
</tbody>
</table>

#### Maxillary Sinus

- T1: Tumor limited to maxillary sinus mucosa with no erosion or destruction of bone
- T2: Tumor causing bone erosion or destruction including extension into the hard palate and/or middle nasal meatus, except extension to posterior wall of maxillary sinus and pterygoid plates
- T3: Tumor invades any of the following: bone of the posterior wall of maxillary sinus, subcutaneous tissues, floor or medial wall of orbit, pterygoid fossa, ethmoid sinuses
- T4a: Tumor invades anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribiform plate, sphenoid or frontal sinuses
- T4b: Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve (V₂), nasopharynx, or clivus

#### Nasal Cavity and Ethmoid Sinus

- T1: Tumor restricted to any subsite, with or without bony invasion
- T2: Tumor invading two subsites in a single region or extending to involve an adjacent region within the nasoethmoidal complex, with or without bony invasion
- T3: Tumor extends to invade the medial wall or floor of the orbit, maxillary sinus, palate, or cribiform plate
- T4a: Tumor invades any of the following: anterior orbital contents, skin of nose or cheek, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid or frontal sinuses
- T4b: Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than (V₂), nasopharynx, or clivus

#### Regional Lymph Nodes (N)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N2a</td>
<td>Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N2b</td>
<td>Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N2c</td>
<td>Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in a lymph node, more than 6 cm in greatest dimension</td>
</tr>
</tbody>
</table>

#### Distant Metastasis (M)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MX</td>
<td>Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

Continued...
### Table 5 - Continued

#### Stage Grouping

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tis</th>
<th>N0</th>
<th>M0</th>
<th>Histologic Grade (G)</th>
<th>Grade cannot be assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
<td>G1</td>
<td>Well differentiated</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
<td>G2</td>
<td>Moderately differentiated</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
<td>G3</td>
<td>Poorly differentiated</td>
</tr>
<tr>
<td>Stage II</td>
<td>T4a</td>
<td>N0</td>
<td>M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>T4a</td>
<td>N1</td>
<td>M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>T1</td>
<td>N2</td>
<td>M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N2</td>
<td>M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N2</td>
<td>M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>T4a</td>
<td>N2</td>
<td>M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>T4b</td>
<td>Any N</td>
<td>M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>N3</td>
<td>M0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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The NCCN Head and Neck (H&N) Cancers guidelines address tumors arising in the lip, oral cavity, oropharynx, hypopharynx, glottic and supraglottic larynx, paranasal (ethmoid and maxillary) sinuses, nasopharynx, and salivary glands, as well as occult primary cancer (see Figure 1). As background to the discussion of these guidelines, a brief overview of the epidemiology and management of H&N cancer is provided.

Incidence and Etiology
Approximately 39,250 new cases of oral cavity, pharyngeal, and laryngeal cancers are estimated to occur in 2005. This accounts for about 3% of new cancer cases in the United States. An estimated 11,090 deaths from H&N cancers will occur in 2005. Alcohol and tobacco abuse are common etiologic factors in cancers of the oral cavity, oropharynx, hypopharynx, and larynx. Moreover, because the entire aerodigestive tract epithelium may be exposed to these carcinogens, patients with H&N cancer are at risk for developing second primary neoplasms of the H&N, lung, and esophagus.

Staging
Stage at diagnosis is the most predictive factor of survival. The TNM staging systems developed by the American Joint Committee on Cancer (AJCC) for the lip and oral cavity, pharynx (nasopharynx, oropharynx, and hypopharynx), larynx, major salivary glands, and nasal cavity and paranasal sinuses are shown in Tables 1, 2, 3, 4, and 5, respectively. The 2002 AJCC staging classification was used as a basis for the NCCN’s treatment recommendations for the pharynx (see Table 2). Definitions for regional lymph node (N) involvement and spread to distant metastatic sites (M) are uniform except for N staging of nasopharyngeal carcinoma. Definitions for staging the primary tumor (T), based on its size, are uniform for the lip and oral cavity as well as the oropharynx. In contrast, T stage is based on subsite involvement and is specific to each subsite for the glottic larynx, supraglottic larynx, hypopharynx, and nasopharynx.

In general, stage I or stage II disease defines a relatively small primary tumor with no nodal involvement. Stage III and stage IV cancers include large primary tumors, which may invade underlying structures and/or spread to regional nodes. Distant metastases are uncommon at presentation. In general, the survival rate of patients with locally advanced (stage III or stage IV) disease is less than 50% of the survival rate of patients with early-stage disease.

Management Approaches
Treating the patient with H&N cancer is complex. Each specific site of disease, the extent of disease, and the pathologic findings dictate the appropriate surgical procedure, radiation fields, dose and
fractionation, and indications for chemotherapy. Single modality treatment with surgery or radiotherapy is generally recommended for the approximately 40% of patients who present with early-stage disease (stage I or stage II). The two modalities result in similar survival in these individuals. In contrast, for the 60% of patients with locally advanced disease at diagnosis, combined modality therapy is generally recommended.

As in other NCCN practice guidelines, participation in clinical trials is emphasized as a preferred or recommended treatment option, particularly for the population with locally advanced disease. In formulating these H&N guidelines, the panel has endeavored to make them evidence based while providing a statement of consensus as to the acceptable range of treatment options.

**Multidisciplinary Team Involvement**

The initial evaluation and development of a plan for treating the patient with H&N cancer require a multidisciplinary team of individuals with expertise in all aspects of the special care needs of these patients. Similarly, managing and preventing sequelae of radical surgery, radiotherapy, and chemotherapy require the involvement of various health care 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 receiving treatment for H&N cancer. Patients should also be encouraged to stop smoking, because smoking decreases the efficacy of treatment. Specific components of patient support and follow-up are listed in the algorithm. Pain and symptom management as well as social work and case management are included in this list because of their importance in addressing the late complications of disease and its therapy. The panel also recommends referring to the NCCN Guidelines for Supportive Care.

**Comorbidity and Quality of Life**

**Comorbidity.** Comorbidity refers to the presence of concomitant disease (in addition to H&N cancer) that may affect the diagnosis, treatment, and prognosis for the patient. Documentation of comorbidity is particularly important in oncology, because the failure to identify comorbid conditions (such as renal, heart, or liver failure) may result in inaccurate attribution of poor outcomes to the cancer. Comorbidity is known to be a strong independent predictor for mortality in H&N cancer patients. Comorbidity has also been shown to influence costs of care, utilization, and quality of life. Numerous indices of comorbidity have been developed. Traditional indices include the Charlson index as well as 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. These tumors have a tremendous effect on basic physiological functions (such as the ability to chew, swallow, and breathe), the senses (taste, smell, and hearing), and uniquely human characteristics (such as appearance and voice). In informal use, the terms health status, function, and quality of life are frequently used interchangeably; however, these terms have important distinctions. Health status describes an individual's physical, emotional, as well as social capabilities and limitations. Function and performance refer to how well an individual is able to perform important roles, tasks, or activities. On the other hand, 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. A recent NIH-sponsored conference recommended the use of patient-completed scales to measure
quality of life. For H&N cancer-specific issues, the three validated measures that have received the most widespread acceptance are: (1) the University of Washington Quality of Life scale (UW-QOL); (2) the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-HN35); and (3) the Functional Assessment of Cancer Therapy Head and Neck module (FACT-HN). A clinician-rated performance scale that has also achieved widespread use is the Performance Status Scale. Numerous other instruments exist to measure generic cancer issues and other aspects of H&N cancer but are beyond the scope of this discussion.

Head and Neck Surgery

Resectable Versus Unresectable Disease

The various site-specific sections of these H&N guidelines pertain to patients with resectable disease. The treatment of patients with locally advanced unresectable disease, metastatic disease, or recurrent disease is addressed in the “Advanced Head and Neck Cancer” section of these guidelines.

The term “unresectable” has resisted formal definition by H&N cancer specialists for decades. No definition of surgical unresectability meets with universal approval. The experience of the surgeon and the support available from reconstructive surgeons, physiatrists, and prosthodontists often strongly influence recommendations. This is particularly common in institutions where few patients with locally advanced H&N cancer 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 doubt their ability to remove all gross tumor on anatomic grounds or if they are certain local control will not be achieved after an operation (even with the addition of radiotherapy to the treatment approach). Typically, such tumors densely involve the cervical vertebrae, brachial plexus, deep muscles of the neck, or carotid artery. Unresectable tumors (i.e., those tumors unable to be removed without imposing unacceptable morbidity) should be distinguished from those tumors in patients whose constitutional state precludes an operation (even if the cancer is 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 were unresectable. Thus, patient choice or a doctor’s expectations regarding cure and morbidity will influence or determine treatment.

Patients with resectable tumors who can also be adequately treated without an operation represent a very important group. Definitive treatment with radiation therapy (RT) alone or RT combined with chemotherapy may represent an equivalent or preferable approaches to resection in these individuals. Although such patients may not undergo surgery, their tumors should not be labeled as unresectable. Their disease is usually far less extensive than disease that truly cannot be removed.

Cervical Lymph Node Dissections

Historically, cervical lymph node dissections have been classified as “radical” or “modified radical” procedures. The less radical procedures preserved the sternocleidomastoid muscle, jugular vein, and spinal accessory nerve. The panel prefers to classify cervical lymphadenectomy differently, 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 are preserved does not affect whether the dissection is comprehensive.

Selective neck dissections have been developed based on an understanding of the common pathways for spread of H&N cancers to regional nodes (see Figure 2).28,29 A supraomohyoid neck dissection is designed to remove the nodes most commonly involved with metastases from the oral cavity. A supraomohyoid neck dissection includes nodes found above the omohyoid muscle (level I, level II, level III, and the superior parts of level V). Similarly, a lateral neck dissection removes the nodes most commonly involved with metastases from the pharynx and larynx. A lateral neck dissection includes nodes in level II, level III, and level IV. H&N squamous cell cancer with no clinical nodal involvement rarely presents with nodal metastasis beyond the confines of an appropriate selective neck dissection (< 10% of the time).30-32 The chief role of neck dissections in these NCCN H&N guidelines is to select patients for possible adjuvant radiotherapy, although there has been some enthusiasm for the use of selective neck dissections as treatment when neck tumor burden is low. In general, patients undergoing selective neck dissection should not have clinical nodal disease. In the guidelines, patients with cervical node metastases who undergo operations are generally treated with comprehensive neck dissections, because often they have disease outside the bounds of selective neck dissections.

The panelists do not agree entirely on the extent of neck dissection needed after definitive radiotherapy (without chemotherapy) has been administered in a preoperative setting to a patient with N2 or N3 disease in the neck. If a complete response has been achieved after radiotherapy for N1 disease, all of the panel members are satisfied with the strategy of observing the patient. Many panelists believe that any patient with a residual mass after radiotherapy should undergo a comprehensive neck dissection, whereas a few of the panelists believe that only removal of the residual mass is necessary (category 3). Similarly, at some institutions, patients with a complete response to radiation of N2 and N3 disease are observed, whereas at other institutions similar patients undergo a comprehensive neck dissection (category 3). Opinions supporting both approaches were strong.

Many factors influence survival and locoregional tumor control in patients with H&N cancer. In most NCCN member institutions, patients with extracapsular nodal spread and/or positive surgical margins receive adjuvant chemoradiotherapy after resection.33-38 Many clinicians also believe that multiple positive nodes (without extracapsular nodal spread) or vascular/lymphatic/perineural invasion are minor adverse features. Patients with massive cancers (even if resected with a seemingly satisfying margin) or with laryngeal tumors that require preoperative tracheotomy are usually treated with postoperative radiotherapy.

Postoperative Management of High-Risk Disease

The role of chemotherapy in the postoperative management of the patient with adverse prognostic risk factors has recently been clarified by two separate multicenter randomized trials68,69 and a combined analysis of data from the two trials.70 The US Intergroup trial R95-01 randomly assigned patients with two or more involved nodes, positive margins, or extracapsular spread of tumor to receive standard postoperative radiotherapy or the same radiotherapy plus
cisplatin 100 mg/m² every 3 weeks for three doses. The European trial was designed using the same treatment but also included as high-risk factors the presence of perineural or perivascular disease and nodal involvement at levels 4 and 5 from an oral cavity or oropharynx cancer. The US trial demonstrated statistically significant improvement in locoregional control and disease-free survival but not overall survival, whereas the European trial found significant improvement in survival as well as the other outcome parameters. To better define risk, a combined analysis of prognostic factors and outcome from the two trials was performed. This analysis demonstrated that patients in both trials with either positive resection margins or extracapsular spread of tumor benefited from the addition of cisplatin to postoperative radiotherapy, whereas those with multiple involved regional nodes without extracapsular spread did not. These publications form the basis for the NCCN recommendations in this updated guideline. Chemoradiation is definitely indicated for risk factors of a microscopic positive margin or extracapsular spread (category 1) and these define major risk factors. The management of patients with multiple nodes only, without extracapsular spread or other adverse risk features was discussed by the panel and a category 2B recommendation given for consideration of chemoradiation. The panel noted that the combined analysis was considered exploratory by the authors because it was not part of the initial protocol design.

Head and Neck Radiotherapy

Radiotherapy for H&N cancer is extremely complex. Only a specially trained team consisting of a radiation oncologist, physicist, dosimetrist, and radiation technologist can achieve optimal results. In addition, modern radiotherapy equipment and techniques should be used. Anatomic, tumor, and clinical circumstances dictate the use of radiation as primary treatment or as an adjuvant to surgery in combination with chemotherapy for H&N cancer. The NCCN radiotherapeutic guidelines are not all inclusive. Much variation in practice exists among various countries and even within different institutions in the same country.

Radiation Doses

Selection of radiation doses depends on the tumor and neck node size, location of the tumor, and clinical circumstances. In general, primary and gross adenopathy require a total of 70 Gy or more at a dosage of 2.0 Gy/day. In contrast, radiation to low-risk nodal stations in the neck requires a total of 50 Gy or more, also at a dosage of 2.0 Gy/day. Postoperative irradiation is recommended based on the tumor stage, tumor histology, and surgical findings after tumor resection. In general, postoperative RT is recommended for minor risk features, including multiple positive nodes (without extracapsular nodal spread) or perineural/lymphatic/vascular invasion. Higher doses of radiation (60-65 Gy) are required for microscopic disease to decrease the chances of locoregional failure because of interruption of the normal vasculature, scarring, and relative hypoxia in the tumor bed.

Fractionation

No single fractionation schedule has proven to be best for all tumors. Historically, most radiation oncology departments in the United States deliver treatment once per day, 5 days per week, at 1.8 to 2.0 Gy/fraction. In recent years, data strongly indicate some squamous cancers can grow rapidly, especially in the face of cell depletion. The upper dose of 2.0 Gy/fraction, delivering 1000 cGy or greater per week, is now the most commonly used dose among the NCCN member institutions. Thus, the guidelines have been revised to indicate that the dose of 2.0 Gy/fraction is preferred, with the
exception of salivary gland tumors, which may have slower cell kinetics. External radiation doses exceeding 75 Gy at conventional fractionation of 1.8 to 2.0 Gy/day may lead to unacceptable normal tissue injury.

Most of the published studies with concurrent chemoradiation have used conventional fractionation at 2.0 Gy per fraction to 70 Gy or more in 7 weeks with single-agent cisplatin given every 3 weeks at 100 mg/m². Use of other fraction sizes (eg, 1.8 Gy, conventional), multiagent chemotherapy, or altered fractionation with chemotherapy has been evaluated, but there is no consensus on the optimal approach. In general, the use of concurrent chemoradiation carries a high toxicity burden, and altered fractionation or multiagent chemotherapy will likely further increase the toxicity burden. 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.

Altered fractionation includes accelerated treatment delivering more than 1000 cGy per week and hyperfractionation. The biological rationale for using hyperfractionation is based on the discovery by Withers and colleagues of a large, consistent difference in repair capacity of late and early responding tissues. Accelerated schedules attempt to compensate for rapid tumor proliferation by compressing the time-dose schedule. During the last decade, a number of phase II trials have suggested an advantage to the use of altered fractionation schemes in various H&N cancers.

Two large, randomized clinical trials have reported improved locoregional control using altered fractionation. The European Organization for Research and Treatment of Cancer (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. At 5 years, there was a statistically significant increase in local control in the hyperfractionation arm (38% versus 56%; \( P = .01 \)) and no increase in late complications. A long-term follow-up analysis has also demonstrated a small survival advantage for hyperfractionation (\( P = .05 \)). Another EORTC protocol (22851) compared accelerated fractionation (1.6 Gy three 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 (excluding cancers of the hypopharynx). Patients in the accelerated fractionation arm did significantly better with regard to locoregional control (\( P = .02 \)) at 5 years. Disease-specific survival showed a trend (\( P = .06 \)) in favor of the accelerated fractionation arm. Acute and late toxicity were increased in this fractionation arm, however, raising questions about the net advantages of accelerated fractionation.

In the United States, the Radiation Therapy Oncology Group (RTOG) has reported preliminary results of a large phase III clinical trial (protocol 90-03) comparing hyperfractionation with two variants of accelerated fractionation. After 2 years of follow-up, both accelerated fractionation with a concomitant boost and hyperfractionation were associated with improved locoregional control and disease-free survival compared with standard fractionation. However, acute toxicity was increased. No significant difference was demonstrated in the frequency of grade 3 or worse late effects reported at 6 to 24 months after treatment start, among the various treatment groups. Consensus regarding altered fractionation schedules with concomitant boost or hyperfractionation for stage III or IV oral cavity, oropharynx, supraglottic larynx, and
Brachytherapy

Brachytherapy is used less often because of improved local control obtained with concurrent chemo/RT. However, brachytherapy still has a role primarily for lip cancer, cancer of the oral cavity, and oropharynx. Several European and North American medical centers have had extensive experience with brachytherapy.\textsuperscript{51-68} The success of brachytherapy techniques is partly dependent on the training, experience, and skills of the implant team.

Intensity-Modulated Radiation Therapy

The intensity of the radiation beam can be modulated in order to decrease doses to normal structures without compromising the doses to the target. Intensity-modulated radiation therapy (IMRT) is an advanced form of 3-D conformal RT with enormous potential to precisely target and to enable escalation of the radiation dose; the net effect is decreased radiation exposure to normal structures. During the past several years, an exponential growth has occurred in the use of IMRT for various malignancies, in particular, prostate and H\&N cancers.

Several institutions have conducted phase II studies to explore the use of beam modulation in H\&N cancer. The objective data from these institutions consistently show a decrease in acute and late toxicities without compromising tumor control.\textsuperscript{60-67} However, no phase III studies have been done to substantiate the results from phase II studies. The RTOG H-0022 and RTOG H-0225 are single-arm studies exploring the feasibility of IMRT in the treatment of oropharyngeal and nasopharyngeal cancer. These trials are currently ongoing. At present, IMRT is not the standard of care for the treatment of H\&N cancers; however, selected patients may benefit from this new technology if they are treated in centers that have expertise in IMRT.

3-D conformal techniques may be used depending on the stage, tumor location, physician training/experience, and available physics support. IMRT techniques are an area of active investigation among the NCCN institutions and others. Target delineation and optimal dose distribution require special training in H\&N imaging, a thorough understanding of patterns of disease spread, and special training in IMRT techniques. Standards for target definition, dose specification, fractionation (with and without concurrent chemotherapy), and normal tissue constraints should emerge within the next few years.

Paranasal Tumors
(Maxillary and Ethmoid Sinus Tumors)

Tumors of the paranasal sinuses are rare and often asymptomatic until late in the course of their disease. Although the most common histology for these tumors is squamous cell carcinoma, multiple histologies have been reported including sarcomas (excluding rhabdomyosarcoma), lymphomas, adenocarcinomas, salivary gland tumors, and esthesioneuroblastomas, and undifferentiated carcinomas. Locoregional control and incidence of distant metastasis are dependent on both T stage and tumor histology. However, T stage remains the most reliable predictor of survival and local regional control (see Table 5).

Management of Incompletely Excised Ethmoid Cancer

Patients with early-stage ethmoid cancer are asymptomatic. These neoplasms are often found after a routine nasal polypectomy or
during the course of a nasal endoscopic procedure. For a patient with gross residual disease who has had a nasal endoscopic surgical procedure, the preferred treatment is complete surgical excision of the residual tumor. This procedure often entails an anterior craniofacial resection to remove the Cribriform plate and to ensure clear surgical margins. Most patients affected by ethmoid sinus cancer present after having had an incomplete excision. The patient who is diagnosed after incomplete excision (e.g., polypectomy, endoscopic surgical procedure)---and has no documented residual disease on physical examination, imaging, and endoscopy---should be treated in a similar fashion if feasible. If no adverse pathologic factors are found, this treatment ensures clear surgical margins and obviates the need for postoperative radiotherapy. However, RT may be used as definitive treatment in patients if pre-biopsy imaging studies and nasal endoscopy demonstrate that the superior extent of the disease does not involve the skull base.

**Treatment of Maxillary Sinus Tumors**

Complete surgical resection for all T stages followed by postoperative therapy remains a cornerstone of treatment. In addition, RT or chemotherapy/RT (category 2B) should be considered for T1-2, N0 tumors with perineural invasion. Neck dissection is indicated in the treatment of the clinically positive neck. Finally, a combination of chemotherapy and RT or definitive RT alone (without chemotherapy) may be used to treat surgically unresectable disease. Patients with maxillary sinus tumors who have adverse characteristics (e.g., positive margins, perineural invasion, or extracapsular nodal spread) should receive surgical resection (if possible) followed by chemotherapy/RT to the primary and neck (category 2B). Participation in clinical trials is favored for patients with malignant tumors of the paranasal sinuses.

**Salivary Gland Tumors**

Salivary gland tumors can arise in the major salivary glands (parotid, submaxillary, or sublingual salivary gland glands) or in one of the minor salivary glands, which are widely spread throughout the aerodigestive tract. Many salivary gland tumors are located on the hard palate. Even though many salivary gland tumors are generally benign, approximately 20% of the parotid gland tumors are malignant; the incidence of malignancy in submandibular and minor salivary gland tumors is approximately 50% and 80%, respectively. These malignant tumors constitute a broad spectrum of histologic types, including mucoepidermoid, acinic, adenocarcinoma, adenoid cystic carcinoma, malignant myoepithelial tumors, and squamous carcinoma. The primary diagnosis of squamous carcinoma of the parotid gland is rare, because most of them are generally metastatic tumors from skin cancers of the temple area. Prognosis and tendency to metastasize vary among these histologic types. Major prognostic factors are histologic grade, tumor size, and local invasion (see Table 4).

**Treatment**

The major therapeutic approach for salivary gland tumors is adequate and appropriate surgical resection. Surgical intervention requires careful planning and execution, particularly in parotid tumor surgery because of the presence of the facial nerve within the gland, which should be preserved if it is not directly involved by the tumor. Most of the parotid gland tumors are located in the superficial lobe, and if the facial nerve is functioning preoperatively, the nerve can be preserved in most patients. The facial nerve should be sacrificed if there is preoperative facial nerve involvement with facial palsy or if there is direct invasion of the tumor into the nerve where the tumor cannot be separated from the nerve. Malignant deep lobe parotid...
tumors are quite rare; however, they are generally a challenge for the surgeon where the patient may require superficial parotidectomy as well as identification and retraction of the facial nerve to remove deep lobe parotid tumor.

Most malignant deep lobe parotid tumors will require postoperative RT because of the limitations of surgical margins in the resection of these tumors. RT is used in an adjuvant setting for tumors with adverse characteristics; chemotherapy/RT (category 2B) can also be considered. Adjuvant radiotherapy is indicated after resection if adverse characteristics are present, such as positive or close margins, neural or perineural infiltration (often seen with adenoid cystic carcinomas), or lymph node metastases. Adjuvant RT is also recommended if the tumor is intermediate or high grade, lymphovascular invasion, or extracapsular spread is present.

For unresectable tumors, RT alone (without chemotherapy) is used as definitive treatment; however, chemoradiation (cisplatin) is also an option (category 2B). The panel was not in agreement regarding chemoradiation, because there are no published trials of this approach for unresectable salivary gland tumors. Chemotherapy may be used for palliation in advanced disease. Various agents (eg, paclitaxel) and combinations (eg, cisplatin, doxorubicin, cyclophosphamide; carboplatin and paclitaxel) have been shown in small series to be active for some salivary gland malignant histologies.

Carcinoma of the Lip

The guidelines for squamous cell carcinoma of the lip generally follow accepted clinical practice patterns established over several decades. No randomized clinical trials have been conducted that can be used to direct therapy. In general, treatment strategies are determined by anticipated functional and cosmetic results. The incidence of lymph node metastases, especially in early-stage lower lip cancer, is low, averaging less than 10%. The risk of lymph node metastases is related to the location, size, and grade of the primary tumor. Elective neck dissection or neck irradiation can be avoided in patients with early-stage disease and a clinically negative neck.

Treatment recommendations are based on clinical stage, medical status of the patient, and patient preference.

Workup and Staging

The workup for patients with squamous cell carcinoma of the lip consists of a physical examination, biopsy, and chest x-ray. A dental Panorex and computerized tomographic (CT) scan or magnetic resonance imaging (MRI) are done if bone invasion is suspected. The AJCC TNM staging system reflects tumor size, extension, and nodal disease (see Table 1). This system does predict the risk for local recurrence. The location of the primary tumor also is predictive. Tumors in the upper lip and commissural areas have a higher incidence of lymph node metastases at the time of diagnosis. Systemic dissemination is rare, occurring in approximately 10% to 15% of patients, most often in those with uncontrolled locoregional disease.

Treatment of the Primary

The treatment of lip cancer is governed by the stage of the disease. The choice of a local treatment modality is based on the expected functional and cosmetic outcome. In early-stage cancers, surgery and radiation are equivalent options in terms of local control. Some very small or superficial cancers are managed more expeditiously with a surgical excision without resultant functional deformity or an undesired cosmetic result. On the other hand, a superficial cancer that occupies most of the lower lip, for example, would be best...
managed with RT. Some advanced lip cancers can cause a great deal of tissue destruction and secondary deformity. Surgery is a more viable option in this clinical setting. Surgery is also the local modality of choice for advanced cancers with extension into the bone. Patients with resectable T3, N0; T4, N0; or any T, N1-3 disease who are a poor surgical risk can be treated with definitive RT or chemotherapy/RT.

Management of the Neck

The management of the neck is also governed by stage, but the location of the tumor should also be taken into account. For example, the lymphatics of the upper lip are very extensive. Thus, tumors in this location are more apt to spread to deep superior jugular nodes. The position of the tumor along the lip also can be helpful in predicting the pattern of lymph node spread. A midline location can place a patient at higher risk for contralateral disease. For patients with advanced disease and an N0 neck, the guidelines recommend a unilateral or bilateral selective neck dissection. When a patient presents with palpable disease, care is taken to ensure all appropriate nodal levels are dissected.

Radiation

Radiotherapy, when used as definitive treatment, may consist of external-beam RT or brachytherapy alone or in combination, depending on the size of the tumor. The dose required also depends on tumor size, but doses of 66 Gy or more are usually adequate to control the disease. For T1 or T2 lesions, the total dose of external-beam RT may be decreased when given in conjunction with brachytherapy. When radiotherapy is given in the adjuvant setting, doses of 60 Gy or more are required, depending on the pathologic features. In both definitive and adjuvant settings, the neck is treated with doses that address major and minor risk features. Patients with positive margins or invasion (perineural, vascular, and/or lymphatic) and T1-2, N0 disease can also be treated with chemotherapy/RT, although the panel disagreed about this recommendation (category 3).

Follow-up/Surveillance

Follow-up for patients with treated cancers of the lip relies solely on periodic physical examinations every 1 to 3 months during year 1, every 2 to 4 months during year 2, every 4 to 6 months during years 3 to 5, and every 6 to 12 months thereafter.

Cancer of the Oral Cavity

The oral cavity includes the following subsites: buccal mucosa, upper and lower alveolar ridge, retromolar trigone, floor of the mouth, hard palate, and anterior two thirds of the tongue. There is a rich lymphatic supply to the area, and initial regional node dissemination is to nodal groups at level I, level II, and level III.

Regional node involvement at presentation is evident in approximately 30% of patients, but the risk varies according to subsite. For example, primaries of the alveolar ridge and hard palate infrequently involve the neck, whereas occult neck metastasis is common (50% to 60%) in patients with anterior tongue cancers. With the exception of patients with T1-2, N0 disease who are treated with definitive radiotherapy (without chemotherapy), all patients undergo some type of neck dissection. The necessity of a bilateral dissection, instead of a unilateral dissection, depends on the assessment of risk of contralateral nodal involvement.

Workup and Staging

Imaging studies to evaluate mandibular involvement and a careful dental evaluation are particularly important for staging (see Table 1) and planning therapy for oral cavity cancers in addition to a physical
examination, biopsy, and chest x-ray; chest CT should be considered for patients at high risk for thoracic metastases.

**Treatment**

Surgery and RT represent the standards of care for early-stage and locally advanced resectable lesions in the oral cavity. The specific treatment is dictated by the TN stage and, if N0 at diagnosis, by the risk of nodal involvement. Multidisciplinary team involvement is particularly important for this site because of the critical physiologic functions of mastication, deglutition, and articulation of speech, which may be affected. Most panelists prefer surgical therapy for resectable oral cavity tumors. Advances in reconstruction using microvascular techniques have led to improved functional outcomes for patients with locally advanced disease.

Postoperative chemotherapy/RT is recommended (category 1) for patients who have oral cavity tumors that are T1-2, N0 with major adverse features. Major risk features include extracapsular nodal spread and/or positive margins. Patients with resectable T3, N0 lesions or those with resectable T1-3, N1-3 lesions can receive postoperative chemotherapy/RT (category 1) if they have major adverse features. Treatment with either chemotherapy/RT or RT only is reserved for patients with unresectable locally advanced, metastatic, or recurrent disease (see “Advanced Head and Neck Cancer”). The concept of organ preservation using chemotherapy in the initial management of locally advanced resectable disease has not been studied in trials specifically designed for this site. Chemotherapy/RT is included in the guidelines as a treatment option for patients with resectable T4, any N lesions; however, this recommendation is category 3 because of strong disagreement among panel members.

**Follow-up/Surveillance**

Follow-up for patients with treated cancers of the oral cavity consists of periodic physical examinations, chest imaging as clinically indicated, and, if the thyroid was irradiated, measurement of the thyrotropin (TSH) level every 6 to 12 months. Speech & swallowing evaluation and rehabilitation may be useful, as indicated.

**Cancer of the Oropharynx**

The oropharynx includes the base of the tongue, tonsils, soft palate, and posterior pharyngeal wall. The oropharynx is extremely rich in lymphatics. Depending on the subsite involved, 15% to 75% of patients present with lymph node involvement. Efforts to improve the outcome of patients with locally advanced disease are ongoing. Participation in clinical trials is strongly recommended.

**Workup and Staging**

A multidisciplinary consultation is encouraged. Accurate staging depends on a thorough physical examination coupled with appropriate imaging studies. Chest CT should be considered for patients at high risk for thoracic metastases. CT with contrast or MRI is recommended for the primary and the neck. Examination of the H&N region should include an examination under anesthesia with laryngoscopy and pharyngoscopy. Bronchoscopy and esophagoscopy are also recommended because of the relative frequency of simultaneous second primaries. A dental evaluation is recommended, with Panorex studies as indicated. Speech and swallowing evaluation may be useful, as indicated.

**Treatment**

The treatment algorithm has been divided into three staging categories: (1) T1-2, N0-1; (2) T3-4, N0; and (3) any T3-4, N+ or any
T, N2-3. Early-stage tumors (T1-2, N0-1) of the tonsil and base of tongue are treated with definitive radiotherapy without chemotherapy (preferred [category 2B]), concurrent chemotherapy/RT (category 2B) for T1-T2, N1 only, or excision of primary with or without unilateral or bilateral neck dissection; the choice of therapy depends on functional issues. Surgery is also reserved for salvage in cases of residual or recurrent disease. Radiotherapy is an option for patients with one positive node (without adverse features). Chemotherapy/RT (eg, carboplatin and 5-FU) is recommended (category 1) for major adverse features.\(^7\) Major risk features include extracapsular nodal spread and/or positive margins.

More advanced disease (T3-4, N0) in the absence of neck adenopathy can be approached using three pathways: (1) concurrent chemotherapy (eg, carboplatin plus 5-fluorouracil [5-FU]) and radiotherapy (category 1) is preferred (salvage surgery is used for managing residual or recurrent disease);\(^7\) (2) surgery plus chemotherapy and radiotherapy for adverse features; or (3) multimodality clinical trial of induction chemotherapy followed by concurrent chemotherapy/RT that includes function evaluation or induction chemotherapy followed by chemo/RT off protocol (category 3).\(^7\)\(^-\)\(^73\)

Three pathways are shown for patients with any T3-4 stage and with positive nodes or any T, N2-3; concurrent chemotherapy/RT (category 1) is preferred.\(^7\) For the concurrent chemotherapy/RT approach, all patients are evaluated for response in the primary site and in the neck. For patients who achieve a complete response in the primary and the neck, the algorithm is divided into initial N1 and initial N2-3 neck disease. Patients with N1 disease are observed. There is controversy about whether patients with more advanced neck disease who achieve a complete response should be observed or undergo a planned neck dissection; both options are provided in the algorithm. There is major disagreement among panelists regarding the type of neck dissection required (category 3 for selective versus comprehensive). Patients who achieve a complete response in the primary but have residual neck disease proceed to neck dissection. Again, there is major disagreement among panelists regarding the type of neck dissection to be performed (category 3 for selective versus comprehensive). Patients with residual tumor in the primary should be offered salvage surgery with neck dissection as indicated.

Concurrent chemoradiotherapy is preferred (category 1) for treatment of locally advanced (T3-4 or N2-3) cancer of the oropharynx. The status of induction chemotherapy added to chemoradiotherapy is an area of controversy for the NCCN panel. The vast majority of randomized trials of induction chemotherapy followed by radiotherapy or surgery (which were published in the 1980s and 1990s) did not demonstrate a survival advantage. Induction chemotherapy had no effect on local control; however, in many trials, it did reduce the distant metastatic rate. A rationale for reevaluating induction chemotherapy added to concurrent chemoradiotherapy is to reduce distant metastases as a site of failure now that improved local control can be achieved with concurrent chemoradiotherapy. Results from two phase III trials that compared induction cisplatin plus infusional 5-FU with or without the addition of a taxane (docetaxel) showed significantly improved response rates with the three drugs compared to two drugs.\(^73\)\(^,\)\(^74\)

Thus, improved chemotherapy regimens may be another reason to reevaluate this approach. The NCCN panel uniformly agreed that clinical trials should be performed to directly answer the question of whether or not induction chemotherapy added to chemoradiotherapy...
improves survival in patients with locally advanced cancer of the oropharynx and other specified sites. Such trials are in progress, and the panel members uniformly agreed that patients should be enrolled in these trials. The panel members differed in their opinion as to whether or not this treatment should be considered a standard treatment option off protocol. A small minority of panel members do advocate this approach off protocol. This disagreement is reflected by a category 3 recommendation in the algorithms.

Altered fractionation is preferred when radiotherapy is used definitively for selected T1, N1 or T2, N0-1 tumors. For patients not receiving concurrent chemoradiation, altered fractionation is preferred. The recommended schedules are: (1) concomitant boost accelerated radiotherapy consisting of 72 Gy delivered over 6 weeks using 1.8 Gy/fractions to the large volume and 1.5 Gy boost as the second daily fraction 6 hours later during the last 12 treatments to a smaller volume; or (2) hyperfractionation consisting of 81.6 Gy given in 7 weeks with 1.2 Gy/fractions twice daily 6 hours apart. This change from standard radiotherapy for large lesions was made on the basis of the results of the RTOG 9003 protocol, which detected a local control advantage for patients who were treated with hyperfractionation and concomitant boost versus those treated with standard fractionation or accelerated fractionation with a break in the treatment schedule. Increased acute toxicity was demonstrated in both altered fractionation schedules when compared with standard radiotherapy. The concomitant boost schedule resulted in prolongation of acute symptoms 6 to 24 months after the initiation of treatment, but no significant difference was demonstrated in the frequency of late effects among schedules. In addition to the RTOG trial, four other randomized trials have demonstrated improved outcomes with hyperfractionation.

Salvage Surgery
Patients with advanced carcinoma of the oropharynx who undergo nonsurgical treatment, such as a combination of concurrent chemotherapy and RT, need very close follow-up both to evaluate the primary for local recurrence and to assess for ipsilateral or contralateral neck recurrence. The patients who do not respond completely to chemoradiation therapy require salvage surgery to the primary and the neck. However, all the panelists emphasized the difficulties in following these patients to detect local or regional recurrence. The radiation-related changes may mask local recurrence, resulting in a delay in diagnosing local or regional recurrence. All the panelists also emphasized the high incidence of complications related to salvage surgery and that laryngectomy is occasionally required to obtain clear surgical margins or to prevent aspiration in patients with advanced oropharyngeal cancer. 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. The patients requiring salvage laryngectomy may have high incidence of pharyngocutaneous fistula and may require either a free flap reconstruction of the laryngopharyngeal defect or if the pharynx can be closed primarily, buttressing the suture line with myocutaneous flap.

Follow-up/Surveillance
The follow-up of patients treated for oropharyngeal cancer continues to rely on physical examination. Chest imaging is recommended as clinically indicated as surveillance for second primary tumors. Patients whose thyroid gland has been irradiated should have TSH levels monitored every 6 to 12 months. Speech and swallowing evaluation and rehabilitation should be done as indicated.
Cancer of the Hypopharynx

The hypopharynx extends from the superior border of the hyoid bone to the lower border of the cricoid cartilage and is essentially a muscular, lined tube extending from the oropharynx to the cervical esophagus. For staging purposes, the hypopharynx is divided into three areas: (1) the pyriform sinus (the most common site of cancer in the hypopharynx); (2) the lateral and posterior pharyngeal walls; and (3) the postcricoid area.

Workup and Staging

A multidisciplinary consultation is encouraged. Accurate staging depends on a thorough physical examination coupled with appropriate imaging studies. Chest CT should be considered for patients at high risk for thoracic metastases. Examination of the H&N region should include an examination under anesthesia with laryngoscopy and pharyngoscopy. Bronchoscopy and esophagoscopy are also recommended because of the relative frequency of simultaneous second primaries. A dental evaluation is recommended, with Panorex studies as indicated. At the time of diagnosis, approximately 60% of patients with cancer of the hypopharynx have locally advanced disease with spread to regional nodes. Furthermore, autopsy series have shown a high rate of distant metastases (60%) involving virtually every organ. Thus, the prognosis for patients with cancer of the hypopharynx is quite poor. Despite standard radical surgery and radiotherapy, the persistent or recurrent locoregional disease, as well as distant dissemination, contribute to the poor outcome for these patients. Speech and swallowing evaluation should be performed in most patients.

Treatment

Patients with resectable disease are divided into two groups: those patients with early-stage cancer (most T1, N0-1; small T2, N0) who do not require a total laryngectomy and those patients with advanced resectable cancer (T1, N2-3; T2-4, any N) who do require laryngectomy. The surgery and radiotherapy options for the former group represent a consensus among the panel members. For patients treated initially with definitive RT (without chemotherapy), surgery is indicated for residual neck disease (category 3 recommendation for a selective versus comprehensive neck dissection). For patients with a complete response of the neck, observation is recommended.

Patients with more advanced disease (defined as T1, N2-3; T2-3, any N) (see Table 2) requiring total laryngectomy and partial or total pharyngectomy may be managed with (1) induction chemotherapy (category 1);77 (2) surgery; (3) concurrent chemoradiation (category 2B); or (4) multimodality clinical trial of induction chemotherapy followed by concurrent chemoradiation that includes function evaluation. The panel uniformly supports the recommendation of induction chemotherapy (category 1) followed by RT if a complete response is achieved at the primary site for patients with (1) T1, N2-3, or (2) T2-3, any N disease.77 Induction regimens include (1) docetaxel, cisplatin, and 5-FU (TPF);74,78 or (2) carboplatin and paclitaxel.72 Given the functional loss resulting from this surgery and the poor prognosis, participation in clinical trials is emphasized.

The recommendation of the induction chemotherapy (cisplatin and 5-FU)/definitive radiotherapy option is based on the results of an EORTC randomized trial.77 This trial enrolled 194 eligible patients with stage II, stage III, or stage IV resectable squamous cell carcinoma of the pyriform sinus (152 patients) and aryepiglottic fold (42 patients), excluding patients with T1 or N2c disease. Patients were randomly assigned either to laryngopharyngectomy and postoperative radiotherapy, or to chemotherapy with cisplatin and 5-
FU for a maximum of three cycles, followed by definitive radiotherapy. In contrast to a similar regimen used for laryngeal cancer, a complete response to induction chemotherapy was required in order to proceed with definitive radiotherapy. The published results showed equivalent survival, with median survival duration and 3-year survival rate of 25 months and 43%, respectively, for the surgery group versus 44 months and 57%, respectively, for the induction chemotherapy group. A functioning larynx was preserved in 42% of patients who did not undergo surgery. Local or regional failure rates did not differ between the surgery-treated patients and chemotherapy-treated patients, although the chemotherapy recipients did demonstrate a significant reduction in distant metastases as a site of first failure ($P = .041$). Adherence to the requirements for complete response to chemotherapy and for inclusion of only patients with the specified TN-stage are emphasized. As noted in the algorithm, surgery is recommended if less than a partial response occurs after three cycles of induction chemotherapy. If there are no adverse features, then RT is recommended. Chemotherapy/RT (category 1) is recommended for major adverse features (such as extracapsular nodal spread and/or positive margins). For minor risk features (multiple positive nodes or perineural/lymphatic/vascular invasion), RT or chemotherapy/RT (multiple positive nodes only [category 2B]) is recommended. If a complete response is achieved, definitive RT is recommended. If a complete response is achieved after definitive RT, observation is recommended.

Options for patients with T4, any N disease include (1) surgery followed by chemotherapy/RT (category 1) \(^ {68,70}\); (2) multimodality clinical trial of induction chemotherapy followed by concurrent chemo/RT that includes function evaluation; or (3) concurrent chemoradiation (category 3).

**Follow-up/Surveillance**

The recommended schedule of follow-up evaluations for patients with cancer of the hypopharynx is the same as for patients with cancer of the oropharynx.

**Occult Primary Cancer**

When patients present with metastatic tumor in a neck node and no primary site can be identified after appropriate investigation, the tumor is defined as an “occult” or unknown primary cancer; this is an uncommon disease, accounting for about 5% of patients presenting to referral centers. H&N cancer of unknown primary site is a highly curable disease. After appropriate evaluation and treatment, most patients experience low morbidity and many will be cured. The primary tumor becomes apparent on follow-up only in a few cases. Patients and oncologists are often concerned when the primary cancer cannot be found. This concern may lead to intensive, fruitless, and costly diagnostic maneuvers.

Most patients older than 40 years who present with a neck mass prove to have metastatic cancer. The source of the lymphadenopathy is almost always discovered in the course of a complete H&N examination, which should be performed on all patients with neck masses before other studies are initiated. Antecedent history of malignancy as well as prior excision, destruction, or regression of cutaneous lesions, should be assessed during office evaluation.

**Workup**

When patients present with a neck mass, fine-needle aspiration (FNA) should be the first study undertaken. Needle aspiration generally guides management and treatment planning. Core or open
biopsy should be avoided, because it may alter or interfere with subsequent treatment. When a needle biopsy demonstrates squamous cell carcinoma, adenocarcinoma, or anaplastic epithelial cancer and no primary site has been found, additional studies are needed. Nasopharyngolaryngoscopy, chest x-ray, and either CT scan with contrast or MRI with gadolinium should be performed. A PET scan should only be done if other tests do not reveal a primary. PET can be used to confirm clinical impressions, detect an unknown primary, and for surveillance. Other imaging studies have very low yield and should not be undertaken. If the FNA proves nondiagnostic, then core or open biopsy may be needed. Open biopsy should not be performed unless the patient is prepared for definitive surgical management of the malignancy documented in the operating room. This management may entail a formal neck dissection. Therefore, an open biopsy of an undiagnosed neck mass should not be undertaken lightly, and patients should be thoroughly apprised of the potential sequelae.

When the imaging studies and thorough office examination (including examination of the nasopharynx, oropharynx, larynx, and hypopharynx as well as attention to the skin) do not reveal a primary tumor, then an examination under anesthesia should be performed. Mucosal sites should be inspected and examined. Appropriate endoscopies with directed biopsies of likely primary sites are recommended, but they seldom disclose a primary cancer. Many primary cancers are identified after tonsillectomy. However, the clinical significance of such tumors is uncertain. When patients have been treated without tonsillectomy, only a few develop a clinically significant primary tumor.

**Treatment**

Comprehensive neck dissection (including level I through level V) is recommended for all patients with squamous cell carcinoma and adenocarcinoma. If the metastatic adenocarcinoma presents high in the neck, parotidectomy may be included with the neck dissection. NCCN member institutions have irreducible differences of opinion regarding the management of patients with poorly differentiated or nonkeratinizing squamous cell, anaplastic cancer of unknown primary site, or other uncommon histologies. Some members believe such patients should be managed with neck dissection, whereas others believe primary RT (category 3) or even chemoradiation (category 3) should be used. If an N1 node was excised in an open biopsy, then all NCCN institutions use elective radiation to the neck although some would radiate the neck only (category 3), whereas most institutions would also radiate the likely occult primary sites based on the level of nodes involved. If extracapsular nodal spread was present or if the patient presented with N2 or N3 disease, then all NCCN institutions use elective radiation to the neck although some would radiate the neck only (category 3), whereas most institutions would also radiate the likely occult primary sites based on the level of nodes involved; chemotherapy/RT is also an option (category 2B). Additional treatment of possible mucosal primary sites is controversial and the source of much disagreement. There is little evidence to support a survival benefit from radiation to all possible primary sites.

**Cancer of the Larynx**

The larynx is divided into three regions: supraglottis, glottis, and subglottis. The distribution of cancers is as follows: 30% to 35% in the supraglottic region, 60% to 65% in the glottic region, and 5% in the subglottic region. The AJCC staging classification for laryngeal primary tumors is determined by the number of subsites involved, vocal cord mobility, and the presence of metastases (see Table 3).
The incidence and pattern of metastatic spread to regional nodes varies with the primary region. More than 50% of patients with supraglottic primaries present with spread to regional nodes because of an abundant lymphatic network that crosses the midline. Bilateral adenopathy is not uncommon with early-stage primaries. Thus, supraglottic cancer is often locally advanced at diagnosis. In contrast, the lymphatic drainage of the glottis is sparse and early-stage primaries rarely spread to regional nodes. Because hoarseness is an early symptom, most glottic cancers are in an early stage at diagnosis. Thus, glottic cancers have an excellent cure rate---in the range of 80% to 90%. As with other cancers of the H&N, nodal involvement decreases survival rates by approximately 50%.

Workup and Staging

The evaluation of the patient to determine tumor stage is similar for glottic and supraglottic primaries. In both sites, the algorithms now explicitly recommend CT scan with contrast and thin cuts through the larynx, or MRI of the primary and neck. These imaging tests are considered particularly important to accurately stage the patient's tumor. Chest CT should be considered for patients at high risk for thoracic metastases. A barium esophagram is recommended for patients with subglottic tumors; speech and swallowing evaluation as well as a dental evaluation should be done if indicated. Multidisciplinary consultation is particularly important for both sites because of the potential for loss of speech and, in some instances, for swallowing dysfunction.

Treatment

The treatment of patients with laryngeal cancer is divided into three categories: (1) tumors of the glottic larynx, (2) tumors of the supraglottic larynx without positive nodes (N0), and (3) tumors of the supraglottic larynx with positive nodes (N+).

For patients with severe dysplasia or carcinoma in situ of the larynx, recommended treatment options include endoscopic removal (stripping, laser, or photodynamic therapy) or RT. NCCN also encourages participation in clinical trials. For invasive cancer, surgery (partial laryngectomy through either endoscopic or open approaches) and radiotherapy are equally effective for early-stage glottic or supraglottic cancers. The choice of treatment modality depends on functional outcome, the patient's wishes, reliability of follow-up, and general medical condition.

Management of the neck is dictated by the risk of occult nodal spread. Participation in clinical trials is preferred for patients with locally advanced laryngeal cancer requiring total laryngectomy. Resectable, advanced-stage supraglottic and glottic primaries can be managed surgically with a combined modality approach consisting of either (1) total laryngectomy, or (2) concurrent chemoradiation (preferred, category 1). In patients with laryngeal cancer, radiotherapy with concurrent administration of cisplatin is superior either to induction chemotherapy followed by radiotherapy or to radiotherapy alone for laryngeal preservation and locoregional control. Selected cases can be managed with conservation surgical techniques that preserve vocal function.

The panel recommends two nonsurgical approaches for patients with locally advanced disease desiring laryngeal preservation. The first option is treatment with concurrent chemoradiation consisting of cisplatin 100 mg/m² on days 1, 22, and 43 and radiotherapy; the second option is definitive RT (without chemotherapy) for patients who are medically unfit or refuse chemotherapy. Surgery is reserved for managing the neck as indicated, for those patients whose disease persists after radiotherapy, or those patients who develop a subsequent locoregional recurrence.
The panel has updated its recommendations for managing locally advanced, resectable glottic and supraglottic cancers requiring laryngectomy to reflect the results of Intergroup trial R91-11. Before 2002, either induction chemotherapy with cisplatin/5-FU followed by radiotherapy or definitive radiotherapy alone (without chemotherapy) were the standard of care options recommended in the NCCN H&N guidelines based on the results of the Veterans Administration (VA) Laryngeal Cancer Study Group trial published in 1991. In the 2002-2005 versions of the guidelines, concurrent radiotherapy and cisplatin 100 mg/m² is the recommended option for achieving laryngeal preservation. R91-11 was a successor trial to the Veterans Administration trial and compared three non-surgical regimens: (1) induction cisplatin/5-FU followed by RT (control arm and identical to that in the VA trial); (2) concurrent RT and cisplatin 100 mg/m² days 1, 22, and 43; and (3) RT alone. Radiotherapy was uniform in all three arms, 70 Gy/7 wks, 2 Gy/fx. Laryngectomy was used for salvage of treatment failures in all arms. Stage III and IV (M0) patients were eligible, excluding T1 primaries and high-volume T4 primaries (tumor extending more than 1 cm into the base of tongue or tumor penetrating through cartilage). The key findings of the trial were a statistically significant higher 2-year laryngeal preservation (local control) rate for concurrent RT with cisplatin, 88%, compared to 74% with induction chemotherapy and to 69% with RT alone; no significant difference in laryngeal preservation between induction and RT alone treatments; and similar survival for all treatment groups. These R91-11 results now change the standard of care to concurrent RT and cisplatin (category 1, preferred) for achieving laryngeal preservation for most T3, N0 and T4, N0 supraglottic cancers and for most T3, any N glottic cancers.

For patients with glottic T4 tumors, the standard approach is a laryngectomy with ipsilateral thyroidectomy and neck dissection as indicated. For selected patients with glottic T4 tumors, the panel recommends clinical trials testing function-preserving surgical or nonsurgical approaches.

For managing T4 supraglottic primaries, the panel made a distinction between (1) high-volume, base-of-tongue involvement (> 1 cm) or tumor penetration through cartilage; and (2) low-volume disease with cartilage penetration on imaging or 1 cm or less extension into the base of the tongue. This later category of T4 supraglottic patients was eligible for Intergroup trial R91-11. The committee prefers nonsurgical, larynx-preserving treatment with concurrent RT and chemotherapy (category 1) for patients with low-volume disease whose tumor does not penetrate through cartilage.

In contrast, the recommended options for those with high-volume T4, N+ disease (eg, cartilage destruction, skin involvement, massive invasion of the base of the tongue) are either (1) laryngectomy, ipsilateral thyroidectomy with ipsilateral or bilateral neck dissection; or (2) a clinical trial. Definitive radiotherapy alone (without chemotherapy) is reserved for patients in the poor medical risk category.

**Follow-up/Surveillance**

It is particularly important for nonsurgically treated patients to have careful and regular follow-up examinations by a trained H&N surgical oncologist so that any local or regional recurrence is detected early, and salvage surgery (and neck dissection as indicated) is performed. Follow-up examinations in many of these patients need to be supplemented with serial endoscopy or high-resolution, advanced radiologic imaging techniques because of the scarring, edema, and fibrosis that occur in the laryngeal tissues and neck after high-dose radiation. Speech & swallowing evaluation and rehabilitation may be useful, as indicated.
Carcinoma of the Nasopharynx

Carcinoma of the nasopharynx is uncommon in the United States. Among H&N cancers, it has the highest propensity to metastasize to distant sites. Nasopharyngeal cancer also poses a significant risk for isolated local recurrences after definitive radiation (without chemotherapy) for locally advanced disease. Oddly enough, regional recurrences are uncommon in this disease, occurring in only 10% to 19% of patients.

The NCCN H&N guidelines for the evaluation and management of carcinoma of the nasopharynx attempt to address risk for both local and distant disease. RT was the standard treatment for all stages of this disease, until the mid-1990s, when trial data showed improved survival for locally advanced tumors treated with concurrent RT and cisplatin.

Stage is accepted as prognostically important. The prognostic significance of histology is still controversial. Several retrospective reviews indicated local control and survival appear to depend on histologic subtypes, whereas one study found no association between histology and these outcomes. The World Health Organization (WHO) classification for nasopharyngeal cancer is used most often. Type 1 represents well to moderately well-differentiated squamous cell cancers. Type 2 denotes nonkeratinizing tumors, including transitional carcinoma and lymphoepithelioma. Type 3 represents undifferentiated carcinomas, including lymphoepithelioma, anaplastic, clear cell, and spindle cell variants.

Workup and Staging

The workup of nasopharyngeal cancer includes a history, physical examination, nasopharyngeal examination and biopsy, dental evaluation, and appropriate diagnostic imaging studies (eg, MRI and/or CT with contrast). These studies are important to determine the full extent of tumor in order to assign stage appropriately and to design radiation ports that will encompass all the disease with appropriate doses. A chest x-ray should also be obtained. Chest CT should be considered for patients at high risk for thoracic metastases. Multidisciplinary consultation is encouraged. The 2002 AJCC staging classification is used as the basis for treatment recommendations (see Table 2). For patients with WHO class 2-3/N2-3 disease, imaging for distant metastases (ie, chest, liver, bone) may include PET scan and/or CT.

Treatment

Treatment options are subdivided according to T, N, and M status, rather than by stage alone. Patients with early-stage nasopharyngeal tumors (T1, N0, M0, and selected T2a, N0, M0 tumors) may be treated with definitive RT alone (without chemotherapy) to the nasopharynx, with elective radiation to the neck. The local control rate for these tumors ranges from 80% to 90%, whereas T3-4 tumors have a control rate of 30% to 65%.

The combination of RT and platinum-based chemotherapy has been shown to increase the local control rate from 54% to 78%. The Intergroup trial 0099, which randomly assigned patients to chemotherapy plus external-beam RT versus external radiation alone, closed early when an interim analysis disclosed a significant survival and progression-free survival advantage favoring the combined chemotherapy and radiation group. The addition of chemotherapy also decreased local, regional, and distant recurrence rates. A similar randomized study conducted in Singapore, which was modeled after the Intergroup treatment regimen, continued to show the benefit of the addition of
Chemotherapy to radiation therapy. Adjuvant chemotherapy after combined chemotherapy and radiation was also given in this trial.\textsuperscript{92} In addition, the administration of the cisplatin dose was spread out over several days, and this regimen appeared to reduce toxicity while still providing a beneficial antitumor effect.

The guidelines recommend combined chemotherapy plus radiotherapy for T1, N1-3; and for T2b-4, any N lesions (stages IIB, III, IVA, IVB). The scheduling and doses of chemotherapy are those used in the intergroup trial 0099. Although an unusual occurrence, a patient with residual disease in the neck and a complete response at the primary should undergo a neck dissection. Initial therapy for patients who present with metastatic disease (stage IV) should consist of a platinum-based combination chemotherapy regimen. If a complete response is achieved, definitive RT alone (without chemotherapy) should be administered to the primary tumor and neck area. For early-stage cancer, radiation doses of at least 70 Gy given with standard fractions are necessary for control of gross tumor. In patients with metastatic carcinoma who have failed platinum-based therapy, a triplet-based combination using paclitaxel, carboplatin, and gemcitabine may be useful.\textsuperscript{93} Likewise, cetuximab plus carboplatin may be useful for patients with recurrent or metastatic nasopharyngeal cancer who have failed platinum-based therapy;\textsuperscript{94} cetuximab monotherapy has also been used in these patients.\textsuperscript{95}

**Follow-up/Surveillance**

For patients whose nasopharyngeal cancer has been treated, the recommended follow-up includes periodic physical examination and an assessment of thyroid function (ie, the TSH level should be determined every 6 to 12 months). Increased TSH levels have been detected in 20% to 25% of patients who received neck irradiation.\textsuperscript{96} Speech & swallowing evaluation and rehabilitation may be useful, as indicated.

**Advanced Head and Neck Cancer**

Advanced H&N cancer includes newly diagnosed but unresectable disease (see “Head and Neck Surgery”), recurrent disease, and metastatic disease. The treatment goal for patients with newly diagnosed but unresectable disease is cure. For the recurrent disease group, the goal is cure (if surgery or radiation remains feasible) or palliation (if the patient has received previous radiotherapy and the disease is unresectable). The goal for patients with metastatic disease is palliation or prolongation of life.

**Treatment**

Participation in clinical trials is preferred for all patients with advanced H&N cancer. For patients with unresectable disease, such trials include testing altered fraction radiotherapy schedules, concurrent chemoradiotherapy, and novel radiosensitizers. For patients with recurrent disease not amenable to curative therapy and patients with metastatic disease, studies include trials of new agents and re-irradiation.

**Unresectable Disease.** For patients with a performance status (PS) of 0 or 1, the standard treatment of newly diagnosed, unresectable disease is concurrent cisplatin (single agent) or carboplatin-based chemotherapy and radiotherapy.\textsuperscript{97} The panel disagreed regarding whether induction chemotherapy (cisplatin) followed by RT should be used (category 3) for patients with a PS of 0 or 1. For those with a PS of 2, the recommended treatment is generally radiotherapy alone; again, the panel disagreed about using induction chemotherapy followed by RT (category 3). For those with PS of 3,
the recommended treatment is generally radiotherapy alone or, in some cases, best supportive care. Altered fractionation (hyperfractionation or concomitant boost) regimens are preferred for RT alone in patients who are medically unfit or who refuse chemotherapy. Many randomized trials and meta-analyses of clinical trials demonstrate significantly improved overall survival, disease-free survival, and local control when concomitant or alternating chemotherapy and radiation is compared with radiotherapy alone. All combined chemoradiotherapy regimens are associated with various degrees of enhanced mucosal toxicities, which require close patient monitoring, ideally provided by a team experienced in treating H&N cancer patients. The various single-agent chemoradiotherapy regimens have not been directly compared in randomized trials. Therefore, no optimal standard regimen is defined. Single-agent cisplatin plus RT is effective and relatively easy to administer. In a phase III randomized trial, cetuximab-based chemoradiotherapy improved locoregional control and overall survival in patients with stage III/IV head and neck cancer. A randomized phase II study in patients with advanced H&N (oral cavity, oropharynx, or hypopharynx) found that cisplatin plus paclitaxel appeared to yield better overall survival than either cisplatin plus 5-FU or hydroxyurea and 5-FU, although statistical comparisons were not possible. A study in patients with recurrent H&N found no difference in survival when comparing cisplatin plus 5-FU versus cisplatin plus paclitaxel. Other regimens using combination therapy include carboplatin plus 5-FU and cetuximab plus cisplatin. Most of the published studies with concurrent chemoradiation have used conventional fractionation at 2.0 g per fraction to 70 Gy or more in 7 weeks with single-agent cisplatin given every 3 weeks at 100 mg/m². Use of other fraction sizes (eg, 1.8 Gy, conventional), multiagent chemotherapy, or altered fractionation with chemotherapy has been evaluated, but there is no consensus on the optimal approach. In general, the use of concurrent chemoradiation carries a high toxicity burden, and 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 aggressive supportive care.

Recurrent Disease. Surgery is recommended for resectable recurrent disease, usually followed by radiation if it has not yet been administered. If the recurrence is unresectable and the patient did not have prior RT, then radiotherapy with concurrent cisplatin or carboplatin-based chemotherapy is recommended for patients with PS of 0 or 1. For patients with recurrent disease not amenable to curative-intent radiation or surgery, treatment is similar to the treatment for patients with metastatic disease. For select patients, re-irradiation in a clinical trial may be appropriate.

Squamous cell carcinomas emerge after the accumulation of multiple genomic events. In a multistep process, there appear to be essential molecular alterations, which confer a survival advantage for cancer cells. The epidermal growth factor receptor (EGFR) is a transmembrane glycoprotein, activation of which triggers a cascade of downstream intracellular signaling events important for regulation of epithelial cell growth. Overexpression of EGFR and/or common ligands has been observed in greater than 90% of squamous cell carcinomas.
of the H&N. This finding has led to the development of EGFR inhibitors, such as the monoclonal antibody cetuximab and small molecule tyrosine kinase inhibitors (such as erlotinib and gefitinib).

In phase II trials, cetuximab was combined with cisplatin in treating patients with tumors refractory to platinum-based chemotherapy.\textsuperscript{115-117} Tumor responses have been observed in 12% to 14% of patients, a striking result in this very poor prognostic group. Moreover, Trigo and colleagues have recently reported responses in 12.5% of patients, similarly platinum refractory, with cetuximab administered as a single agent.\textsuperscript{95}

A randomized placebo-controlled trial assessed cisplatin and cetuximab versus cisplatin in recurrent or metastatic squamous cell carcinomas of the H&N as first-line therapy.\textsuperscript{114,118} With 123 patients enrolled, a 26% response rate was observed in the experimental arm versus 10% in the controlled arm ($P = .029$). Bonner and colleagues have randomly assigned 424 patients with locally advanced and measurable squamous cell carcinomas of the H&N to receive definitive radiotherapy with or without cetuximab.\textsuperscript{110} Locoregional control and survival were significantly improved in patients treated with radiotherapy and cetuximab compared to radiotherapy alone.

This sequence of trials has provided data demonstrating the potential efficacy for cetuximab in treating squamous cell carcinomas of the H&N. Radiotherapy and cetuximab may provide a therapeutic option for patients not considered optimal candidates for standard chemoradiotherapy regimens. Certainly more study is needed.

**Metastatic Disease.** Palliative adjunctive measures include radiotherapy to areas of symptomatic disease, analgesics, and investigational agents aimed at controlling locally advanced tumors. Single agents and combination systemic chemotherapy regimens are both used. Response rates to single agents range from 15% to 35%. The most active agents include cisplatin, carboplatin, paclitaxel, docetaxel, 5-FU, methotrexate, ifosfamide, bleomycin, gemcitabine (for nasopharyngeal cancer), and cetuximab. The most active regimens include (1) cisplatin or carboplatin, plus 5-FU; or (2) cisplatin or carboplatin, plus a taxane. These regimens result in higher response rates of 30% to 40%.

Randomized trials assessing a combination of cisplatin plus 5-FU versus single-agent therapy with cisplatin, 5-FU, or methotrexate have demonstrated significantly higher response rates for the combination regimen. No difference in overall survival, however, is demonstrable.\textsuperscript{113,119-121} The median survival with chemotherapy is approximately 6 months, and the 1-year survival rate is approximately 20%. Achievement of a complete response is associated with longer survival and, although infrequent, has been reported more often with combination regimens.

The standard treatment of patients with incurable, recurrent, or metastatic H&N cancer should be dictated, in large part, by the patient's PS. Individuals with a good PS (0-1) may be offered combination or single-agent chemotherapy. Patients should be fully informed about the goals of treatment and the cost of combination chemotherapy as well as the potential for added toxicity. For patients with a PS of 2, single-agent chemotherapy or best supportive care is most appropriate. For patients with a good PS who relapse after first-line chemotherapy, second-line treatment in a clinical trial or best supportive care is appropriate. For patients with a PS of 3, best supportive care is appropriate.
Disclosures for the NCCN Head and Neck Cancers Guidelines Panel

At the beginning of each panel meeting to develop NCCN guidelines, panel members disclosed the names of companies, foundations, and/or funding agencies from which they received research support; for which they participate in speakers’ bureau, advisory boards; and/or in which they have equity interest or patents. Members of the panel indicated that they have received support from the following: Amgen Inc; AstraZeneca; Bristol Myers-Squibb; CEL-SCI; Eastern Collaborative Oncology Group; Eli Lilly; GEM Pharmaceuticals; Genentech Inc; GlaxoSmithKline; ImClone Systems Inc; MedImmune Inc; NCI; NeoPharm Inc; NIAID; NPS Pharmaceuticals; OSI Pharmaceuticals; Pfizer Inc; Roche Pharmaceuticals; and Sanofi-Aventis. Some panel members do not accept any support from industry. The panel did not regard any potential conflicts of interest as sufficient reason to disallow participation in panel deliberations by any member.
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