Overview

This shortened version of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Head and Neck (H&N) Cancers addresses tumors arising in the oral cavity, oropharynx, hypopharynx, and nasopharynx (see Figure 1). Other types of H&N cancer (e.g., lip, larynx, paranasal sinus, salivary gland, mucosal melanoma, and occult primary cancer) are included in the complete version of the H&N guidelines available on the NCCN Web site.
By definition, the NCCN Guidelines cannot incorporate all possible clinical variations and are not intended to replace good clinical judgment or individualization of treatments. Exceptions to the rule were discussed among the members of the panel while developing these guidelines. A 5% rule (i.e., omitting clinical scenarios that comprise < 5% of all cases) was used to eliminate uncommon clinical occurrences or conditions from these guidelines.

Incidence and Etiology

An estimated 36,500 new cases of and 7900 deaths from oral cavity and pharyngeal cancers occurred in 2010 in the United States.\textsuperscript{2,3} Squamous cell carcinoma or a variant is the histologic type in more than 90% of these tumors. Alcohol and tobacco abuse are common etiologic factors in cancers of the oral cavity, oropharynx, and hypopharynx. 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, esophagus, and other sites that share these risk factors.

Human papillomavirus (HPV) infection is now well accepted as a risk factor for the development of squamous cancers of the oropharynx (particularly cancers of the lingual and palatine tonsils, and base of tongue).\textsuperscript{4-10} The overall incidence of HPV-positive H\&N cancer is increasing in the United States.
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.

**MULTIDISCIPLINARY TEAM**

- 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 (including cytopathology)
- Diagnostic radiology
- Adjunctive services
  - Neurosurgery
  - Ophthalmology
  - Psychiatry
  - Addiction services
  - Audiology
  - Palliative care

**SUPPORT AND SERVICES**

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

- General medical care
- Pain and symptom management
- Nutritional support
  - Enteral feeding
  - Oral supplements
- Dental care for RT effects
- Xerostomia management
- Smoking and alcohol cessation
- Speech and swallowing therapy
- Audiology
- Tracheotomy care
- Wound management
- Depression assessment and management
- Social work and case management
- Supportive care (See NCCN Clinical Practice Guidelines in Oncology [NCCN Guidelines] for Palliative Care*)

*To view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.
Buccal mucosa, floor of mouth, anterior tongue, alveolar ridge, retromolar trigone, hard palate

WORKUP

• H&P including a complete head and neck exam; mirror and fiberoptic examination as clinically indicated
• Biopsy
• Chest imaging
• CT with contrast and/or MRI with contrast of primary and neck as indicated
• Consider PET-CT for stage III-IV disease
• Examination under anesthesia with endoscopy, if indicated
• Preanesthesia studies
• Dental/prosthodontic evaluation, including jaw imaging as indicated
• Nutrition, speech & swallowing evaluation/therapy as indicated

Multidisciplinary consultation as indicated

CLINICAL STAGING

T1–2, N0 — See Treatment of Primary and Neck (page 600)

T3, N0 — See Treatment of Primary and Neck (page 601)

T1–3, N1–3 — See Treatment of Primary and Neck (page 601)

T4a, any N — See Treatment of Primary and Neck (page 601)

T4b, any N, or unresectable nodal disease — See Treatment of Very Advanced Head and Neck Cancer (page 616)

*See Discussion.
Buccal mucosa, floor of mouth, anterior tongue, alveolar ridge, retromolar trigone, hard palate

CLINICAL STAGING  TREATMENT OF PRIMARY AND NECK  ADJUVANT TREATMENT  FOLLOW-UP

T1–2, N0

- Excision of primary (preferred) ± ipsilateral or bilateral neck dissection (guided by tumor thickness)\(^b\)
- External-beam RT\(^c\) ± brachytherapy

No adverse features\(^d\)

- One positive node without adverse features\(^d\) → RT\(^c\) optional (category 2B)
- Extracapsular spread and/or positive margin
  - Adverse features\(^d\)
  - Other risk features

Follow-up (See page 619)

- Chemo/RT\(^c,e\) (preferred; category 1)
  - Re-excision\(^f\) or RT\(^c\)
  - Consider chemo/RT\(^c,e\)

Recurrent or Persistent Disease (See page 617)

- No residual disease
- Residual disease → Salvage surgery

- One positive node with adverse features\(^d\)

- No residual disease
- Residual disease

- Adverse risk features: extracapsular nodal spread, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, nodal disease in levels IV or V, perineural invasion, vascular embolism (see Discussion).

- Consider re-excision to achieve negative margins, if feasible.

\(^a\) See Principles of Surgery (pages 620-624).
\(^b\) See Principles of Radiation Therapy (page 602).
\(^c\) Adverse risk features: extracapsular nodal spread, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, nodal disease in levels IV or V, perineural invasion, vascular embolism (see Discussion).
\(^d\) See Principles of Systemic Therapy (pages 626 and 627).
\(^e\) Consider re-excision to achieve negative margins, if feasible.
Buccal mucosa, floor of mouth, anterior tongue, alveolar ridge, retromolar trigone, hard palate

**CLINICAL STAGING**

<table>
<thead>
<tr>
<th>T3,N0; T4a, any N; T1-3, N1-3</th>
<th>Surgery(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0, N1, N2a-b, N3</td>
<td>Excision of primary, ipsilateral or bilateral neck dissection(^b) (guided by tumor thickness, extent of disease)</td>
</tr>
<tr>
<td>N2c (bilateral)</td>
<td>Excision of primary and bilateral neck dissection(^b)</td>
</tr>
</tbody>
</table>

**TREATMENT OF PRIMARY AND NECK**

- **No adverse features\(^d\)**
  - RT\(^c\) (optional)
- **Extracapsular spread and/or positive margin**
  - Chemo/RT\(^c,e\) (preferred)\(^c,e\) (category 1)
  - or Re-excision\(^f\)
  - or RT\(^c\)
  - or Consider chemo/RT\(^c,e\)

**ADJUVANT TREATMENT**

- **Adverse risk features**
  - Other risk features
  - RT\(^c\)
  - or Consider chemo/RT\(^c,e\)

**FOLLOW-UP**

- **Follow-up** (See page 619)
- **Recurrent or Persistent Disease** (See page 617)

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\(^b\) See Principles of Surgery (pages 620-624).
\(^c\) See Principles of Radiation Therapy (page 602).
\(^d\) Adverse risk features: extracapsular nodal spread, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, nodal disease in levels IV or V, perineural invasion, vascular embolism (see Discussion).
\(^e\) See Principles of Systemic Therapy (pages 626 and 627).
\(^f\) Consider re-excision to achieve negative margins, if feasible.
Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.
Head and Neck Cancers Version 2:2011

Base of tongue, tonsil, posterior pharyngeal wall, soft palate

WORKUP

- H&P including a complete head and neck exam; mirror and fiber optic examination as clinically indicated
- Biopsy
- Tumor HPV testing suggested
- Chest imaging
- CT with contrast and/or MRI with contrast of primary and neck
- Consider PET-CT for stage III-IV disease
- Dental evaluation, including panorex as indicated
- Nutrition, speech & swallowing evaluation/therapy and audiogram as indicated
- Examination under anesthesia with endoscopy as indicated
- Preanesthesia studies

Multidisciplinary consultation as indicated

CLINICAL STAGING

- T1-2, N0-1
  - See Treatment of Primary and Neck (page 604)
- T3-4a, N0-1
  - See Treatment of Primary and Neck (page 605)
- Any T, N2-3
  - See Treatment of Primary and Neck (page 606)
- T4b, any N, or unresectable nodal disease
  - See Treatment of Head and Neck Cancer (page 616)

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aImmunohistochemical staining for p16 is recommended. Although not used to guide treatment, HPV testing is valuable prognostically. The results of HPV testing should not change management decisions except in the context of a clinical trial.

bAnatomical imaging is also recommended.
Base of tongue, tonsil, posterior pharyngeal wall, soft palate

**Clinical Staging**

**Treatment of Primary and Neck Follow-Up**

| T1-2, N0-1 |     |

- **Definitive RT**
  - Complete clinical response
  - Residual disease
- **Excision of primary ± ipsilateral or bilateral neck dissection**
  - One positive node without adverse features
- **Adverse features**
  - Extracapsular spread ± positive margin
  - Positive margin
  - Other risk features
- **Residual disease**
  - Salvage surgery
- **Consider RT**
  - Chemo/RT (category 1)

- **For T2, N1 only, RT** + systemic therapy (category 2B for systemic therapy)
  - Complete clinical response
- **Residual disease**
  - Salvage surgery

- **Consider re-excision to achieve negative margins, if feasible.**

- **See Principles of Radiation Therapy (page 607).**
- **See Principles of Surgery (pages 620-624).**
- **See Principles of Systemic Therapy (pages 626 and 627).**

Adverse features: extracapsular nodal spread, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, nodal disease in levels IV or V, perineural invasion, vascular embolism (see Discussion).

Recurrence or Persistent Disease (See page 617)

Follow-up (See page 619)
## Head and Neck Cancers Version 2:2011

### CANCER OF THE OROPHARYNX

<table>
<thead>
<tr>
<th>Base of tongue, tonsil, posterior pharyngeal wall, soft palate</th>
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</thead>
<tbody>
<tr>
<td><strong>CLINICAL STAGING</strong></td>
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<tr>
<td><strong>TREATMENT OF PRIMARY AND NECK</strong></td>
</tr>
<tr>
<td><strong>ADJUVANT TREATMENT</strong></td>
</tr>
<tr>
<td><strong>FOLLOW-UP</strong></td>
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</tbody>
</table>

#### T1-2, N0-1

<table>
<thead>
<tr>
<th>No adverse features</th>
<th>Complete clinical response</th>
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<tr>
<th>One positive node without adverse features</th>
<th>Consider RT</th>
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<tr>
<th>Complete clinical response</th>
<th>Residual disease</th>
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<tr>
<th>Salvage surgery</th>
<th>RTc</th>
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#### T3-4a, N0-1

<table>
<thead>
<tr>
<th>Induction chemotherapy followed by RTc or chemo/RTc (category 3)</th>
<th>Complete clinical response</th>
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</table>

<table>
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<tr>
<th>Residual disease</th>
<th>Salvage surgery</th>
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<tr>
<th>Surgery for primary and neck</th>
<th>RTc</th>
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<table>
<thead>
<tr>
<th>Other risk features</th>
<th>Consider chemo/RTc</th>
</tr>
</thead>
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<table>
<thead>
<tr>
<th>Extracapsular spread and/or positive margin</th>
<th>Chemo/RTc (category 1)</th>
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</thead>
</table>

<table>
<thead>
<tr>
<th>RTc or Consider chemo/RTc</th>
<th>Follow-up (See page 619)</th>
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</thead>
</table>

<table>
<thead>
<tr>
<th>Recurrent or Persistent Disease (See page 617)</th>
</tr>
</thead>
</table>

#### Adverse features:
- Extracapsular nodal spread
- Positive margins
- pT3 or pT4 primary
- N2 or N3 nodal disease
- Nodal disease in levels IV or V
- Perineural invasion
- Vascular embolism

- Consider re-excision to achieve negative margins, if feasible.

---

**c** See Principles of Radiation Therapy (page 607).

**d** See Principles of Surgery (page 620-624).

**e** See Principles of Systemic Therapy (pages 626 and 627).

**f** Adverse features: extracapsular nodal spread, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, nodal disease in levels IV or V, perineural invasion, vascular embolism (see Discussion).

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

#### DEFINITIVE RT
- Conventional fractionation: 66-74 Gy (2.0 Gy/fraction; daily Monday-Friday) in 7 wk
- Altered fractionation:
  - 6 fractions/wk accelerated; 66-74 Gy to gross disease, 44-64 Gy to subclinical disease
  - Concomitant boost accelerated RT: 72 Gy/6 wk (1.8 Gy/fraction, large field; 1.5 Gy boost as second daily fraction during last 12 treatment days)
  - Hyperfractionation: 81.6 GY/7 wk (1.2 Gy/fraction, twice daily)

#### POSTOPERATIVE RT
- Preferred interval between resection and postoperative RT is ≤ 6 wk
- Primary: 60-66 Gy (2.0 Gy/fraction)
- Neck
  - Involved nodal stations: 60-66 Gy (2.0 Gy/fraction)
  - Uninvolved nodal stations: 44-64 Gy (1.6-2.0 Gy/fraction)

Postoperative chemoradiation
- Concurrent single agent cisplatin at 100 mg/m² every 3 wk x 3 doses is recommended

Concurrent chemoradiation
- Conventional fractionation: 2
  - Primary and gross adenopathy: ≥ 70 Gy (2.0 Gy/fraction)
  - Neck
    - Uninvolved nodal stations: 44-64 Gy (1.6-2.0 Gy/fraction)

IMRT is a preferred technique for cancers of the oropharynx in order to minimize dose to critical structures.

---

1 See Radiation Techniques (page 625) and Discussion.
2 Based on published data, concurrent chemoradiation most commonly uses conventional fractionation at 2.0 Gy per fraction to ≥ 70 Gy in 7 wk with single agent cisplatin given every 3 wk at 100 mg/m² x 3 doses. Other fraction sizes (e.g., 1.8 Gy, conventional), multiagent chemotherapy, other dosing schedules of cisplatin, altered fractionation with chemotherapy are efficacious, and there is no consensus on the optimal approach. In general, the use of concurrent chemoradiation carries a high toxicity burden; altered fractionation or multiagent chemotherapy will likely further increase the toxicity burden. For any chemoradiation approach, close attention should be paid to published reports for the specific chemotherapy agent, dose, and schedule of administration. Chemoradiation should be performed by an experienced team and should include substantial supportive care.
Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.

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Primary site: complete clinical response

Definitive RT

Primary site: residual tumor

Surgery: partial laryngopharyngectomy (open or endoscopic) + ipsilateral or bilateral neck dissection

No adverse features

Extracapsular spread ± positive margin

Chemo/RT (category 1)

Positive margins

Re-excision or RT

Other risk features

RT or Consider chemo/RT

Follow-up (See page 619)

Recurrent or Persistent Disease (See page 617)

Adverse features: extracapsular nodal spread, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism (see Discussion).

Adverse features: extracapsular nodal spread, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism (see Discussion).

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Adverse features: extracapsular nodal spread, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism (see Discussion.).

Consider re-excision to achieve negative margins, if feasible.
**CLINICAL STAGING**

**TREATMENT OF PRIMARY AND NECK**

Induction chemotherapy

- No adverse features
  - Extracapsular spread and/or positive margin
  - Other risk features
    - Complete clinical response
    - Neck dissection

- Residual tumor in neck
  - Chemo/RT (category 1)
  - RT
    - or
    - Consider chemo/RT

- Complete clinical response of neck
  - Negative
    - Observe
  - Positive
    - Neck dissection

- Salvage surgery + neck dissection as indicated

**ADJUVANT TREATMENT**

- Recurrent or Persistent Disease (See page 617)

**FOLLOW-UP**

- Follow-up (See page 619)

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**CANCER OF THE HYOPHARYNX**

**Head and Neck Cancers Version 2:2011**

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Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.
**Head and Neck Cancers Version 2:2011**

**CANCER OF THE HYPOPHARYNX**

**RESPONSE ASSESSMENT**

- **Primary site: complete response (CR)**
  - Definitive RT\textsuperscript{b} (category 1) or Consider chemo/RT\textsuperscript{b,e} (category 2B)
  - Complete clinical response of neck
  - Posttreatment evaluation\textsuperscript{h}
  - Neck dissection\textsuperscript{c}
    - Negative: Observe
    - Positive: Neck dissection\textsuperscript{c}

- **Primary site: partial response (PR)**
  - Chemo/RT\textsuperscript{b,e} (category 2B)
  - Residual disease
  - Salvage surgery
  - Observe
  - Follow-up (See page 619)
  - Recurrent or Persistent Disease (See page 617)

- **Primary site: < partial response**
  - Surgery\textsuperscript{c}
  - No adverse features\textsuperscript{d}
    - RT\textsuperscript{b}
  - Adverse features\textsuperscript{d}
    - Extracapsular spread and/or positive margin
      - Chemo/RT\textsuperscript{b,e} (category 1)
    - Other risk features
      - RT\textsuperscript{b}
      - Consider chemo/RT\textsuperscript{b,e}

\textsuperscript{b}See Principles of Radiation Therapy (page 613).
\textsuperscript{c}See Principles of Surgery (pages 620-624).
\textsuperscript{d}Adverse features: extracapsular nodal spread, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism (See Discussion).
\textsuperscript{e}See Principles of Systemic Therapy (pages 626 and 627).
\textsuperscript{h}In randomized clinical trials, assessment of response has been done after 2 or 3 cycles.
\textsuperscript{h}See Post Chemoradiation or RT Neck Evaluation (page 624).
Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.
STAGING

any N

See Principles of Radiation Therapy

i

See Discussion on induction chemotherapy.

See Principles of Surgery (pages 620-624).

See Post Chemoradiation or RT Neck Evaluation (page 624).

In randomized clinical trials, assessment of response has been done after 2 or 3 cycles.

See Principles of Systemic Therapy (pages 626 and 627).

Multimodality clinical trials

or

systemic therapy/RT

Concurrent

or

(category 3)

therapy

chemo-

Induction

or

(preferred)

Surgery + neck dissection

(category 3)b,e

In neck progression

< PR or

Primary site:

neck
disease in

and stable
CR or PR

Primary site:

≥

(page 613).

rt

residual tumor

Primary site:

response

clinical
complete

chemo/RT

chemo/RT;

consider

rt or

For CR:

b,e

b,e

tumor in neck

Primary site:

Residual

of neck

response

clinical
Complete

response

Complete

tumor in

Residual

evaluation

Posttreatment

evaluation

Posttreatment

Salvage surgery + neck dissection as indicatedc

Salvage surgery + neck dissection as indicatedc

Neck dissectionc

Neck dissectionc

Chemo/RT

or

RT

Positive

Negative

Positive

Negative

b,e

dissectionc

Neck

Observe

dissectionc

Neck

Observe

Disease Persistent

or

Recurrent

(See page 619)

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WORKUP

- H&P including a complete head and neck exam; mirror and fiberoptic examination as clinically indicated
- Nasopharyngeal exam and biopsy
- Chest imaging
- MRI with gadolinium of nasopharynx and base of skull to clavicles and CT (as indicated) with contrast
- Consider PET-CT for stage III-IV disease
- Dental evaluation as indicated
- Nutrition, speech & swallowing evaluation/therapy, and audiogram 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 as indicated

CLINICAL STAGING

- T1, N0, M0
- T1, N1-3; T2-T4, Any N
- Any T, Any N, M1

Definitive RT to nasopharynx and elective RT to neck

TREATMENT OF PRIMARY AND NECK FOLLOW-UP

Neck:
- Residual tumor
- Complete clinical response
- Neck dissection

Concurrent chemo/RT (category 1)
or
Induction chemotherapy followed by chemo/RT (category 3)

Platinum-based combination chemotherapy

Neck:
- Observe

WHO class 2-3/N2-3 disease (may include PET scan and/or CT)

MRI with gadolinium of nasopharynx and base of skull to clavicles and CT (as indicated) with contrast

Imaging for distant metastases (chest, liver, bone)

Multidisciplinary consultation as indicated

Follow-up (see page 619)

See Principles of Radiation Therapy (below).

See Principles of Systemic Therapy (pages 626 and 627).

See Discussion on induction chemotherapy.

Can be used for select patients with distant metastasis in limited site or with small tumor burden, or for patients with symptoms in the primary or any nodal site.

See Principles of Surgery (pages 620-624).

Recurrent or Persistent Disease (see page 617)

Definitive RT

Primary and gross adenopathy:
- 66-70 Gy (2.0 Gy/fraction; daily Monday-Friday) in 7 wk

Neck
- Uninvolved nodal stations: 44-64 Gy (1.6-2.0 Gy/fraction)

Concurrent Chemoradiation

Conventional fractionation:
- Primary and gross adenopathy: 70 Gy (2.0 Gy/fraction)

Neck
- Uninvolved nodal stations: 44-64 Gy (1.6-2.0 Gy/fraction)

IMRT is a preferred technique in cancer of the nasopharynx to minimize dose to critical structures.

1See Radiation Techniques (page 625) and Discussion.

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

Definitive RT to nasopharynx and elective RT to neck

Concurrent chemo/RT (category 1) or Induction chemotherapy followed by chemo/RT (category 3)

Platinum-based combination chemotherapy

Concurrent chemo/RT

**FOLLOW-UP**

Adjuvant chemotherapy

Neck: residual tumor

Neck dissection

Observe

RT to primary and neck or Chemo/RT as clinically indicated

Follow-up (See page 619)

Recurrent or Persistent Disease (See page 617)

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**PRINCIPLES OF RADIATION THERAPY**

- **Definitive RT**
  - Primary and gross adenopathy: 66-70 Gy (2.0 Gy/fraction; daily Monday-Friday) in 7 wk
  - Neck
    - Uninvolved nodal stations: 44-64 Gy (1.6-2.0 Gy/fraction)

- **Concurrent Chemoradiation**
  - Conventional fractionation:
    - Primary and gross adenopathy: 70 Gy (2.0 Gy/fraction)
    - Neck
      - Uninvolved nodal stations: 44-64 Gy (1.6-2.0 Gy/fraction)

IMRT is a preferred technique in cancer of the nasopharynx to minimize dose to critical structures.

---

*See Principles of Surgery (pages 620-624).*

1See Radiation Techniques (page 625) and Discussion.
Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.

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NCCN Clinical Practice Guidelines in Oncology

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Head and Neck Cancers Version 2:2011  VERY ADVANCED HEAD AND NECK CANCER

**DIAGNOSIS**

- **Locoregional recurrence without prior RT**
  - Resectable
  - Chemotherapy
  - Observation
  - Reirradiation

- **Locoregional recurrence or second primary with prior RT**
  - Resectable
  - Surgery ± chemotherapy, clinical trial preferred
  - Reirradiation ± chemotherapy, clinical trial preferred

- **Unresectable**
  - Chemotherapy, clinical trial preferred
  - Observation

- **Distant metastases**
  - PS 0-1
    - Combination chemotherapy
    - Single-agent chemotherapy
  - PS 2
    - Single-agent chemotherapy
    - Best supportive care
  - PS 3
    - Best supportive care

**TREATMENT OF HEAD AND NECK CANCER**

- **Newly diagnosed (M0); T4b, any N, or unresectable nodal disease**
  - Clinical trial preferred
  - Standard therapy

- **Recurrent or Persistent Disease**
  - Surgery
  - Adverse features
    - Extracapsular spread and/or positive margin
    - Other risk features
  - RT
    - Chemo/RT (category 1)
  - Salvage therapy for persistent disease as indicated

**Follow-up** (See page 619)

**PS = Performance Status (ECOG)**

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### PRINCIPLES OF RADIATION THERAPY

#### Concurrent Chemoradiation (preferred)

**Conventional fractionation:**
- Primary and gross adenopathy: $\geq 70$ Gy (2.0 Gy/fraction)
- Neck
  - Uninvolved nodal stations:
    - 44-64 Gy (1.6-2.0 Gy/fraction)

**Chemoradiation**

Based on published data, concurrent chemoradiation most commonly uses conventional fractionation at 2.0 Gy per fraction to $\geq 70$ Gy in 7 wk with single-agent cisplatin given every 3 wk at 100 mg/m$^2$ x 3 doses. Other fraction sizes (e.g., 1.8 Gy, conventional), multiagent chemotherapy, other dosing schedules of cisplatin, altered fractionation with chemotherapy are efficacious, and there is no consensus on the optimal approach. In general, the use of concurrent chemoradiation carries a high toxicity burden; altered fractionation or multiagent chemotherapy will likely further increase the toxicity burden. For any chemoradiation approach, close attention should be paid to published reports for the specific chemotherapy agent, dose, and schedule of administration. Chemoradiation should be performed by an experienced team and should include substantial supportive care.

#### Definitive RT

- Conventional fractionation:
  - Primary and gross adenopathy: 70-74 Gy (2.0 Gy/fraction; daily Monday-Friday) in 7 wk
  - Neck
    - Uninvolved nodal stations:
      - 44-64 Gy (1.6-2.0 Gy/fraction)

- Altered fractionation:
  - 6 fractions/wk accelerated; 70 Gy to gross disease, $> 50$ Gy to subclinical disease
  - Concomitant boost accelerated RT:
    - 72 Gy/6 wk (1.8 Gy/fraction, large field; 1.5 Gy boost as second daily fraction during last 12 treatment days)
  - Hyperfractionation:
    - 81.6 Gy/7 wk (1.2 Gy/fraction, twice daily)
  - Modified fractionation total dose $> 70$ Gy and treatment course $< 7$ wk

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1See Radiation Techniques (page 625) and Discussion.
FOLLOW-UP RECOMMENDATIONS

- History and physical exam1:
  - 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
- Posttreatment baseline imaging of primary (and neck if treated) recommended within 6 mo of treatment2 (category 2B)
  - Further reimaging as indicated based on signs/symptoms; not routinely recommended for asymptomatic patients
- Chest imaging as clinically indicated
- Thyroid-stimulating hormone (TSH) every 6-12 mo if neck irradiated
- Speech/hearing and swallowing evaluation and rehabilitation as clinically indicated
- Smoking cessation and alcohol counseling as clinically indicated
- Dental evaluation:
  - Recommended for oral cavity
  - As indicated for oropharynx, hypopharynx, and nasopharynx
  - As indicated for other sites, if significant intraoral radiation
- Consider Epstein-Barr virus (EBV) monitoring for nasopharynx

1For mucosal melanoma, physical exam should include endoscopic inspection for paranasal sinus disease.
2For cancer of the oropharynx, hypopharynx, glottic larynx, supraglottic larynx, and nasopharynx: imaging recommended for T3-4 or N2-3 disease only.
Head and Neck Cancers Version 2:2011

PRINCIPLES OF SURGERY

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

- To review the adequacy of biopsy material, review staging and imaging to determine the extent of disease, exclude the presence of a synchronous primary tumor, assess current functional status, and evaluate for potential surgical salvage if initial treatment is nonsurgical.
- To participate in the multidisciplinary team discussions regarding patient treatment options with the goal of maximizing survival with preservation of form and function.
- To develop a prospective surveillance plan that includes adequate dental, nutritional, and health behavior evaluation and intervention and any other ancillary evaluations that would provide for comprehensive rehabilitation.
- For patients undergoing planned surgery, the surgical procedure, margins, and reconstructive plan should be developed and designed to resect all gross tumor with adequate tumor free surgical margins. The surgical procedure should not be modified based on any response observed before therapy except in instances of tumor progression that mandates a more extensive procedure to encompass the tumor at the time of definitive resection.

Integration of Therapy
- It is critical that multidisciplinary evaluation and treatment be coordinated and integrated prospectively by all modalities involved in patient care.

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

- Involvement of the pterygoid muscles particularly when associated with severe trismus or pterygopalatine fossa involvement with cranial neuropathy;¹
- Gross extension of tumor to the skull base (e.g., erosion of the pterygoid plates or sphenoid bone, widening of the foramen ovale);
- Direct extension to superior nasopharynx or deep extension into the Eustachian tube and lateral nasopharyngeal walls;
- Suspected invasion (encasement) of the common or internal carotid artery. Encasement is usually assessed radiographically and defined as tumor surrounding the carotid artery > 270º;
- Direct extension of neck disease to involve the external skin;¹
- Direct extension to mediastinal structures, prevertebral fascia or cervical vertebrae.¹

¹In selected cases, surgery might still be considered.

Cont. on facing page
Primary Tumor Resection

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

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

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

Surgical Management of Cranial Nerves VII, X (Including the Recurrent Laryngeal Nerve), XI, and XII
Operative management of the facial nerve and other major cranial nerves during primary or regional node resection is influenced by the preoperative clinical function of the nerve.

- When the nerve is functioning, every attempt should be made to preserve the structure and function of the nerve (main trunk and/or branches) even if wide tumor margins are not achieved recognizing that the surgeon should leave no gross residual disease.
- Adjuvant postoperative radiation or chemoradiation is generally prescribed when microscopic residual or gross residual tumor is suspected.
- Direct nerve invasion by tumor and/or preoperative paralysis of the nerve may warrant segmental resection and nerve grafting at the discretion of the surgeon if tumor free margins are assured throughout the remainder of the procedure.
Head and Neck Cancers Version 2:2011

PRINCIPLES OF SURGERY (Cont.)

Neck Management
The surgical management of regional lymphatics is dictated by the extent of tumor at initial tumor staging. These guidelines apply to the performance of neck dissections as part of treatment for the primary tumor. In general, patients undergoing surgery for resection of the primary tumor will undergo neck dissection of the ipsilateral neck that is at greatest risk for metastases.

- Tumor sites that frequently have bilateral lymphatic drainage (e.g., base of tongue, palate, supraglottic larynx, deep space pre-epiglottic involvement) should often have both sides of the neck dissected with the extent of dissection determined as suggested below. For those patients with tumors at or approaching the midline, both sides of the neck are at risk for metastases, and bilateral neck dissections should be performed. This may vary for elective dissection if postoperative radiation is planned.

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

- The type of neck dissection (comprehensive or selective) is defined according to preoperative clinical staging and is determined at the discretion of the surgeon and based on the initial preoperative staging as follows:

N0 Selective neck dissection
- Oral cavity at least levels I-III
- Oropharynx at least levels II-IV
- Hypopharynx at least levels II-IV and level VI when appropriate
- Larynx at least levels II-IV and level VI when appropriate

N1-N2a-c Selective or comprehensive neck dissection (see Discussion)

N3 Comprehensive neck dissection

- Level VI neck dissections are performed for certain primary sites (such as larynx and hypopharynx) as required to resect the primary tumor and any clinically evident neck nodes. Elective dissection depends on primary tumor extent and site. Infraglottic laryngeal cancers are sites where elective level VI dissections are often considered appropriate.

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

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

- Tumor evaluations must be performed by specialists skilled in head and neck clinical examination
- The frequency of evaluation is summarized elsewhere in the NCCN Guidelines (See Follow-up Recommendations, page 619)
- Post chemoradiation or RT neck evaluation (See Principles of Surgery-Neck Evaluation, page 624)

Cont. on page 624
If a PET-CT is performed and negative for suspicion of persistent cancer, further cross-sectional imaging is optional.

PET-positive = PET suspicious for disease.

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

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Target delineation and optimal dose distribution require experience in head and neck imaging, and a thorough understanding of patterns of disease spread. Standards for target definition, dose specification, fractionation (with and without concurrent chemotherapy), and normal tissue constraints are still evolving. IMRT, 3D, and 2D conformal techniques may be used as appropriate depending on the stage, tumor location, physician training/experience, and available physics support. Close interplay exists between radiation technology, techniques, fractionation, and chemotherapy options resulting in a large number of combinations that may impact toxicity or tumor control. Close cooperation and interdisciplinary management are critical to treatment planning and radiation targeting, especially in the postoperative setting or after induction chemotherapy.

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

IMRT and Fractionation
A number of ways exist to integrate IMRT, target volume dosing, and fractionation. The Simultaneous Integrated Boost (SIB) technique uses differential "dose painting" (66-74 Gy to gross disease; 50-60 Gy to subclinical disease) for each fraction of treatment throughout the entire course of radiation. SIB is commonly used in conventional (5 fractions/wk) and the "6 fractions/wk accelerated" schedule. The Sequential (SEQ) IMRT technique typically delivers the initial (lower dose) phase (wk 1-5) followed by the high-dose boost volume phase (wk 6-7) using 2-3 separate dose plans, and is commonly applied in standard fractionation and hyperfractionation. The Concomitant Boost Accelerated schedule may use a "Modified SEQ" dose plan by delivering the dose to the subclinical targets once a day for 6 wk, and a separate boost dose plan as a second daily fraction for the last 12 treatment days.

### PRINCIPLES OF SYSTEMIC THERAPY

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

#### Squamous Cell Cancers

**Oral Cavity, Oropharynx, Hypopharynx:**

- **Primary Systemic Therapy + Concurrent RT**
  - Cisplatin alone¹ ² (preferred) (category 1)
  - Cetuximab¹ (category 1)
  - 5-FU/hydroxyurea³
  - Cisplatin/paclitaxel⁴
  - Cisplatin/infusional 5-FU⁵
  - Carboplatin/infusional 5-FU⁶
  - Carboplatin/paclitaxel⁷ (category 2B)

- **Postoperative Chemoradiation**
  - Cisplatin alone⁸-¹¹ (category 1 for high risk)

- **Induction*/Sequential Chemotherapy**
  - Docetaxel/cisplatin/5-FU¹²-¹⁴ (category 1 if induction is chosen)
  - After induction, agents to be used with concurrent chemoradiation typically include weekly platinums, weekly taxanes, or cetuximab.¹⁵

#### Nasopharynx

- **Chemoradiation Followed by Adjuvant Chemotherapy**
  - Cisplatin + RT followed by cisplatin/5-FU¹⁶,¹⁷ (category 1)

- **Recurrent, Unresectable, or Metastatic (Incurable)**

  - **Combination Therapy**
    - Cisplatin or carboplatin + 5-FU + cetuximab (non-nasopharyngeal)¹⁸ (category 1)
    - Cisplatin or carboplatin + docetaxel¹⁹ or paclitaxel²⁰
    - Cisplatin/cetuximab (non-nasopharyngeal)²¹
    - Cisplatin + 5-FU²⁰,²²

  - **Single Agents**
    - Cisplatin
    - Carboplatin
    - Paclitaxel
    - Docetaxel
    - 5-FU
    - Methotrexate
    - Ifosfamide
    - Bleomycin
    - Gemcitabine²³ (nasopharyngeal)
    - Cetuximab (non-nasopharyngeal)²⁴

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See references on facing page

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*Induction chemotherapy should only be done in a tertiary setting.
Induction chemotherapy should only be done in a tertiary setting.

Postoperative Chemoradiation
- Squamous Cell Cancers
  - Cisplatin alone
  - taxanes, or cetuximab.

After induction, agents to be used with concurrent chemoradiation typically include weekly platinums, weekly (category 1 if induction is chosen)
- Docetaxel/cisplatin/5-FU
- Carboplatin/infusional 5-FU
- Cisplatin/paclitaxel
- Cetuximab (category 1)

References:
whereas the incidence of HPV-negative (primarily tobacco- and alcohol-related) cancer is decreasing.\textsuperscript{11} A strong causal relationship has been established between HPV type 16 and the development of oropharyngeal cancer (see page 636).\textsuperscript{4} Whether HPV vaccination will decrease the incidence of HPV-positive oropharyngeal cancer has not been shown.

**Staging**

Stage at diagnosis predicts survival rates and guides management in patients with H\&N cancer. The 2010 American Joint Committee on Cancer (AJCC) staging classification (7th edition), which became effective January 1, 2010, was used as a basis for the NCCN’s treatment recommendations for H\&N cancer.\textsuperscript{12,13} However, no major changes in the T classification or stage groupings for the other sites have been made in the revisions for H\&N cancer; the minor changes are described herein.

The TNM staging systems developed by the AJCC for the oral cavity and pharynx (nasopharynx, oropharynx, and hypopharynx) are shown in Tables 1 and 2, respectively, on the NCCN Web site (www.NCCN.org).\textsuperscript{13} Definitions for regional lymph node (N) involvement and spread to distant metastatic sites (M) are uniform except for N staging of nasopharyngeal carcinoma (see Table 2, available online, in these guidelines, at www.NCCN.org [ST-3]). Definitions for staging the primary tumor (T), based on its size, are uniform for the oral cavity and oropharynx. In contrast, T stage is based on subsite involvement and is specific to each subsite for the hypopharynx and nasopharynx.

In general, stage I or II disease defines a relatively small primary tumor with no nodal involvement. Stage III or IV cancers include larger primary tumors, which may invade underlying structures and/or spread to regional nodes. Distant metastases are uncommon at presentation. More advanced TNM stages are associated with worse survival.

The anatomic criteria for definitions of T4a and T4b for the oropharynx and hypopharynx remain unchanged in the 7th edition of the AJCC staging manual. However, the words “resectable” (T4a) and “unresectable” (T4b) have been replaced by the terms “moderately advanced” (T4a) and “very advanced” (T4b).\textsuperscript{12} These changes were deemed necessary, because a substantial proportion of advanced-stage malignancies of the H\&N, although resectable, are being treated nonsurgically. Furthermore, a clear consensus in criteria for resectability can be difficult to obtain. For example, some tumors deemed unresectable are in fact anatomically resectable, but surgery is not pursued because of medical contraindications to surgery or because surgery is not anticipated to improve prognosis (see Resectable Versus Unresectable Disease, page 630).

This change in terminology allows revising of stage IV disease into moderately advanced local/regional disease (stage IVA), very advanced local/regional disease (stage IVB), and distant metastatic disease (stage IVC) for many sites (e.g., oral cavity, oropharynx, hypopharynx). Notably, a designation of stage IV disease does not necessarily mean the disease is incurable, particularly in the absence of distant metastases.

Minor changes were made in the T staging categories for the nasopharynx in the 7th edition of the AJCC (see Table 2, available online, in these guidelines, at www.NCCN.org [ST-3]).\textsuperscript{12} Thus, former T2a lesions are now designated T1; therefore, former stage IIA is now stage I. Lesions previously staged as T2b are now T2; therefore, former stage IIB is now
stage II. Regardless of unilateral or bilateral location, retropharyngeal lymph nodes are considered N1.

Management Approaches
Treating patients with H&N cancer is complex. The specific site of disease, extent of disease (stage), and pathologic findings guide the appropriate surgical procedure, radiation targets, dose and fractionation, and indications for chemotherapy. Single-modality treatment with surgery or radiotherapy is generally recommended for the approximately 30% to 40% of patients who present with early-stage disease (stage I or II). The 2 modalities result in similar survival in these individuals. In contrast, combined modality treatment with surgery or radiotherapy is generally recommended for the approximately 60% of patients with locally or regionally advanced disease at diagnosis. The treatment of patients with locally advanced T4b or unresectable nodal disease, metastatic disease, or recurrent disease for certain sites, including the oral cavity and pharynx, is addressed in these guidelines on pages 616–618.

Participation in clinical trials is a preferred or recommended treatment option in many situations. During development of these NCCN Guidelines, the panel tried to make evidence-based recommendations while providing a statement of consensus as to the acceptable range of treatment options.

Multidisciplinary Team Involvement
The initial evaluation and treatment plan for patients with H&N cancer require a multidisciplinary team of health care providers with expertise in caring for these patients. Similarly, managing and preventing sequelae of radical surgery, radiotherapy, and chemotherapy (e.g., pain, xerostomia, speech and swallowing problems, depression) require professionals who are familiar with the disease. Follow-up for these sequelae should include a comprehensive H&N examination. Adequate nutritional support can help to prevent severe weight loss in patients undergoing treatment for H&N cancer; thus, patients should be encouraged to see a dietician. Patients should also be encouraged to stop smoking and modify alcohol consumption if excessive, because these habits may decrease the efficacy of treatment and adversely affect other health outcomes. Programs using behavioral counseling combined with FDA-approved medications that promote smoking cessation can be very useful (http://www.ahrq.gov/path/tobacco.htm). Specific components of patient support and follow-up are listed in the algorithm on page 598. The panel also recommends referring to the NCCN Guidelines for Palliative Care (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).

Comorbidity and Quality of Life

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

Quality of Life
Health-related quality-of-life issues are paramount in H&N cancer. These tumors affect basic physiologic functions (e.g., the ability to chew, swallow, and breathe), the senses (taste, smell, and hearing), and uniquely human characteristics (e.g., appearance and voice). Health status describes an individual’s physical, emotional, and social capabilities and limitations. Function and performance refer to how well an individual is able to perform important roles, tasks, or activities. 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 National Institutes of Health (NIH)–sponsored conference recommended the use of patient-completed scales to measure quality of life. For H&N cancer–specific issues, the 3 most widely accepted validated measures are: 1) the University of Washington Quality of Life scale (UW-QOL); 2) the
EORTC Quality of Life Questionnaire (EORTC-HN35); and 3) the Functional Assessment of Cancer Therapy-Head and Neck module (FACT-HN). The Performance Status scale for patients with H&N cancer is a clinician-rated performance scale—with a narrower focus than the previously mentioned scales—that is also widely used.

Head and Neck Surgery

Principles of Surgery
All patients should be evaluated by an H&N surgical oncologist before treatment. In addition, multidisciplinary evaluation and treatment must be well coordinated. Evaluation, integration of therapy, assessment of resectability, primary tumor resection, margins, surgical management of cranial nerves (VII, X–XII), neck management, management of recurrences, and surveillance (including posttreatment neck evaluation) are discussed in Principles of Surgery, pages 620–624.1,39 Resectable disease, neck dissection, postoperative management, and salvage surgery of high-risk disease are discussed in the following sections.

Resectable Versus Unresectable Disease
The term unresectable has resisted formal definition by H&N cancer specialists. The experience of the surgeon and the support available from reconstructive surgeons, physiatrists, and prosthodontists often strongly influence recommendations, especially in institutions that treat only a few patients with locally advanced H&N cancer. The NCCN Member Institutions have teams experienced in the treatment of H&N cancer and maintain the multidisciplinary infrastructure needed for reconstruction and rehabilitation. A patient’s cancer is deemed unresectable if H&N surgeons at NCCN Member Institutions do not believe they can remove all gross tumor on anatomic grounds or if they are certain local control will not be achieved after surgery (even with the addition of radiotherapy to the treatment approach). Typically, these unresectable tumors densely involve the cervical vertebrae, brachial plexus, deep muscles of the neck, or carotid artery (see pages 620–624). Tumor involvement of certain sites is associated with poor prognosis (i.e., direct extension of neck disease to involve the external skin, direct extension to mediastinal structures, prevertebral fascia, or cervical vertebrae).

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

Patients with resectable tumors who can also be adequately treated without surgery represent a very important group. Definitive treatment with radiotherapy alone or radiotherapy combined with chemotherapy may represent equivalent or preferable approaches to resection in these individuals. Although these 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.

Neck Dissection
Historically, cervical lymph node (i.e., neck) dissections have been classified as “radical” or “modified radical” procedures. The less radical procedures preserved the sternocleidomastoid muscle, jugular vein, spinal accessory nerve, or selective lymph node levels. The panel prefers to classify cervical lymphadenectomy using contemporary nomenclature, thus classifying cervical lymph node dissections as either “comprehensive” or “selective.” A comprehensive neck dissection is one that removes all lymph node groups that would be included in a classic radical neck dissection. Whether the sternocleidomastoid muscle, jugular vein, or spinal accessory nerve is preserved does not affect whether the dissection is classified as comprehensive. Depending on the site, comprehensive neck dissection is often recommended for N3 disease (see specific site guidelines in the algorithm and Neck Management, pages 623 and 624).

Selective neck dissections were developed based on an understanding of the common pathways for spread of H&N cancers to regional nodes (see Figure 2). Depending on the site, selective neck dissection is often recommended for N0 disease (see specific
site guidelines in the algorithm, and pages 623 and 624). To remove the nodes most commonly involved with metastases from the oral cavity, a selective neck dissection is recommended, which includes the nodes found above the omohyoid muscle (levels I–III and sometimes the superior parts of level V). Similarly, to remove the nodes most commonly involved with metastases from the pharynx, a selective neck dissection is recommended, which includes the nodes in levels II through IV and level VI when appropriate.

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). The chief role of selective neck dissections in these NCCN Guidelines for H&N Cancers is to select patients for possible adjuvant therapy (i.e., chemo/RT or RT), although selective neck dissections may be used as treatment when neck tumor burden is low. In general, patients undergoing selective neck dissection should not have clinical nodal disease; however, selective neck dissection may prevent morbidity in patients with nodal disease and may be appropriate in certain patients with N1 to N2 disease.

In the guidelines, patients with cervical node metastases who undergo operations with therapeutic intent are generally treated with comprehensive neck dissections, because often they have disease outside the bounds of selective neck dissections. Determining whether an ipsilateral or bilateral neck dissection is needed depends on tumor thickness, the extent of the tumor, and tumor site. For example, bilateral neck dissection is often recommended for tumors at or near the midline and/or for tumor sites with bilateral drainage.

It is particularly important for patients treated nonsurgically 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) can be performed. After either RT or chemoradiation, posttreatment evaluation with imaging (e.g., CT and/or MRI with contrast, PET-CT) guides the use of neck dissection (see Post Chemo-radiation or RT Neck Evaluation, page 624). If PET-CT is used for follow-up, the first scan should be performed at approximately 12 weeks after treatment to reduce the false-positive rate.

Note that a complete clinical response (i.e., clinically negative) may be defined as no visible or palpable neck disease and no radiographic findings (i.e., the absence of either focally abnormal lymph nodes or large nodes [> 1.5 cm]); a complete pathologic response requires pathologic confirmation. If a complete clinical response is seen in patients who were N0 at initial staging, all panel members recommend observation. In patients who have a clinically negative neck, a negative PET-CT is 90% reliable and further imaging is optional. Panelists also concur that any patient with residual disease or suspected progression in the neck after radiotherapy or chemoradiation should undergo a neck dissection.

Postoperative Management of High-Risk Disease

Many factors influence survival and locoregional tumor control in patients with H&N cancer. The role of chemotherapy in the postoperative management of the patient with adverse prognostic risk factors has been clarified by 2 separate multicenter randomized trials and a combined analysis of data from the 2 trials for patients with high-risk cancers of the oral cavity, oropharynx, or hypopharynx. The US Intergroup trial RTOG 95-01 randomly assigned patients with 2 or more involved nodes,
positive margins, or extracapsular nodal spread of tumor to undergo standard postoperative radiotherapy or the same radiotherapy plus cisplatin \(100\ \text{mg/m}^2\) every 3 weeks for 3 doses.\(^{63}\) The European trial EORTC 22931 was designed using the same chemotherapy treatment and similar radiotherapy dosing, but also included as high-risk factors the presence of perineural or perivascular disease and nodal involvement at levels IV and V from an oral cavity or oropharynx cancer.\(^{61}\) The RTOG trial showed statistically significant improvement in locoregional control and disease-free survival but not overall survival, whereas the EORTC trial found significant improvement in survival and the other outcome parameters. A schedule using cisplatin at 50 mg intravenously weekly has also shown improved survival in this setting.\(^{64}\)

To better define risk, a combined analysis of prognostic factors and outcomes from the 2 trials was performed. This analysis showed that patients in both trials with extracapsular nodal spread of tumor and/or positive resection margins benefited from the addition of cisplatin to postoperative radiotherapy. For those with multiple involved regional nodes without extracapsular spread, no survival advantage was seen.\(^{63}\) The panel noted that the combined analysis was considered exploratory by the authors because it was not part of the initial protocol design.\(^{65}\) These publications form the basis of the NCCN recommendations.

In NCCN Member Institutions, patients with extracapsular nodal spread and/or positive surgical margins undergo adjuvant chemoradiotherapy after resection.\(^{64-65}\) The presence of other adverse risk factors—multiple positive nodes (without extracapsular nodal spread), vascular/lymphatic/perineural invasion, pT3 or pT4 primary, and oral cavity or oropharynx primary cancers with positive level IV or V nodes—are established indications for postoperative radiotherapy. Because patients with these other adverse features were also included in the EORTC 22931 trial that showed a survival advantage for patients receiving cisplatin concurrent with postoperative radiotherapy compared with radiotherapy alone, the panel added “consider chemoradiation” for these features.\(^{61}\)

**Salvage Surgery**

Patients with advanced carcinoma (any T, N2–3) who undergo nonsurgical treatment, such as concurrent chemotherapy and radiotherapy, need very close follow-up to evaluate for both local recurrence and to assess for ipsilateral or contralateral neck recurrence (see follow-up recommendations in the algorithm). Patients who do not have a complete clinical response to chemohtherapy/radiotherapy require salvage surgery plus neck dissection as indicated. However, all panelists emphasized that it may be difficult to detect local or regional recurrence because of radiation-related tissue changes, and this may result in a delayed diagnosis of persistent or recurrent disease.

The panelists also emphasized the increased risk of complications when salvage surgery is attempted. Some of these patients may require microvascular free flap reconstruction to cover the defects at the primary site. The patients undergoing neck dissection may develop complications related to delayed wound healing, skin necrosis, or carotid exposure. Laryngectomy may be required to obtain clear surgical margins or prevent aspiration (e.g., in patients with advanced oropharyngeal cancer). The patients requiring salvage laryngectomy may have a high incidence of pharyngocutaneous fistula and may require either a free flap reconstruction of the laryngopharyngeal defect, or a myocutaneous flap to buttress the suture line if the pharynx can be closed primarily.

**H&N Radiotherapy**

The radiotherapy recommendations were revised for each site in this version of the NCCN Guidelines. Radiotherapy for H&N cancer has grown increasingly complex. The availability and technical precision of intensity-modulated radiotherapy (IMRT) has markedly increased, perhaps beyond confidence in estimating location of small subsites of microscopic disease. A thorough understanding of natural history, anatomy, clinical circumstances, and imaging continue to guide the use of radiation as primary or adjuvant treatment. The NCCN radiotherapeutic guidelines are not all inclusive. Although technical guidelines are rapidly evolving and becoming more specific, advanced technologies provide much opportunity for variations and individualization in targeting and dose delivery, challenging traditional notions of “standard” fields and targets.

**Radiation Doses**

Selection of radiation total dose depends on the primary tumor and neck node size, fractionation, and clinical circumstances, including whether to use concurrent chemotherapy (see page 625 and the in-
dividual Principles of Radiation Therapy guidelines for each primary site). In general, the primary tumor and gross adenopathy require a total of 66 to 74 Gy (2.0 Gy/fraction) and up to 81.6 Gy (1.2 Gy/fraction) in hyperfractionation. External radiation doses exceeding 75 Gy using conventional fractionation (2.0 Gy/fraction) may lead to unacceptable rates of normal tissue injury.

In contrast, elective irradiation to low- and intermediate-risk nodal stations in the neck requires 44 to 64 Gy, depending on the estimated level of tumor burden and fraction size. Postoperative irradiation is recommended based on stage, histology, and surgical–pathologic findings. In general, postoperative radiotherapy is recommended for selected risk factors, including advanced T stage, depth of invasion, multiple positive nodes (without extracapsular nodal spread), or perineural/lymphatic/vascular invasion. Higher doses of radiation alone (60–66 Gy) or with chemotherapy are recommended for the high-risk features of extracapsular disease or positive margins. The preferred interval between resection and commencement of postoperative radiotherapy is 6 weeks or less.

**Fractionation in Radiotherapy Alone**

No single fractionation schedule has proven to be best for all tumors. Data strongly indicate squamous cancers of the H&N can grow rapidly, and may compensate for radiotherapy-induced cell loss through the mechanism of accelerated repopulation.\(^1\)\(^2\)–\(^3\)\(^3\) Especially in radiotherapy-alone settings, schedules delivering at least 1000 cGy/wk are recommended.\(^7\)\(^4\)–\(^7\)\(^8\)

Two large, randomized clinical trials from Europe have reported improved locoregional control using altered fractionation. The EORTC protocol 22791 compared hyperfractionation (1.15 Gy twice daily, or 80.5 Gy over 7 weeks) with conventional fractionation (2 Gy once daily, or 70 Gy over 7 weeks) in the treatment of T2, T3, N0–1 oropharyngeal carcinoma excluding base of tongue primaries. At 5 years, a statistically significant increase was seen in local control in the hyperfractionation arm (38% vs. 56%; \(P = .01\)) and no increase in late complications.\(^7\)\(^9\)

A long-term follow-up analysis has also shown a small survival advantage for hyperfractionation (\(P = .05\)).\(^8\)\(^0\) Another EORTC protocol (22851) compared accelerated fractionation (1.6 Gy 3 times daily, or 72 Gy over 5 weeks) with conventional fractionation (1.8–2.0 Gy once daily, or 70 Gy over 7–8 weeks) in various intermediate to advanced H&N cancers (excluding cancers of the hypopharynx). Patients in the accelerated fractionation arm had significantly better locoregional control at 5 years (\(P = .02\)). Disease-specific survival showed a trend favoring the accelerated fractionation arm (\(P = .06\)). Acute and late toxicity were increased with acceleration, however, raising questions about the net advantages of accelerated fractionation.\(^8\)\(^1\)

The RTOG reported the initial 2-year results and subsequent mature results (after a median follow-up of 8.5 years) of a 4-armed phase III randomized clinical trial (protocol 90-03) comparing hyperfractionation and 2 variants of accelerated fractionation against standard fractionation.\(^8\)\(^2\)–\(^8\)\(^3\) After 2 years of follow-up, both accelerated fractionation with a concomitant boost (AFX-C) 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 seen among the various treatment groups in the frequency of grade 3 or worse late effects reported at 6 to 24 months after treatment initiation. Long-term follow-up confirmed a statistically significant improvement in locoregional control with either AFX-C or hyperfractionation compared with standard fractionation. However, neither disease-free survival nor overall survival was significantly improved.

A meta-analysis of updated individual patient data from 15 randomized trials analyzing the effect of hyperfractionated or accelerated radiotherapy on survival of patients with H&N cancer has been published.\(^8\)\(^4\) Standard fractionation constituted the control arm in all of the trials in this meta-analysis. An absolute survival benefit of 3.4% at 5 years (hazard ratio [HR], 0.92; 95% CI, 0.86–0.97; \(P = .003\)) was reported. This benefit, however, was limited to patients younger than 60 years.\(^8\)\(^5\) Consensus regarding altered fractionation schedules with concomitant boost or hyperfractionation for stage III or IV oral cavity and oropharyngeal cancers has not yet emerged among NCCN Member Institutions.\(^8\)\(^3\)–\(^8\)\(^6\)

**Fractionation in Concurrent Chemoradiation**

No consensus exists regarding the optimal radiation dose-fractionation scheme when administered with concurrent chemotherapy. Most published studies 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. Other fraction sizes (e.g., 1.8 Gy, conventional), other dosing schedules of cisplatin, other single agents, multiagent chemotherapy, and altered fractionation with chemotherapy have been evaluated alone or in combination. Numerous trials have shown that modified fractionation and concurrent chemotherapy are more efficacious than modified fractionation alone. However, whether modified fractionation with concurrent chemotherapy is superior to standard fractionation and concurrent chemotherapy is currently unknown. RTOG 0129 is assessing accelerated fractionation versus standard fractionation with concurrent cisplatin. Preliminary results suggest that accelerated fractionation does not improve survival over standard fractionation. Concurrent chemoradiation increases acute toxicity compared with radiation alone, although an increase in late toxicity beyond that caused by radiotherapy alone is less clear. Altered fractionation and/or multiagent chemotherapy may further increase the toxicity burden. For any chemotherapy- and/or multiagent chemotherapy approach, close attention should be paid to published reports for the specific chemotherapy agent, dose, and schedule of administration. Chemoradiation should be performed by an experienced team and should include substantial supportive care.

Radiation Techniques and IMRT

The intensity of the radiation beam can be modulated to decrease doses to normal structures without compromising the doses to the cancer targets (http://www.icru.org/index.php?option=com_content&view=article&id=171). IMRT is an advanced form of conformal radiotherapy permitting more precise targeting of cancer while reducing dose to normal tissues. Xerostomia is a common long-term side effect of radiotherapy, which can be reduced with IMRT, drug therapy (e.g., pilocarpine, cevimeline), and other novel approaches (e.g., acupuncture). IMRT dose painting refers to the method of assigning different dose levels to different structures within the same treatment fraction (e.g., 2.0 to gross tumor, 1.7 to microscopic tumor, and < 1.0 Gy to parotid gland), resulting in different total doses to different targets (e.g., 70 Gy, 56 Gy, < 26 Gy). Although dose painting has been used to simplify radiation planning, hot spots associated with higher toxicity can occur. Alternatively, separate dose plans for the low versus higher dose targets can be delivered sequentially ("reduce target size and boost") or on the same day as separate fractions in twice-daily schemes (see Radiation Techniques, page 625).

IMRT is now widely used in H&N cancer and is the predominant technique used at NCCN Member Institutions. It is useful in reducing long-term toxicity in oropharyngeal and nasopharyngeal cancers through reducing the dose to one or more major salivary glands, temporal lobes, mandible, auditory structures (including cochlea), and optic structures. However, overall survival is similar among patients treated with IMRT and those receiving conventional RT. In-field recurrences, low-grade mucositis in areas away from the cancer targets, and posterior neck hair loss can occur with IMRT. The application of IMRT to other sites (e.g., oral cavity, hypopharynx) is evolving and may be used at the discretion of treating physicians.

Numerous phase II studies show a decrease in late toxicity (xerostomia) without compromising tumor control for nasopharyngeal and other sites. More recently, 3 randomized trials have supported the clinical benefits of IMRT in H&N cancer with regard to the reduction in xerostomia. Pow et al. evaluated treatment of early-stage nasopharyngeal carcinoma with conventional radiotherapy techniques versus IMRT. The results showed a statistical improvement in salivary flow and patient-reported quality-of-life parameters. In the study by Kam et al., patients with nasopharyngeal carcinoma were randomized to either IMRT or conventional 2-dimensional radiotherapy. At 1 year after treatment, patients in the IMRT arm had significantly lower rates of clinician-rated severe xerostomia than patients in the 2-dimensional radiotherapy arm (39.3% vs. 82.1%; P = .001). Salivary flow rates were also higher with IMRT. The mean parotid dose was 32 Gy in the IMRT group and 62 Gy in the conventional group. Although a trend for improvement in patient-reported dry mouth was observed after IMRT, recovery was incomplete and no significant difference was seen in patient-reported outcomes between the arms. The authors concluded that other salivary glands may also be important and merit protection.

Recent data from the PARSPORT phase III randomized trial indicate that IMRT decreases xerostomia compared with conventional radiotherapy in patients with non-nasopharyngeal carcinoma. In this trial, patients with T1–T4, N0–N3, M0 disease were treated...
with either conventional radiotherapy (i.e., parallel opposed technique) or IMRT to a total dose of 60 or 65 Gy in 30 fractions; 80 patients with oropharyngeal and 14 with hypopharyngeal tumors were included. Grade 2 or worse (LENT-SOMA scale) xerostomia 1 year after treatment was seen in 74% of patients receiving conventional radiotherapy versus 38% of patients in the IMRT group ($P = .003$). No differences were seen in the rates of locoregional control or survival.

**Follow-Up After Radiotherapy**

For patients whose cancer has been treated with radiotherapy, the recommended follow-up includes an assessment of thyroid function (i.e., the thyroid stimulating hormone [TSH] level should be determined every 6–12 months). Increased TSH levels have been detected in 20% to 25% of patients who received neck irradiation.

**Brachytherapy**

Brachytherapy is used less often in recent years because of improved local control obtained with concurrent chemoradiation.

**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 levels I through 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%–60%) in patients with anterior tongue cancers. In general, all patients undergo either ipsilateral or bilateral selective neck dissection, which is guided by tumor thickness. If definitive radiotherapy is chosen for treatment of T1–2, N0 disease, at least 44–64 Gy is given to the neck (see page 602).

**Workup and Staging**

Imaging studies to evaluate mandibular involvement and a careful dental evaluation (including Panorex, as indicated) are particularly important for staging (see Table 1, available online, in these guidelines, at www.NCCN.org [ST-1]) and planning therapy for oral cavity cancers, in addition to a complete H&N examination, biopsy, and other appropriate studies (see page 599). For patients who appear to have stage III/IV disease, PET-CT may alter management by upstaging patients.

**Treatment**

Surgery and radiotherapy 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 (see pages 599–601). 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, even for more advanced tumors. The concept of organ preservation using chemotherapy in the initial management of these patients has received less attention in the management of oral cavity cancers, because the functional outcome after primary surgical management is often good, given advances in reconstruction using microvascular techniques. Primary radiotherapy may be offered to select patients who are medically inoperable or refuse surgery.

Postoperative chemotherapy/radiotherapy (preferred, category 1) or reexcision of positive margins (if technically feasible) is recommended for all patients who have resected oral cavity cancers with the adverse pathologic features of extracapsular nodal spread and/or a positive mucosal margin. For other risk features, such as pT3 or pT4 primary, N2 or N3 nodal disease, nodal disease in levels IV or V, or perineural invasion or vascular tumor embolism, clinical judgment should be used when considering whether to add chemotherapy to radiotherapy or treat with radiotherapy alone.

**Follow-Up/Surveillance**

Recommendations for surveillance are provided in the algorithm.

**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 (see Table 2, available online, at www.NCCN.org) depends on complete H&N examination coupled with appropriate imaging studies (see page 603). The panel notes that HPV testing may prompt questions about prognosis (i.e., a favorable vs. less favorable forecast) and sexual history that the clinician should be prepared to address. Thus, without a specific reason for testing, HPV information may add anxiety and stress for some patients. Alternatively, understanding the cause of the cancer can result in reduced anxiety for some patients.

HPV Testing
Several studies have recently documented an increase in the incidence of HPV-related cancer, now estimated to constitute up to 60% to 70% of newly diagnosed cancers of the oropharynx in the United States and parts of the European Union. A strong causal relationship has been established, particularly between HPV type 16 and the development of oropharyngeal cancer. Prospective and retrospective analyses of clinical trials indicate that patients with HPV-positive cancers have improved response to treatment and improved survival and progression-free survival when compared with HPV-negative tumors. How this information should be used in routine clinical decision-making and in the design of clinical trials is currently a matter of intense investigation among NCCN Member Institutions. There is growing consensus that HPV status should be used as a stratification factor or should be addressed in separate trials (HPV related vs. unrelated disease) for which patients with oropharyngeal cancer are eligible.

Except for in cancers of unknown primary (see NCCN Clinical Practice Guidelines in Oncology for Occult Primary, available online, in these guidelines, at www.NCCN.org (OCC-1–6 and OCC-A)), the panel believes that HPV status currently should not be a routine consideration in treatment selection. Additional studies are needed to better understand the effect of HPV status on response to different therapies, treatment outcome, and patterns of failure, and in relation to other prognostic or predictive factors, such as smoking history and stage. Several clinical trial groups are reporting retrospective analyses of response to therapy in HPV-related versus HPV-unrelated oropharynx cancers. The panel strongly urges that patients with HPV-related cancers be enrolled in clinical trials evaluating biologic and treatment-related questions, when available.

HPV testing options in a clinical setting include HPV in situ hybridization (ISH) and a surrogate marker, p16 immunohistochemistry (which is a more widely available test that has been shown in several studies to strongly correlate with HPV status and is similarly associated with improved prognosis). Sufficient pathologic material for HPV testing can be obtained by fine-needle aspiration (FNA). The panel notes that HPV testing may prompt questions about prognosis (i.e., a favorable vs. less favorable forecast) and sexual history that the clinician should be prepared to address. Thus, without a specific reason for testing, HPV information may add anxiety and stress for some patients. Alternatively, understanding the cause of the cancer can result in reduced anxiety for some patients.

Treatment
The treatment algorithm has been divided into 3 staging categories: 1) T1–2, N0–1; 2) T3–4a, N0–1; and 3) any T, N2–3. Notably, T4b, any N, or unresectable nodal disease is treated as advanced cancer (see pages 616–618).

Early-stage (T1–2, N0–1) oropharyngeal cancers may be treated with primary surgery, including neck dissection, as indicated, or with definitive radiotherapy. The panel members felt that the third option of radiotherapy plus systemic therapy (category 2B for systemic therapy) was only appropriate for T2, N1 (see page 604). Adjuvant chemotherapyradiotherapy is recommended (category 1) for adverse pathologic features of extracapsular nodal spread and/or positive mucosal margin.

For locally advanced resectable disease (T3–4a, N0–1; or any T, N2–3), 3 treatment approaches are recommended, in addition to enrollment in a multimodality clinical trial that includes function evaluation. The 3 approaches are: 1) concurrent systemic therapyradiotherapy cisplatin (category 1; salvage surgery is used for managing residual or recurrent disease); 2) surgery with appropriate adjuvant therapy (chemo/radiotherapy or radiotherapy); or 3) induction chemotherapy followed by radiotherapy or chemo/radiotherapy, for which there was major disagreement among panel members.

Concurrent systemic therapyradiotherapy with cisplatin alone (category 1) is preferred for treat-
ment of locally or regionally advanced cancer (T3–
4a, N0–1, or any T, N2–3) of the oropharynx. Panel
members differed in their opinion as to whether
induction chemotherapy should be considered a
standard treatment option for T3–4a, N0–1 disease.
This disagreement is reflected by a category 3 rec-
ommendation in the algorithms (see the following
section on The Induction Chemotherapy Contro-
sery).91,137–146 Notably, for patients with any T, N2–3
disease, the category designation is 2B for induction
chemotherapy because of the increased risk for dis-
tant metastases in patients with more advanced neck
disease (see page 606).

The Induction Chemotherapy Controversy
Defining the optimal role of induction chemotherapy
in the management of locally or regionally advanced
H&N cancer has generated considerable discussion
among the panel in recent years. The algorithm for
the management of advanced oropharyngeal cancer il-
ustrates well the lack of consensus among NCCN
Member Institutions despite the extensive discus-

Thus, induction chemotherapy has a category 3 designation (major disagreement) for the manage-
ment of T3–4a, N0–1 oropharyngeal disease. In ad-

tion, induction chemotherapy has a category 2B designation (non-uniform consensus, no major dis-
agreement) for any T, N2–3 oropharyngeal disease.
However, the lack of consensus is not unique to the
oropharyngeal cancer algorithm; it is also apparent
in other algorithms (see pages 608–613, 614 and
615, and 616–618) in which category 3 designations
are common. Only for hypopharyngeal cancers less
than T4a in extent (which, if managed surgically,
would require total laryngectomy) is the use of in-
duction chemotherapy—used here as part of a larynx
preservation strategy—associated with a higher level
of panel consensus (i.e., category 2A).
A brief review of the available data helps provide
some perspective on the panel’s deliberations. Most
randomized trials of induction chemotherapy fol-
lowed by radiotherapy and/or surgery compared with
locoregional treatment alone published in the 1980s
and 1990s did not show an improvement in overall
survival with the incorporation of chemotherapy.142
However, a change in the pattern of failure with
less-distant metastases was noted in some studies147;
also, a correlation seemed to be present between re-
sponse to induction chemotherapy and subsequent
durable response to radiation.147,148 Thus, the con-
cept developed that in selected patients, induction
chemotherapy could facilitate organ preservation,
avoid morbid surgery, and improve overall quality of
life even though overall survival was not improved.
Because total laryngectomy is among the procedures
most feared by patients,149 larynx preservation was
the focus of initial studies.

Two randomized studies, the Veterans Affairs
(VA) Laryngeal Cancer Study Group trial in ad-
vanced larynx cancer and the EORTC trial predomi-
nantly in advanced hypopharynx cancer, established
the role of induction cisplatin/5-FU chemotherapy
followed by definitive radiotherapy in responding
patients as an alternative treatment to primary to-
total laryngectomy and postoperative radiation, of-
fering potential larynx preservation without com-
promise in survival (see page 639).147,148 Yet even
in this setting, the role of induction chemotherapy
decreased with time. Randomized trials and related
meta-analyses indicated that concurrent chemor-
diotherapy (with cisplatin being the best-studied
agent) offered superior locoregional tumor control
and survival over radiation alone,150–160 and shorter
duration of therapy than induction therapy followed
by radiation. Meta-analyses reported that concur-
rent chemoradiotherapy was more efficacious than
an induction chemotherapy strategy.142,146 In the lar-
ynx preservation setting, Intergroup 91-11 compared
radiation alone, concurrent cisplatin/radiation, and
induction cisplatin/5-FU followed by radiation, all
with surgery for salvage. The concurrent arm had the
highest larynx preservation rate (see Cancer of the
Larynx, in these guidelines, online, at www.NCCN.
org [MS-19]).161

Nonetheless, renewed interest has been shown
in the role of induction chemotherapy for a few rea-
sons. Given improvements in locoregional control
now achieved with advances in surgery, radiotherapy,
and concurrent chemotherapy/radiotherapy, the role
of distant metastases as a source of treatment failure
has increased and induction chemotherapy allows
greater drug delivery for this purpose.162 Concern has
been growing regarding the long-term morbidity of
concurrent chemoradiotherapy and related increas-
ing interest in exploring alternative approaches that
might have a different and hopefully more favorable
side effect profile. Finally, a more effective triplet
chemotherapy regimen has been identified compared
with the standard cisplatin/5-FU used in induction tri-
als of the 1980s and 1990s, and the related meta-analyses. Results from 3 phase III trials, which compared induction cisplatin plus infusional 5-FU with or without the addition of a taxane (docetaxel or paclitaxel) followed by the same locoregional treatment, showed significantly improved outcomes (response rates, disease-free survival, or overall survival depending on the trial) for patients in the 3-drug induction group compared with those receiving 2 drugs (cisplatin plus 5-FU). A randomized trial in the larynx preservation setting similarly showed superior larynx preservation outcomes when induction docetaxel/cisplatin/5-FU (TPF) and cisplatin/5-FU were compared.

However, a clear advantage in overall survival from the addition of induction chemotherapy to concurrent chemoradiation has not been shown yet. A randomized phase II study in patients with stage III or IV squamous cell H&N cancer of induction TPF followed by concurrent cisplatin/5-FU with radiotherapy versus concurrent cisplatin/5-FU with radiotherapy alone did report a higher radiologic complete response rate with the incorporation of induction chemotherapy. However, a randomized 3-arm study comparing concurrent cisplatin/radiotherapy versus induction chemotherapy with TPF or cisplatin/5-FU followed by concurrent cisplatin/radiotherapy reported a decrease in time to treatment failure with the incorporation of induction therapy, but no difference in survival. Furthermore, approximately 3 times as many patients were not included in the efficacy assessments on the induction arms, suggesting potential toxicity concerns.

There also remains considerable uncertainty and disagreement among panel members concerning which radiation or chemoradiation plan should follow induction. Panel members agree that high-dose cisplatin (100 mg/m² every 21 days × 3) may not be feasible for many patients in this setting, raising concerns that any efficacy gains of induction may be offset by the use of better-tolerated but potentially less-effective concurrent programs or poorer patient compliance with the radiation-based part of treatment. No one concurrent chemotherapy regimen is preferred. Panel members agreed that many different alternatives are reasonable (including concurrent low-dose weekly cisplatin, weekly taxanes, cetuximab, or combinations thereof), but are inadequately studied, to be specifically recommended.

After induction chemotherapy, the use of cetuximab is supported by data from the TREMPLIN study, in which patients with advanced laryngeal or hypopharyngeal cancer who had a major response to induction TPF were randomized to high-dose cisplatin for 3 cycles versus weekly cetuximab concurrent with radiotherapy. Patients on the cetuximab arm tolerated therapy better, had better compliance with drug delivery, and had similar 3-month laryngeal preservation rates to those observed in patients on the cisplatin arm. Some panel members specifically considered exclusive use of low-dose weekly carboplatin in this setting to be inadequate. Some evidence suggests that chemotherapy with weekly carboplatin might be equivalent to cisplatin; however, data are from the nasopharyngeal setting. Other sequential induction-concurrent regimens, using less-aggressive induction or less-intensive concurrent chemotherapy, seem to have higher compliance rates. However, a definitive study has not compared these newer strategies with concurrent chemoradiotherapy alone.

Because of these uncertainties, enrolling patients in appropriate clinical trials is particularly encouraged. Outside of a clinical trial, proceeding directly to concurrent chemoradiotherapy, cisplatin preferred, remains a standard treatment option for these patients, and is the preferred approach from the panel’s perspective in several settings as indicated. When induction chemotherapy is used, randomized data have clearly proven that the addition of a taxane to cisplatin/5-FU, of which TPF is the most extensively studied, is more efficacious than cisplatin/5-FU.

Radiation Therapy Fractionation

Standard conventional fractionation is preferred when radiotherapy is used definitively for T1–2, N0 tumors. Altered fractionation is appropriate for selected T1–2, N1 tumors, particularly if concurrent chemotherapy is not used. The recommended schedules are shown in the algorithm (see pages 603–607).

Follow-Up/Surveillance

Recommendations for surveillance are provided in the algorithm.

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 3 areas: 1) the pyriform sinus (the most common site of cancer in the hypopharynx); 2) the lateral and posterior pharyngeal walls; and 3) the posterior cricoid area.

**Workup and Staging**

A multidisciplinary consultation is encouraged. Accurate staging (see Table 2, available online, in these guidelines, at www.NCCN.org [ST-3]) depends on a complete H&N examination coupled with appropriate studies (see page 608).12

At 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.172 Thus, the prognosis for patients with cancer of the hypopharynx can be poor despite aggressive combined modality treatment.

**Treatment**

Patients with resectable disease are divided into 2 groups: 1) those with early-stage cancer (most T1, N0; selected T2, N0) who do not require a total laryngectomy; and 2) those with advanced resectable cancer (T1, N+; T2–4a, any N) who do require laryngectomy. The surgery and radiotherapy options for the former group (see page 610) represent a consensus among the panel members.

Patients with more advanced disease (defined as T1, N+; T2–3, any N) requiring total laryngectomy and partial or total pharyngectomy may be managed with 3 approaches (see page 610) in addition to enrollment in multimodality clinical trials: 1) induction chemotherapy followed by definitive radiotherapy if a complete response was achieved at the primary site147 or followed by other options depending on the response (see page 611); 2) surgery with neck dissection and postoperative radiation or chemoradiation as dictated by pathologic risk features; or 3) concurrent chemotherapy/radiotherapy, cisplatin preferred. Given the functional loss resulting from this surgery and the poor prognosis, participation in clinical trials is emphasized.

The recommendation of the induction chemotherapy/definitive radiotherapy option is based on the results of an EORTC randomized trial.147 This trial enrolled 194 eligible patients with stage II, III, or IV resectable squamous cell carcinoma of the pyriform sinus (n = 152) and aryepiglottic fold (n = 42), 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 3 cycles, followed by definitive radiotherapy. A complete response to induction chemotherapy was required 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.147 A functioning larynx was preserved in 42% of patients who did not undergo surgery. Local or regional failure rates did not differ between patients treated with surgery and those treated with chemotherapy, although the chemotherapy recipients showed 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 is emphasized.

A recently published randomized trial showed that an alternating program of cisplatin/5-FU with radiotherapy yielded larynx preservation, progression-free interval, and overall survival rates equivalent to those obtained with induction platinum/5-FU followed by radiotherapy.173 Given available randomized data showing the superiority of TPF compared with PF for induction chemoradiation, the triplet is now recommended as induction for this approach.149,154,163

As noted in the algorithm, surgery is recommended if less than a partial response occurs after induction chemotherapy (see page 611). In this situation, or when primary surgery is the selected management path, postoperative chemotherapy/radiotherapy is recommended (category 1) for the adverse pathologic features of extracapsular nodal spread and/or positive mucosal margin. For other risk features, clinical judgment should be used when deciding to use radiotherapy alone or when considering adding chemotherapy to radiotherapy.

Options for patients with T4a, any N disease (see page 612) include surgery plus neck dissection (preferred) followed by adjuvant chemotherapy/radiotherapy; multimodality clinical trials; or category 3 recommendations.
Follow-Up/Surveillance
Recommendations for surveillance are provided in the algorithm.

Cancer of the Nasopharynx
Carcinoma of the nasopharynx is uncommon in the United States. Among H&N cancers, it has among 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. Regional recurrences are uncommon in this disease, occurring in only 10% to 19% of patients.

These NCCN Guidelines for the evaluation and management of carcinoma of the nasopharynx attempt to address risk for both local and distant disease. Stage is accepted as prognostically important. The prognostic significance of histology is still controversial. Radiotherapy 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 radiotherapy and cisplatin.

Workup and Staging
The workup of nasopharyngeal cancer includes a complete H&N examination and other studies (see page 614), which are important for determining the full extent of tumor to assign appropriate stage and to design radiation ports that will encompass all disease with appropriate doses. Multidisciplinary consultation is encouraged. The 2010 AJCC staging classification (7th edition) is used as the basis for treatment recommendations (see Table 2, available online, in these guidelines, at www.NCCN.org [ST-3]).

Treatment
Patients with T1, N0, M0 nasopharyngeal tumors may be treated with definitive radiotherapy alone (see page 615). For early-stage cancer in this setting, radiation doses of 66 to 70 Gy given with standard fractions are necessary for control of gross tumor (see page 615). The local control rate for these tumors ranges from 80% to 90%, whereas T3–4 tumors have a control rate of 30% to 65% with radiotherapy alone.

The combination of radiotherapy and concurrent platinum-based chemotherapy followed by adjuvant cisplatin/5-FU 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 radiotherapy 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 radiotherapy. Adjuvant chemotherapy after combined chemotherapy and radiation was also given in this trial. In addition, the administration of the cisplatin dose was spread out over several days, and this regimen seemed to reduce toxicity while still providing a beneficial antitumor effect.

Another phase III randomized trial showed that concurrent chemo/radiotherapy (using weekly cisplatin) increased survival compared with radiotherapy alone. The 5-year overall survival was 70% for the chemo/radiotherapy group versus 59% for the radiotherapy group. A randomized trial compared chemo/radiotherapy using cisplatin versus carboplatin and found that the 3-year overall survival rates were similar (78% vs. 79%). However, these NCCN Guidelines recommend cisplatin for chemo/radiotherapy in patients who do not have a contraindication to the drug, because more randomized data support the use of cisplatin in this setting.

These NCCN Guidelines recommend concurrent chemotherapy (cisplatin) plus radiotherapy (category 1) followed by adjuvant cisplatin/5-FU for T1, N1–3; and for T2–T4, any N lesions (see page 615). Although an unusual occurrence, patients 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 should consist of a platinum-based combination chemotherapy regimen (see page 615).

The management of patients with recurrent or persistent nasopharyngeal cancer is described on page 617. When chemotherapy is indicated, commonly used active agents alone or in combination include gemcitabine, paclitaxel, docetaxel, cisplatin, or carboplatin. Cetuximab plus carboplatin has been studied for patients with recurrent or metastatic naso-
pharyngeal cancer for whom platinum-based therapy has failed; however, this regimen is not currently recommended in these NCCN Guidelines.

Follow-Up/Surveillance
Recommendations for surveillance are provided in the algorithm.

Very Advanced H&N Cancers
Very advanced H&N cancers include newly diagnosed locally advanced T4b or unresectable nodal disease, metastatic disease, or recurrent disease. The treatment goal for patients with newly diagnosed but unresectable disease is cure (see Head and Neck Surgery, page 630). 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 very advanced H&N cancers.

Newly Diagnosed Advanced Disease: For patients with a performance status (PS) of 0 or 1, the standard treatment of newly diagnosed, very advanced disease is concurrent cisplatin chemotherapy and radiotherapy (category 1). The panel had a major disagreement regarding whether induction chemotherapy (TPF) followed by radiotherapy or chemoradiation should be used for patients with a PS of 0 or 1, which is reflected in the category 3 recommendation (see The Induction Chemotherapy Controversy, page 637). Other options for patients with PS 2 or 3 are described in the algorithm (see page 616).

Many randomized trials and meta-analyses of clinical trials show significantly improved overall survival, disease-free survival, and local control when a concomitant or alternating chemotherapy and radiation regimen is compared with radiotherapy alone for advanced disease. 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 patients with H&N cancer. Limited data are available comparing the efficacy of different chemoradiotherapy regimens. Single-agent cisplatin plus radiotherapy is effective and easy to administer, and typically uses conventional fractionation at 2.0 Gy/fraction to 70 Gy or more in 7 weeks, with single-agent cisplatin given every 3 weeks at 100 mg/m² (see page 618).

Bonner et al. randomly assigned 424 patients with locally advanced and measurable stage III/IV squamous cell carcinomas of the H&N to receive definitive radiotherapy with or without cetuximab. Locoregional control and median overall survival (49 vs. 29.3 months; \( P = .03 \)) were significantly improved in patients treated with radiotherapy and cetuximab compared with radiotherapy alone. Radiotherapy and cetuximab may provide a therapeutic option for patients not considered medically fit for standard chemoradiotherapy regimens.

Other preferred chemoradiation options were also identified by the panel (see page 626). Limited data are available comparing combination chemoradiation with a single-agent used concurrently with radiotherapy.

Recurrent or Persistent Disease: Surgery is recommended for resectable recurrent or persistent locoregional disease; adjuvant therapy depends on the risk factors (see page 617). If the recurrence is unresectable and the patient did not have prior radiotherapy, then radiotherapy with concurrent systemic therapy is recommended, depending on the PS (see page 617). The treatment approach for patients with recurrent disease not amenable to curative-intent radiation or surgery is the same as that for patients with metastatic disease; enrollment in a clinical trial is preferred.

Metastatic Disease: Palliative adjunctive measures include radiotherapy to areas of symptomatic disease, analgesics, and other measures to control other manifestations of disease spread (e.g., hypercalcemia). Single agents and combination systemic chemotherapy regimens are both used (see page 626). Response rates to single agents range from 15% to 35%. The most active single agents include cisplatin, carboplatin, paclitaxel, docetaxel, 5-FU, methotrexate, ifosfamide, bleomycin, gemcitabine (for nasopharyngeal cancer), and cetuximab (for non-nasopharyngeal cancer). Active combination regimens include 1) cisplatin or carboplatin, plus 5-FU with cetuximab (for non-nasopharyngeal cancer); 2) cisplatin or carboplatin, plus a taxane with cetuximab (for non-nasopharyngeal cancer); 3) cisplatin with cetuximab (for non-nasopharyngeal cancer); or 4) cisplatin
with 5-FU. These regimens, on average, result in a doubling of response rates compared with single agents.

Randomized trials assessing a cisplatin-based combination regimen (e.g., cisplatin plus 5-FU) versus single-agent therapy with cisplatin, 5-FU, or methotrexate have shown significantly higher response rates for the combination regimen. No difference in overall survival has been seen. A randomized phase III trial comparing cisplatin plus 5-FU with cisplatin plus paclitaxel in patients with metastatic or recurrent H&N cancer found no significant differences in survival.

The epidermal growth factor receptor (EGFR) is a trans-membrane glycoprotein; activation of EGFR 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 H&N squamous cell carcinomas. This finding has led to the development of EGFR inhibitors, such as the monoclonal antibody cetuximab and small molecule tyrosine kinase inhibitors (i.e., erlotinib and gefitinib).

Data from phase II studies indicate that in the cisplatin-refractory setting, the single-agent response rate of cetuximab is 12% to 14%. Burtness et al. compared cisplatin plus cetuximab versus cisplatin plus placebo as first-line treatment of recurrent disease and reported a significant improvement in response rate with cetuximab (26% vs. 10%, respectively). Notably, a phase III randomized trial (EXTREME) of 442 patients with recurrent or metastatic squamous cell carcinoma found that cetuximab plus cisplatin/5-FU or carboplatin/5-FU improved median survival compared with the standard chemotherapy doublet (10.1 vs. 7.4 months; \( P = .04 \)).

The response rate was also improved with cetuximab (20%–36%; \( P < .001 \)). Available data for tyrosine kinase inhibitors (such as erlotinib and gefitinib) have not established them as treatment options for recurrent or metastatic H&N cancer outside of a clinical trial. In one randomized trial, treatment with 2 different dosing schedules of gefitinib offered no survival advantage over treatment with methotrexate.

The standard treatment of patients with incurable, recurrent, or metastatic H&N cancer should be largely dictated by the patient’s PS (see page 616). Patients should be fully informed about the goals of treatment, cost of combination chemotherapy, and potential for added toxicity.

### Recommended Reading List


Head and Neck Cancers


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Dr. Hughes has disclosed that she has a patent, equity, or royalty in Myriad Genetic Laboratories, Inc.; Affymetrix; and Qiagen NV. The remaining guidelines staff have disclosed that they have no conflicts of interest.