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NCCN Guidelines Panel Disclosures

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## Summary of the Guidelines updates

Summary of changes in the 1.2010 version of the Head and Neck Cancers guidelines from the 1.2009 version include:

### Global Changes

- The order of the algorithms was revised ([Table of Contents](#)).
- In the workup section of most sites, after H&P, the following statement was added, “including a complete head and neck exam; mirror and fiberoptic examination as clinically indicated”.
- Workup: The recommendations “CT with contrast and/or MRI with contrast of primary and neck”, “Consider PET-CT for Stage III-IV disease,” and “Nutrition, speech & swallowing evaluation/therapy as indicated,” were added for most sites, if not previously listed.
- “Selective neck dissection” and “comprehensive neck dissection” changed to “neck dissection”, because a new “Principles of Surgery” section was added ([SURG-A](#)).
- The phrase “(reconstruction as indicated)” was removed after “neck dissection”.
- Complete response was clarified as “Complete clinical response”.
- “Gy/day” changed to “Gy/fraction” for all Principle of Radiation Therapy pages in all sites.
- In the footnotes, “Risk features” changed to “Adverse features” in all sites.
- The bullets “physical exam, contrast enhanced CT or MRI, PET (minimum 12 weeks)”, with corresponding footnote regarding a negative PET-CT and further cross sectional imaging optional, were removed from “Post-treatment evaluation” and placed on a new page entitled Post Chemoradiation or RT Neck Evaluation ([SURG-A 6 of 6](#)).
- For treatment of primary and neck, “Multimodality clinical trials that include function evaluation” changed to “Multimodality clinical trials.”
- The follow-up section for all head and neck cancer sites was removed and placed on a separate page ([FOLL-A](#)).
- The Staging tables were updated to reflect the 7th edition (2010) of the AJCC Staging Manual ([ST-1](#)) to ([ST-11](#)).

### TEAM-1

- Multidisciplinary Team:
  - After pathology, “(including cytopathology)” was added.
  - Palliative care was added as an “Adjunctive service”.

### LIP-1

- “Resectable” was removed from T3, T4a, N0; Any T, N1-3.
- “T4b or unresectable nodal disease” changed to “T4b, N any, or unresectable nodal disease”. (Also for other sites)

### LIP-2

- Treatment of primary and neck: After surgical excision (preferred), “(neck dissection not recommended)” was added.
- External-beam RT + brachytherapy changed to “External-beam RT to primary site ± brachytherapy”.
- Footnote “c” that states, “No elective treatment to neck preferred for T1-2, N0” is new to the page.

### LIP-3

- Adjuvant Treatment for extracapsular spread and/or positive margin: Chemo/RT is now listed as a preferred option. “RT (selected patients)” changed to “RT”. (Also for [OR-2](#), [OR-3](#))

### LIP-A

- Definitive RT
  - Primary and gross adenopathy: “≥ 66 Gy” changed to “66-74 Gy”.
  - Neck; Uninvolved nodal stations: “≥ 50 Gy (2.0 Gy/day)” changed to “44-64 Gy (1.6-2.0 Gy/fraction)”. (Also for Postoperative RT.)
  - The statement, “Consider elective neck RT in T3-T4 disease for perineural invasion or lymphovascular invasion” is new to the page.
Summary of the Guidelines updates

Summary of changes in the 1.2010 version of the Head and Neck Cancers guidelines from the 1.2009 version include:

Cancer of the Oral Cavity

**OR-2**
- T1-2, N0: After Adverse features, a new pathway for “Positive margin (T1, N0 only)” was created. (Also for ORPH-2, HYPO-2)

**OR-A**
- Definitive RT:
  - Primary and gross adenopathy: Conventional RT dose changed from “≥ 66 Gy” to “66-74 Gy”.
  - Altered fractionation dose changed from “6 fractions/week accelerated; 70 Gy to gross disease, ≥ 50 Gy to subclinical” to “…66-74 Gy to gross disease, 44-64 Gy to subclinical disease”.
- Neck; Uninvolved nodal stations changed from “≥ 50 Gy (2.0 Gy/day)” to “44-64 Gy (1.6-2.0 Gy/fraction)”.
  (Also for Postoperative RT)
- Postoperative RT:
  - Selected pT2, N0-N1 disease was added to the first bullet.

Cancer of the Oropharynx

**ORPH-1**
- Workup: The third bullet was clarified as “Tumor HPV testing suggested”.
- Footnotes “a” and “b” are new to the page.

**ORPH-2**
- The bottom pathway changed from “For T1-T2, N1 only: RT + systemic therapy (category 3)” to “For T2, N1 only: RT + systemic therapy (category 2B for systemic therapy)”.

**ORPH-3**
- For T3-4a, N0-1 disease:
  - Surgery was clarified as “for primary and neck”.

ORPH-3—continued
- “Induction chemotherapy followed by chemo/RT (category 3)” changed to “Induction chemotherapy followed by RT or chemo/RT (category 3)”.

**ORPH-4**
- For Any T, N2-3 disease: “Induction chemotherapy followed by chemo/RT (category 2B)” changed to “Induction chemotherapy followed by RT or chemo/RT (category 2B)”.

**ORPH-A**
- Definitive RT
  - Conventional fractionation: “70 Gy” changed to “66-74 Gy”.
  - Altered fractionation dose changed from “6 fractions/week accelerated; 70 Gy to gross disease, ≥ 50 Gy to subclinical” to “…66-74 Gy to gross disease, 44-64 Gy to subclinical disease”.
- Neck; Uninvolved nodal stations changed from “≥ 50 Gy (2.0 Gy/day)” to “44-64 Gy (1.6-2.0 Gy/fraction)”.
  (Also for Postoperative RT)
- Postoperative RT:
  - First bullet: selected pT2, N0-N1 was removed.
  - Involved nodal stations: “≥ 60 Gy” changed to “60-66 Gy”.
  - Uninvolved nodal stations: “≥ 50 Gy (2.0 Gy/day)” changed to “44-64 Gy (1.6-2.0 Gy/fraction)”.
- Concurrent chemoradiation; Conventional fractionation; Uninvolved nodal stations: “44-50 Gy (2.0 Gy/day)” changed to “44-64 Gy (1.6-2.0 Gy/fraction)”.
- The statement “IMRT is a preferred technique for oropharynx cancers in order to minimize dose to critical structures” was added to the page.
  (A comparable statement was also made on NASO-A and MAXI-A)

Cancer of the Hypopharynx

**HYPO-1**
- Clinical Staging: “T Stage not requiring total laryngectomy” changed to “Not requiring total laryngectomy.” “Resectable advanced cancer requiring total laryngectomy” changed to “Advanced cancer requiring total laryngectomy.”

Continued on next page
Summary of the Guidelines updates

Summary of changes in the 1.2010 version of the Head and Neck Cancers guidelines from the 1.2009 version include:

Cancer of the Nasopharynx

**NASO-1**
- Top pathway was changed to “T1,N0, M0” and Second pathway changed to “T1, N1-3; T2-T4, Any N” to reflect new AJCC staging.

Cancer of the Glottic Larynx

**GLOT-1**
- “Resectable” was removed as a bullet from the third and fourth pathways.

**GLOT-2**
- Carcinoma in situ pathway: “Endoscopic removal (stripping/laser)” was clarified as “Endoscopic resection”.
- Total laryngectomy not required pathway: The second and third treatment recommendations were combined to read “Partial laryngectomy/endoscopic or open resection as indicated” and (selected superficial lesions) was removed.

**GLOT-3**
- Treatment of Primary and Neck: “RT if patient not candidate for concurrent chemo/RT” was previously the last option. It is now combined into the top pathway after “Concurrent systemic therapy/RT”.

**GLOT-4**
- “Induction chemotherapy x 3 cycles (category 2B)” changed to “Induction chemotherapy (category 3).”

Continued on next page
Summary of the Guidelines updates

Summary of changes in the 1.2010 version of the Head and Neck Cancers guidelines from the 1.2009 version include:

**Cancer of the Glottic Larynx**—continued.

**GLOT-5**
- This is a new page that provides recommendations for response assessment and treatment after induction chemotherapy.

**GLOT-6**
- The bottom pathway changed to “Selected T4a patients who decline surgery”.

**GLOT-A**
- Definitive RT: “Elective nodal RT ≥ 50 Gy (2.0 Gy/day)” changed to “Uninvolved nodal stations: 44-64 Gy (1.6-2.0 Gy/fraction)”.
  (Also for Postoperative RT)
- Postoperative RT: Involved nodal stations: “≥ 60 Gy” changed to “60-66 Gy”.

**Cancer of the Supraglottic Larynx**
- The algorithms were revised including page deletions and updated pagination.

**SUPRA-1**
- Clinical Staging: In the second pathway: “T4a, N0” was removed as a bullet and the third pathway changed from “T4, N0” to “T4a, N0”.

**SUPRA-2**
- Pathology stage: New pathways were added for Node negative (T1-T2, N0) and Node negative (T3-T4a, N0).
- Adjuvant Treatment:
  - Adverse features; positive margins: “Further surgery” changed to “Re-excision”
  - Adverse features; extracapsular spread: Chemo/RT changed from category 2B to “category 1”. RT was clarified as category 2B for select patients.

**SUPRA-3**
- Treatment of Primary and Neck: Third option was clarified as “RT if patient not medical candidate for concurrent systemic therapy/RT”.
  - “Induction chemotherapy (category 3)” was added as a treatment option.

**SUPRA-4**
- Clinical Staging: Top pathway “T3-4a, N0-1” changed to “T3, N0-1”.
  Third pathway changed from “T4a, N2-3” to “T4a, N0-N3”.

**SUPRA-5**
- Treatment of Primary and Neck: “Induction chemotherapy (category 3)” was added as an option.
  - Third pathway: No adverse features: After Observe, “RT” was added as an option.

**SUPRA-7**
- This is a new page that provides recommendations for response assessment and treatment after induction chemotherapy.

**SUPRA-8**
- T4a, N0-N3: “Clinical trial” was removed as an option and placed in the bottom pathway.
- The page now includes a new pathway for “T4a, N0-N3 patients who decline surgery”.

**SUPRA-A**
- Definitive RT:
  - Conventional fractionation: Neck, uninvolved nodal stations: “≥ 50 Gy (2.0 Gy/day)” changed to “44-64 Gy (1.6-2.0 Gy/fraction)”.
    (Also for Postoperative RT)
  - Altered fractionation: 6 fractions/week accelerated; “70 Gy to gross disease, ≥ 50 Gy to subclinical disease” changed to “66-74 Gy to gross disease, 44-64 Gy to subclinical disease.”
- Postoperative RT
  - Primary: Changed from “≥ 60 Gy (2.0 Gy/day)” to “60-66 Gy (2.0 Gy/fraction)”. (Also for Neck; Involved nodal stations)

**Ethmoid Sinus Tumors**

**ETHM-1**
- A new column entitled “Clinical Presentation” was added with pathway “Unresected mass or Incompletely resected mass”.
- The “Diagnosed with incomplete excision” pathway was removed.

Continued on next page
Summary of the Guidelines updates

Summary of changes in the 1.2010 version of the Head and Neck Cancers guidelines from the 1.2009 version include:

Ethmoid Sinus Tumors

ETHM-1—continued

- “Biopsy” changed to “Biopsy unless prior tissue available”.
- Under Pathology (Also for MAXI-1)
  - Third bullet: Clarified as “Minor salivary gland”.
  - “Mucosal melanoma” was added.

ETHM-2

- Clinical Presentation
  - “Resectable” was removed from “Newly diagnosed T3, T4a”.
  - Bottom pathway: “…and no disease on physical exam…” changed to “…and no residual disease on physical exam…”
- Primary Treatment; Bottom pathway: “See newly diagnosed T1, T2” was added after “Surgery, if feasible”.
- “Observation for T1 only (category 2B)” was added as an option for Adjuvant Treatment for Newly diagnosed patients and patients diagnosed after incomplete excision and no residual disease. Corresponding footnote “d” was added to define the pathologic features for observation.

Maxillary Sinus Tumors

MAXI-1

- Footnote “b”: The sentence “Consider referral to a major medical center that specializes in this disease” was added.

MAXI-2

- After Infrastructure, “Observation” was added as an option for adjuvant treatment. “RT per indication” changed to “RT”.
- Footnote regarding “Ohngren’s line” was moved to the new Principles of Surgery section (SURG-A 2 of 6).

MAXI-A

- Definitive RT:
  - Primary and gross adenopathy: Conventional RT dose changed from “≥ 66 Gy” to “66-74 Gy”.

MAXI-A—continued

- Definitive RT:
  - Altered fractionation dose changed from “6 fractions/week accelerated; 70 Gy to gross disease, ≥ 50 Gy to subclinical” to “…66-74 Gy to gross disease, 44-64 Gy to subclinical disease”.
  - RT dosing for Neck; Uninvolved nodal stations changed from “≥ 50 Gy (2.0 Gy/day)” to “44-64 Gy (1.6-2.0 Gy/fraction)”.
  - (Also for Postoperative RT)

- Postoperative RT:
  - Primary: “≥ 60 Gy” changed to “60-66 Gy”.
  - Neck; Involved nodal stations changed from “≥ 60 Gy” to “60-66 Gy”.

Advanced Head and Neck Cancer

ADV-1 (Very Advanced Head and Neck Cancer)

- Page title changed to “Very Advanced Head and Neck Cancer”.
- “Unresectable” was removed after “Newly diagnosed (M0)” in the first column.
- After standard therapy for PS 0-3, all patients now go to “Residual neck disease + primary site controlled: Neck dissection, if feasible”.

ADV-2 (Recurrent/Persistent Disease)

- Page title changed to “Recurrent/Persistent Disease”.
- Locoregional recurrence without prior RT; Resectable pathway: Surgery ± RT changed to “Surgery” with subsequent recommendations for “No adverse features” and “Adverse features” with corresponding footnotes. “Salvage surgery for persistent disease as indicated” was added after the Chemo/RT option.
- Locoregional recurrence or Second primary with prior RT:
  - Resectable pathway: “Surgery clinical trial preferred” changed to “Surgery ± reirradiation ± chemotherapy, clinical trial preferred”.
  - Unresectable pathway: “Reirradiation, clinical trial preferred” changed to “Reirradiation ± chemotherapy, clinical trial preferred”.
- Distant metastases; PS 0-1: “Chemotherapy on clinical trial” changed to “Chemotherapy, clinical trial preferred”.
- Footnotes “e” and “f” are new to the page.
Summary of the Guidelines updates

Summary of changes in the 1.2010 version of the Head and Neck Cancers guidelines from the 1.2009 version include:

**Advanced Head and Neck Cancer---continued**

**ADV-A**
- Definitive RT: Conventional fractionation; Neck, Uninvolved nodal stations: Changed from “≥ 50 Gy/day (2.0 Gy/day)” to “44-64 Gy (1.6-2.0 Gy/fraction)”.
- Concurrent chemoradiation: Neck, Uninvolved nodal stations changed from “44-60 Gy” to “44-64 Gy (1.6-2.0 Gy/fraction)”.

**Occult Primary**
- Note: The Primary Therapy for Occult Primary- Melanoma algorithm (formerly OCC-6) was moved to the new Mucosal Melanoma Melanoma algorithm (MM-1)

**OCC-1**
- Second column: H&P added. Complete head and neck exam with attention to skin; mirror and fiberoptic examination as indicated to visualize nasopharynx, oropharynx, hypopharynx, and larynx.
- Third column: Fine-needle aspiration is now “preferred” and “Open biopsy” is listed as an option.
- Footnote “a”: Changed to “…for uncertain or non-diagnostic histologies.”

**OCC-2**
- Third column: Adenocarcinoma was clarified as “of neck node”.
- The “Poorly differentiated…” and “Squamous cell carcinoma…” pathways were combined.

**OCC-3**
- Top pathway; Surgery: “(levels I-V)” was removed after Neck dissection. The post neck dissection options were revised.
- Definitive Treatment: Chemotherapy/RT changed from category 3 to “category 2B”.
- No residual tumor changed to “Complete clinical response”.

**OCC-4**
- N1 with open biopsy changed to “N1 without extracapsular spread”.
- Level 1 only pathway: Observe (category 3) was removed as an option.

**OCC-5**
- Second column: “Extracapsular spread or N2, N3” changed to “N2, N3 without extracapsular spread”.

**OCC-6**
- This is a new page that provides recommendations for patients with Extracapsular spread after neck dissection.

**OCC-A**
- Altered fractionation: “70 Gy to gross disease, ≥ 50 Gy to subclinical disease” changed to “66-74 Gy to gross disease, 44-64 Gy subclinical disease.”
- Neck, Uninvolved nodal stations: “≥ 50 Gy (2.0 Gy/day)” changed to “44-64 Gy (1.6-2.0 Gy/fraction).”

**Salivary Gland Tumors**

**SALI-1, SALI-2, SALI-3, SALI-4**
- The entire salivary gland tumors algorithm was revised.

**SALI-A**
- “Photon/electron therapy” changed to “Photon or photon/electron therapy”.
- Definitive RT:
  - “Unresectable disease” changed to “T4b disease”.
  - Uninvolved nodal stations: “45-54 Gy (1.8-2.0 Gy/day)” changed to “44-64 Gy (1.6-2.0 Gy/fraction)” (Also for Postoperative RT)

**Mucosal Melanoma**

**MM-1, MM-2, MM-3, MM-4, MM-A**
- This is a new algorithm that provides workup, treatment, follow-up, and radiation recommendations for mucosal melanoma.

Continued on next page
Summary of changes in the 1.2010 version of the Head and Neck Cancers guidelines from the 1.2009 version include:

**FOLL-A** Follow-up Recommendations
- This is a new page that provides follow-up recommendations for all of the sites in the Head and Neck Cancers Guidelines.

**SURG-A** Principles of Surgery
- This is a new section that provides general principles for managing patients undergoing surgery and includes recommendations for:
  - Evaluation, Integration of Therapy, Assessment of Resectability (SURG-A 1 of 6)
  - Primary Tumor Resection (SURG-A 2 of 6)
  - Margins, Surgical Management of Cranial Nerves VII, X (including the recurrent laryngeal nerve), XI, and XII (SURG-A 3 of 6)
  - Neck Management (SURG-A 4 of 6)
  - Management of Recurrences (SURG-A 5 of 6)
  - Post Chemoradiation or RT Neck Evaluation (SURG-A 6 of 6)

**RAD-A** Radiation Techniques
- Intensity-Modulated Radiotherapy (IMRT): “IMRT has been shown to be particularly useful in reducing long-term toxicity…” changed to “IMRT has been shown to be useful in reducing long-term toxicity…”

**CHEM-A** Principles of Systemic Therapy
- Squamous Cell Cancers: Lip, Oral Cavity, Oropharynx, Hypopharynx, Glottic larynx, Supraglottic larynx, Ethmoid Sinus, Maxillary Sinus, Occult Primary:
  - Primary Systemic Therapy + concurrent RT
    - Cisplatin alone (preferred) changed from category 2A to “category 1”.
    - Cetuximab changed from category 2A to “category 1”.
    - Carboplatin/taxol (category 2B) was added.
  - Postoperative Chemoradiation
    - Cisplatin alone was designated category 1 for high risk.
  - Induction/Sequential chemotherapy
    - Docetaxel/cisplatin/5-FU designated (category 1 if induction is chosen)
    - Footnote that states, “Induction chemotherapy should only be done in a tertiary setting” is new to the page.
    - The statement, “Following induction, agents to be used with concurrent chemoradiation typically include weekly platinums, weekly taxanes, or cetuximab” is new to the page.
- Nasopharynx
  - Chemoradiation followed by adjuvant chemotherapy
    - Cisplatin + RT followed by Cisplatin/5-FU changed from category 2A to “category 1”.
- Recurrent, Unresectable, or Metastatic (incurable):
  - Combination therapy
    - “Cisplatin or carboplatin + 5-FU ± cetuximab” changed to “Cisplatin or carboplatin + 5-FU + cetuximab (category 1).”
    - Cisplatin + 5-FU was added.
MULTIDISCIPLINARY TEAM

The management of patients with head and neck cancers is complex. All patients need access to the full range of specialists and support services with expertise in the management of patients with head and neck cancer for optimal treatment and follow-up.

- Head and neck surgery
- Radiation oncology
- Medical oncology
- Plastic and reconstructive surgery
- Specialized nursing care
- Dentistry/prosthodontics
- Physical medicine and rehabilitation
- Speech and swallowing therapy
- Clinical Social work
- Nutrition support
- Pathology (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 head and neck cancer patients 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 Palliative Care Guideline)

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

- H&P including a complete head and neck exam; mirror and fiberoptic examination as clinically indicated
- Biopsy
- Chest imaging
- As indicated for primary evaluation
  - Panorex
  - CT/MRI
- Preanesthesia studies
- Dental evaluation
- Multidisciplinary consultation as indicated

CLINICAL STAGING

T1-2, N0

- Surgical candidate
  - See Treatment of Primary and Neck (LIP-2)

T3, T4a, N0
Any T, N1-3

- Poor surgical risk
  - Definitive RT\textsuperscript{a} to primary and nodes or Chemo/RT\textsuperscript{b}
  - Follow-up (See FOLL-A)

T4b, N any, or unresectable nodal disease

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

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

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

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

T1-2, N0
- Surgical excision (preferred) (neck dissection not recommended)\(^d\)
  - or
  - External-beam RT to primary site\(^a,c\) ± brachytherapy
  - Positive margins, perineural/vascular/lymphatic invasion
    - Re-excision or RT\(^a\)
    - No adverse pathologic findings
      - Follow-up (See FOLL-A)

Recurrence (See ADV-2)

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

\(^a\) See Principles of Radiation Therapy (LIP-A).
\(^b\) No elective treatment to neck preferred for T1-2, N0.
\(^c\) See Principles of Surgery (SURG-A).
CLINICAL STAGING:
T3, T4a, N0; Any T, N1-3

TREATMENT OF PRIMARY AND NECK

Surgery (preferred)

N0
Excision of primary ± unilateral or bilateral neck dissection

N1
Excision of primary, ipsilateral neck dissection ± contralateral neck dissection

N2a-b, N3
Excision of primary, ipsilateral neck dissection ± contralateral neck dissection

or

N2c (bilateral)
Excision of primary and bilateral neck dissection

External RT ± brachytherapy or Chemo/RT

ADJUVANT TREATMENT

FOLLOW-UP

Chemo/RT preferred (category 1) or Re-excision (category 1) or RT

Follow-up (See FOLL-A)

Recurrence (See ADV-2)

One positive node without adverse features
RT optional

Extracapsular spread and/or positive margin
RT or Re-excision (category 1)

Other risk features
RT or Consider chemo/RT

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
CLINICAL STAGING:
T3, T4a, N0; Any T, N1-3

TREATMENT OF PRIMARY AND NECK

External RT\textsuperscript{a} ± brachytherapy or Chemo/RT\textsuperscript{b}

Primary site: Complete clinical response (N0 at initial staging)

Primary site: Complete clinical response (N+ at initial staging)

Primary site: < complete clinical response

Residual tumor in neck

Complete clinical response of neck

Salvage surgery + neck dissection as indicated\textsuperscript{d}

Final evaluation

Follow-up

Recurrence

Neck dissection\textsuperscript{d}

Negative
Observe

Positive
Neck dissection\textsuperscript{d}

Post-treatment evaluation\textsuperscript{g}

ADJUVANT TREATMENT

FOLLOW-UP

\begin{itemize}
  \item \textsuperscript{a} See Principles of Radiation Therapy (LIP-A).
  \item \textsuperscript{b} See Principles of Systemic Therapy (CHEM-A).
  \item \textsuperscript{d} See Principles of Surgery (SURG-A).
  \item \textsuperscript{g} See Post Chemoradiation Neck Evaluation (SURG-A 6 of 6).
\end{itemize}

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

<table>
<thead>
<tr>
<th>Type</th>
<th>Dose Range</th>
<th>Fraction Size</th>
</tr>
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<tbody>
<tr>
<td>Definitive RT</td>
<td>66-74 Gy</td>
<td>2.0 Gy/fraction</td>
</tr>
<tr>
<td>Primary and gross adenopathy</td>
<td>50-60 Gy</td>
<td>2.0 Gy/fraction</td>
</tr>
<tr>
<td>External-beam RT ± brachytherapy</td>
<td>50-66 Gy</td>
<td>2.0 Gy/fraction</td>
</tr>
<tr>
<td>Involved nodal stations:</td>
<td>44-64 Gy</td>
<td>1.6-2.0 Gy/fraction</td>
</tr>
<tr>
<td>Uninvolved nodal stations:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative RT</td>
<td>&gt;= 60 Gy</td>
<td>2.0 Gy/fraction</td>
</tr>
<tr>
<td>Primary</td>
<td>60 Gy</td>
<td>2.0 Gy/fraction</td>
</tr>
<tr>
<td>Involved nodal stations:</td>
<td>60-66 Gy</td>
<td>2.0 Gy/fraction</td>
</tr>
<tr>
<td>Uninvolved nodal stations:</td>
<td>44-64 Gy</td>
<td>1.6-2.0 Gy/fraction</td>
</tr>
</tbody>
</table>

Consider elective neck RT in T3-T4 disease for perineural invasion or lymphovascular invasion.

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1 See Radiation Techniques (RAD-A).
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, if indicated
- Preanesthesia studies
- Dental evaluation, including panorex as indicated
- Nutrition, speech & swallowing evaluation/therapy as indicated
- Multidisciplinary consultation as indicated

CLINICAL STAGING

\[ \text{T1–2, N0} \quad \rightarrow \quad \text{See Treatment of Primary and Neck (OR-2)} \]
\[ \text{T3, N0} \quad \rightarrow \quad \text{See Treatment of Primary and Neck (OR-2)} \]
\[ \text{T1–3, N1–3} \quad \rightarrow \quad \text{See Treatment of Primary and Neck (OR-3)} \]
\[ \text{T4a, any N} \quad \rightarrow \quad \text{See Treatment of Primary and Neck (OR-3)} \]
\[ \text{T4b, N any, or unresectable nodal disease} \quad \rightarrow \quad \text{See Treatment of Head and Neck Cancer (ADV-1)} \]

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

**CLINICAL TREATMENT OF PRIMARY AND NECK STAGING**

- **T1–2, N0**
  - Excision of primary (preferred) ± unilateral or bilateral neck dissection
  - External-beam RT ± brachytherapy

- **T3, N0**
  - Excision of primary as indicated and unilateral or bilateral neck dissection

**ADJUVANT TREATMENT**

- No adverse features
  - One positive node without adverse features
  - Extracapsular spread and/or positive margin
  - Adverse features
  - Adverse features (T1, N0 only)
  - Other risk features

- Positive margin
  - RT (optional)
  - RT (preferred) (category 1)
  - Consider chemo/RT

- No residual disease
  - RT (preferred) (category 1)
  - RT (preferred) (category 1)

- Residual disease
  - Salvage surgery
  - Re-resection or RT
  - Consider chemo/RT

- Other risk features
  - RT (preferred) (category 1)
  - RT (preferred) (category 1)

**FOLLOW-UP**

- Follow-up
  - (See FOLL-A)
  - Recurrence
    - (See ADV-2)

---

*a See Principles of Surgery (SURG-A).

b Adverse risk features: extracapsular nodal spread, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, selected pT2N0-N1 disease, nodal disease in levels IV or V, perineural invasion, vascular embolism.

c For positive margin only, re-excite if technically feasible.

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

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

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

**CLINICAL STAGING**

- **N0, N1, N2a-b, N3**
- **T4a, Any N; T1-3, N1-3** → Surgery
- **N2c (bilateral)**

**TREATMENT OF PRIMARY AND NECK**

- **Excision of primary, ipsilateral neck dissection ± contralateral neck dissection**
- **No adverse features**
  - **RT (optional)**
  - **Chemo/RT (preferred) (category 1)** or **Re-excision (category 1) or RT**
- **Adverse features**
  - **Extracapsular spread and/or positive margin**
  - **Other risk features**
  - **RT or Consider chemo/RT**

**ADJUVANT TREATMENT**

- **Follow-up**
  - (See FOLL-A)
- **Recurrence**
  - (See ADV-2)

**FOLLOW-UP**

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

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

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**a See Principles of Surgery (SURG-A).**

**b** Adverse risk features: extracapsular nodal spread, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, selected pT2N0-N1 disease, nodal disease in levels IV or V, perineural invasion, vascular embolism.

**c** For positive margin only, re-excise if technically feasible.

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

**e** See Principles of Systemic Therapy (CHEM-A).
PRINCIPLES OF RADIATION THERAPY

Definitive RT
- Primary and gross adenopathy:
  - Conventional fractionation: 66-74 Gy (2.0 Gy/fraction; daily Monday-Friday)
  - Altered fractionation:
    - 6 fractions/week accelerated; 66-74 Gy to gross disease, 44-64 Gy to subclinical disease.
    - Concomitant boost accelerated RT: 72 Gy/6 weeks (1.8 Gy/fraction, large field; 1.5 Gy boost as second daily fraction during last 12 treatment days)
    - Hyperfractionation: 81.6 Gy/7 weeks (1.2 Gy/fraction, twice daily)
- Neck
  - Uninvolved nodal stations:
    - 44-64 Gy (1.6-2.0 Gy/fraction)

Postoperative RT
- Indicated for pT3 or pT4 primary; N2 or N3 nodal disease, selected pT2, N0-N1 disease, nodal disease in levels IV or V, perineural invasion, vascular embolism.
- Preferred interval between resection and postoperative RT is \( \leq \) 6 weeks.
- Primary: \( \geq \) 60 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
- Indicated for extracapsular nodal spread and/or positive margins
- Consider for other risk features: pT3 or pT4 primary; N2 or N3 nodal disease, nodal disease in levels IV or V, perineural invasion, vascular embolism.
- Concurrent single agent cisplatin at 100 mg/m\(^2\) every 3 wks is recommended.

See Radiation Techniques (RAD-A).

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

**WORKUP**
- H&P including a complete head and neck exam; mirror and fiberoptic 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 as indicated
- Examination under anesthesia with endoscopy
- Preanesthesia studies
- Multidisciplinary consultation as indicated

**CLINICAL STAGING**

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

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*a* Immunohistochemical 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.

*b* Anatomical imaging is also recommended.

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

**CLINICAL STAGING**

**TREATMENT OF PRIMARY AND NECK**

- Complete clinical response
- Residual disease
- No adverse features
- One positive node without adverse features
- Excision of primary ± unilateral or bilateral neck dissection
- Adverse features
- Positive margin (T1, N0 only)
- Other risk features
- Complete clinical response
- Residual disease
- Salvage surgery

**ADJUVANT TREATMENT**

- Salvage surgery
- Consider RT
- Consider chemo/RT (category 1)
- Re-resection or RT
- Consider chemo/RT

**FOR T2, N1 ONLY, RT + systemic therapy (category 2B for systemic therapy)**

- Extracapsular spread and/or positive margin
- RT or Consider chemo/RT

**Follow-up (See FOLL-A)**

- Recurrence (See ADV-2)

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

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See Principles of Radiation Therapy (ORPH-A).
See Principles of Surgery (SURG-A).
See Principles of Systemic Therapy (CHEM-A).

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.
Base of tongue/tonsil/posterior pharyngeal wall/soft palate

**CLINICAL STAGING**

**TREATMENT OF PRIMARY AND NECK**

**ADJUVANT TREATMENT**

- **Concurrent systemic therapy/RT**<sup>c,e</sup> cisplatin (category 1) preferred
  - Complete clinical response
  - Residual disease
  - Salvage surgery

- **No adverse features**<sup>f</sup>
  - RT<sup>c</sup>

- **Surgery for primary and neck**<sup>d</sup>
  - Extraplanar spread and/or positive margin
  - Chemo/RT<sup>c,e</sup> (category 1)
  - Follow-up (See FOLL-A)

- **Other risk features**
  - RT<sup>c</sup> or Consider chemo/RT<sup>c,e</sup>

- **Induction chemotherapy**<sup>e</sup> followed by RT or chemo/RT (category 3)
  - Complete clinical response
  - Residual disease
  - Salvage surgery

- **Multimodality clinical trials**

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<sup>c</sup>See Principles of Radiation Therapy (ORPH-A).
<sup>d</sup>See Principles of Surgery (SURG-A).
<sup>e</sup>See Principles of Systemic Therapy (CHEM-A).

<sup>f</sup>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.

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

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

CLINICAL STAGING

TREATMENT OF PRIMARY AND NECK

Concurrent systemic therapy/RT\textsuperscript{c,e}\textsubscript{,} cisplatin (category 1) preferred

or

Induction chemotherapy\textsuperscript{e} followed by RT or chemo/RT (category 2B)

Any T, N2-3

or

Surgery\textsuperscript{d}

primary and neck

or

Multimodality clinical trials

Residual tumor in neck

Primary site: Complete clinical response

Complete clinical response of neck

Post-treatment evaluation\textsuperscript{g}

Salvage surgery + neck dissection as indicated\textsuperscript{d}

No adverse features\textsuperscript{f}

Primary site: residual tumor

Excision of primary, ipsilateral neck dissection\textsuperscript{d}

Excision of primary and bilateral neck dissection\textsuperscript{d} (bilateral is category 3 if neck nodes contralateral only)

Adverse features\textsuperscript{f}

Other risk features

Neck dissection\textsuperscript{d}

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 Principles of Radiation Therapy (ORPH-A).

See Principles of Surgery (SURG-A).

See Principles of Systemic Therapy (CHEM-A).

Follow-up (See FOLL-A)

Recurrence (See ADV-2)

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

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

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)

Postoperative chemoradiation

- Indicated for extracapsular nodal spread and/or positive margins
- Concurrent single agent cisplatin at 100 mg/m² every 3 wks x 3 doses is recommended.
- Consider for other risk features: pT3 or pT4 primary; N2 or N3 nodal disease, nodal disease in levels IV or V, perineural invasion, vascular embolism.

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

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1 See Radiation Techniques (RAD-A).

2 Based on published data, concurrent chemoradiation typically uses conventional fractionation at 2.0 g per fraction to ≥ 70 Gy in 7 wks with single agent cisplatin given every 3 wks at 100 mg/m² x 3 doses. Use of other fraction sizes (eg, 1.8 Gy, conventional), multiagent chemotherapy, or altered fractionation with chemotherapy has been evaluated with no consensus on the optimal approach. In general, the use of concurrent chemoradiation carries a high toxicity burden—altered fractionation or multiagent chemotherapy will likely further increase toxicity burden. For any chemoradiation approach, close attention should be paid to published reports for the specific chemotherapy agent, dose, and schedule of administration. Chemoradiation should be performed by an experienced team and should include substantial supportive care.


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

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

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**Clinical Staging**

- **Not requiring total laryngectomy**
  - Most T1, N0, selected T2, N0 → See Treatment of Primary and Neck (HYPO-2)

- **Advanced cancer requiring total laryngectomy**
  - T1, N+; T2-3, Any N → See Treatment of Primary and Neck (HYPO-3)
  - T4a, Any N → See Treatment of Primary and Neck (HYPO-5)
  - T4b, N any, or unresectable nodal disease → See Treatment of Head and Neck Cancer (ADV-1)

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*a*Anatomical imaging is also recommended.

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

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

See Principles of Radiation Therapy (HYPO-A).
See Principles of Surgery (SURG-A).
Adverse features: extracapsular nodal spread, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, selected pT1-T2, N0-N-1, perineural invasion, vascular embolism.
See Principles of Systemic Therapy (CHEM-A).
**Head and Neck Cancers**

**Cancer of the Hypopharynx**

**CLINICAL STAGING**

**TREATMENT OF PRIMARY AND NECK**

- Induction chemotherapy (category 1)
  - or
  - Laryngopharyngectomy + neck dissection, including level VI

**ADJUVANT TREATMENT**

- See Response After Induction Chemotherapy (HYPO-4)

**T1, N+; T2-3, any N (if total laryngectomy required)**

- No adverse features
  - Extracapsular spread and/or positive margin
    - Chemo/RT (category 1)

- Adverse features
  - Other risk features
    - RT or Consider chemo/RT
  - Primary site: complete clinical response
    - Complete clinical response of neck
      - Post-treatment evaluation
      - Negative → Observe
      - Positive → Neck dissection
  - Residual tumor in neck
    - Neck dissection

- Salvage surgery + neck dissection as indicated

**MULTIMODALITY CLINICAL TRIALS**

- Concurrent systemic therapy/RT cisplatin preferred
- Multimodality clinical trials

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

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

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**References**

b See Principles of Radiation Therapy (HYPO-A).

c See Principles of Surgery (SURG-A).

d Adverse features: extracapsular nodal spread, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, selected pT1-T2, N0-N-1, perineural invasion, vascular embolism.

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

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

g See Post Chemoradiation Neck Evaluation (SURG-A 6 of 6).
Cancer of the Hypopharynx

**RESPONSE ASSESSMENT**

**Primary site:**
- **Complete response (CR)**
  - Definitive RT (category 1)
  - or Consider chemo/RT (category 2B)
- **Partial response (PR)**
  - Chemo/RT (category 2B)
- **< Partial response**
  - Surgery

**Residual tumor in neck**
- Neck dissection
  - Neck dissection
  - Observe

**Complete clinical response of neck**
- Post-treatment evaluation
  - Positive
  - Neck dissection
  - Observe

**Residual disease**
- Salvage surgery
- Observation

**No adverse features**
- Observation
- RT

**Extracapsular spread and/or positive margin**
- RT
  - or Consider chemo/RT

**Adverse features**
- Observation
- RT or Consider chemo/RT

**Other risk features**
- Observation
- RT or Consider chemo/RT

**Follow-up**
- (See FOLL-A)

**Recurrence**
- (See ADV-2)

---

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

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See Principles of Surgery (SURG-A).

Adverse features: extracapsular nodal spread, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, selected pT1-T2, NO-N1, perineural invasion, vascular embolism.

See Principles of Systemic Therapy (CHEM-A).

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

See Post Chemoradiation Neck Evaluation (SURG-A 6 of 6).
**CLINICAL STAGING**

**TREATMENT OF PRIMARY AND NECK**

- Surgery + neck dissection\(^c\) (preferred)
- Induction chemotherapy\(^e,f\) (category 3)
- Concurrent systemic therapy/RT\(^e\) (category 3)
- Multimodality clinical trials

**ADJUVANT TREATMENT**

- Primary site: clinical complete response
- Residual tumor in neck
- RT\(^b\) or Chemo/RT\(^b,e\)
- Neck dissection\(^c\)
- Complete clinical response of neck
- Post-treatment evaluation\(^g\)
- Negative → Observe
- Positive → Neck dissection\(^c\)
- Primary site: residual tumor
- Salvage surgery + neck dissection as indicated\(^c\)
- RT or Chemo/RT
- Residual tumor in neck
- Neck dissection\(^c\)
- Complete clinical response of neck
- Post-treatment evaluation\(^g\)
- Negative → Observe
- Positive → Neck dissection\(^c\)
- Primary site: residual tumor
- Salvage surgery + neck dissection as indicated\(^c\)

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\(^b\) See Principles of Radiation Therapy (HYPO-A).
\(^c\) See Principles of Surgery (SURG-A).
\(^e\) See Principles of Systemic Therapy (CHEM-A).
\(^f\) In randomized clinical trials, assessment of response has been done after 2 or 3 cycles.
\(^g\) See Post Chemoradiation Neck Evaluation (SURG-A 6 of 6).

**Note:** All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Definitive RT
- Primary and gross adenopathy:
  Conventional fractionation: 66-74 Gy (2.0 Gy/fraction; daily Monday-Friday)
  Altered fractionation:
    ▶ 6 fractions/week accelerated; 66-74 Gy to gross disease, 44-64 Gy to subclinical disease.
    ▶ Concomitant boost accelerated RT:
      72 Gy/6 weeks (1.8 Gy/fraction, large field; 1.5 Gy boost as second daily fraction during last 12 treatment days)
    ▶ Hyperfractionation: 81.6 Gy/7 weeks (1.2 Gy/fraction, twice daily)
- Neck
  Uninvolved nodal stations:
    44-64 Gy (1.6-2.0 Gy/fraction)

Postoperative RT
- Indicated for pT3 or pT4 primary, N2 or N3 nodal disease, selected pT1-T2, N0-N1, perineural invasion, vascular embolism.
- Preferred interval between resection and postoperative ≤ RT is 6 weeks.
- Primary: ≥ 60 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
- Indicated for extracapsular nodal spread and/or positive margins
- Consider for other risk features: pT3 or pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism.
- Concurrent single agent cisplatin at 100 mg/m² every 3 wks is recommended.

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1 See Radiation Techniques (RAD-A).
2 Particular attention to speech and swallowing needs during therapy.
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 as indicated
- Imaging for distant metastases (chest, liver, bone) for WHO class 2-3/N2-3 disease (may include PET scan and/or CT)

Multidisciplinary consultation

CLINICAL STAGING

T1, N0, M0 → See Treatment of Primary and Neck (NASO-2)

T1, N1-3; T2-T4, Any N → See Treatment of Primary and Neck (NASO-2)

Any T, Any N, M1 → See Treatment of Primary and Neck (NASO-2)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
CLINICAL STAGING  
T1, N0, M0  
Definitive RT\textsuperscript{a} to nasopharynx and elective RT to neck

T1, N1-3; T2-T4, any N  
Cisplatin 100 mg/m\textsuperscript{2} on days 1, 22, 43 or cisplatin 40 mg/m\textsuperscript{2} every wk + RT (≥ 70 Gy) to primary and gross nodal disease (category 1) and bilateral neck: ≥ 50 Gy or Induction chemotherapy\textsuperscript{b} followed by chemo/RT (category 3)

Any T, any N, M1  
Platinum-based combination chemotherapy\textsuperscript{b}

TREATMENT OF PRIMARY AND NECK

Cisplatin, 80 mg/m\textsuperscript{2} day 1+ 5-FU, 1,000 mg/m\textsuperscript{2}, CI x 4 days; repeat every 4 wk x 3 courses

Neck: residual tumor  
Neck dissection\textsuperscript{c}

Neck: complete clinical response  
Observe

FOLLOW-UP

Follow-up (See FOLL-A)  
Recurrence (See ADV-2)

If complete clinical response  
Definitive RT\textsuperscript{a} to primary and neck or Chemo/RT

\textsuperscript{a} See Principles of Radiation Therapy (NASO-A).
\textsuperscript{b} See Principles of Systemic Therapy (CHEM-A).
\textsuperscript{c} See Principles of Surgery (SURG-A).

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

Definitive RT
- Primary and gross adenopathy: 66-70 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.

1 See Radiation Techniques (RAD-A).

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

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

Multidisciplinary consultation as indicated

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**CLINICAL STAGING**

- Carcinoma in situ
  - See Treatment (GLOT-2)
- Total laryngectomy not required
  - Most T1-2, N0
  - See Treatment (GLOT-2)
- Requiring total laryngectomy
  - Most T3, N0-1
  - See Treatment of Primary and Neck (GLOT-3)
  - Requiring total laryngectomy
  - Most T3, N2-3
  - See Treatment of Primary and Neck (GLOT-4)
- T4a disease
  - See Treatment of Primary and Neck (GLOT-6)
- T4b, N any, or unresectable nodal disease
  - See Treatment of Head and Neck Cancer (ADV-1)

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**TREATMENT OF PRIMARY AND NECK**

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

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

---

*aComplete workup not indicated for Tis, T1.*
Carcinoma in situ → Clinical trial or Endoscopic resection\(^b\) or RT\(^c\)

- Total laryngectomy not required
- Most T1-2, N0, N+ rare

RT\(^c\) → Partial laryngectomy/ endoscopic or open resection\(^b\) as indicated

N0 → Observe

Follow-up (See FOLL-A) → Recurrence (See ADV-2)

\(^b\) See Principles of Surgery (SURG-A).
\(^c\) See Principles of Radiation Therapy (GLOT-A).

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

Complete clinical response of neck

Primary site: residual tumor

Salvage surgery + neck dissection as indicated

Primary site: Complete clinical response (N0 at initial staging)

Laryngectomy with ipsilateral thyroidectomy ± unilateral or bilateral neck dissection

Laryngectomy with ipsilateral thyroidectomy, ipsilateral neck dissection ± contralateral neck dissection

No adverse features

Extracapsular spread and/or positive margin

Adverse features

Other risk features

Neck dissection

Negative → Observe

Positive → Neck dissection

Follow-up (See FOLL-A)

Recurrence (See ADV-2)

CLINICAL STAGING

TREATMENT OF PRIMARY AND NECK

ADJUVANT TREATMENT

Concurrent systemic therapy/RT (category 1) preferred or RT if patient not candidate for systemic therapy/RT

Surgery

N0

N1

Primary site: Complete clinical response (N+ at initial staging)

Residual tumor in neck

Complete clinical response of neck

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

- Requiring total laryngectomy
- Most T3, N2-3

**TREATMENT OF PRIMARY AND NECK**

- Concurrent systemic therapy/RT\(^d\) cisplatin (category 1) preferred

- **Primary site:** Complete clinical response
  - Complete clinical response of neck
  - Post-treatment evaluation\(^e\)
  - Salvage surgery + neck dissection as indicated\(^b\)

- **Primary site:** residual tumor
  - Laryngectomy with ipsilateral thyroidectomy, ipsilateral or bilateral neck dissection\(^b\)

- Surgery\(^b\)

- Induction chemotherapy\(^d\) (category 3)

**ADJUVANT TREATMENT**

- Neck dissection\(^b\)

- Negative → Observe

- Positive → Neck dissection\(^b\)

**Follow-up** (See FOLL-A)

- Recurrence (See ADV-2)

**RECURRENT RISK FEATURES**

- Extracapsular spread and/or positive margin

- Other risk features

- RT\(^c\)

- Consider chemo/RT\(^c,d\)

**CLINICAL STAGING**

- No adverse features\(^f\)

**Adverse features:** extracapsular nodal spread, positive margins, pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism.

- Extracapsular spread and/or positive margin

- Other risk features

- RT\(^c\)

- Consider chemo/RT\(^c,d\)

**Response Assessment** (GLOT-5)

\(^b\) See Principles of Surgery (SURG-A).
\(^c\) See Principles of Radiation Therapy (GLOT-A).
\(^d\) See Principles of Systemic Therapy (CHEM-A).
\(^e\) See Post Chemoradiation Neck Evaluation (SURG-A 6 of 6).
\(^f\) Adverse features: extracapsular nodal spread, positive margins, pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism.

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

**Primary site: Complete response (CR)**
- Definitive RT (category 1) or Consider chemo/RT (category 2B)
  - Residual tumor in neck
    - Neck dissection<br>
    - Negative: Observe
   - Positive: Neck dissection

**Primary site: Partial response (PR)**
- Chemo/RT (category 2B)
  - Complete clinical response of neck
    - Post-treatment evaluation
      - Negative: Observe
      - Positive: Neck dissection
  - Residual disease
    - Salvage surgery

**Primary site: < Partial response**
- Surgery<br>
  - No adverse features<br>
    - RT
  - Adverse features<br>
    - Extracapsular spread and/or positive margin
      - Chemo/RT (category 1)
    - Other risk features
      - RT or Consider chemo/RT

**Response after induction chemo-therapy**
- Adverse features: extracapsular nodal spread, positive margins, pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism.

**Adverse features**

**Follow-up**
- (See FOLL-A)

**Recurrence**
- (See ADV-2)

---

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

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

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**See Principles of Surgery (SURG-A).**
**See Principles of Systemic Therapy (CHEM-A).**
**See Post Chemoradiation Neck Evaluation (SURG-A 6 of 6).**
**Adverse features: extracapsular nodal spread, positive margins, pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism.**
**In randomized clinical trials, assessment of response has been done after 2 or 3 cycles.**
**Clinical Staging**

**T4a, Any N → Surgery**

- N0 → Laryngectomy with ipsilateral thyroidectomy ± unilateral or bilateral neck dissection
- N1 → Laryngectomy with ipsilateral thyroidectomy, ipsilateral neck dissection ± contralateral neck dissection
- N2-3 → Laryngectomy with ipsilateral thyroidectomy, ipsilateral or bilateral neck dissection

**Adjuvant Treatment**

- Chemo/RT (category 1)

**Selected T4a patients who decline surgery**

- Consider concurrent chemoradiation or Clinical trial for function preserving surgical or nonsurgical management or Induction chemotherapy followed by chemo/RT (category 2B)

**Response**

- Primary site: Complete clinical response
- Residual tumor in neck
- Post-treatment evaluation
- Negative → Observe
- Positive → Neck dissection

**Surgery**

- Primary site: residual tumor
- Salvage surgery + neck dissection as indicated

**Follow-up**

- (See FOLL-A)

**Reurrence**

- (See ADV-2)

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

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See Principles of Surgery (SURG-A).
See Principles of Radiation Therapy (GLOT-A).
See Principles of Systemic Therapy (CHEM-A).
See Post Chemoradiation Neck Evaluation (SURG-A 6 of 6).
Definitive RT
- T1, N0: 63-66 Gy in 2.25-2.0 Gy/fraction
- T1-2: > 66 Gy using conventional fractionation (2.0 Gy/fraction)
- ≥ T2 and gross adenopathy:
  - Conventional fractionation: 70 Gy (2.0 Gy/fraction) in 7 weeks
  - Altered fractionation:
    - Concomitant boost accelerated RT: 72 Gy/6 weeks
      (1.8 Gy/fraction, large field; 1.5 Gy boost as second daily fraction during last 12 treatment days)
    - Hyperfractionation: 79.2-81.6 Gy/7 weeks (1.2 Gy/fraction, twice daily)
- Uninvolved nodal stations:
  44-64 Gy (1.6-2.0 Gy/fraction)

Postoperative RT
- Indicated for pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism.
- Preferred interval between resection and postoperative RT is ≤ 6 weeks.
- 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
- Indicated for extracapsular nodal spread and/or positive margins
- Consider for other risk features: pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism
- Concurrent single agent cisplatin at 100 mg/m² every 3 wks is recommended.

1 See Radiation Techniques (RAD-A).

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

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

CLINICAL STAGING

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

- Requiring total laryngectomy
  - T3, N0
  - See Treatment of Primary and Neck (SUPRA-3)

- T4a, N0
  - See Treatment of Primary and Neck (SUPRA-8)

- Node positive disease
  - See Clinical Staging (SUPRA-4)

- T4b, N any or unresectable nodal disease
  - See Treatment of Head and Neck Cancer (ADV-1)

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

**Clinical Staging**
- Not requiring total laryngectomy
- Most T1-2, N0

**Treatment of Primary and Neck**
- Endoscopic resection ± neck dissection\(^a\)
- Open partial supraglottic laryngectomy ± neck dissection\(^a\)
- Definitive RT\(^b\)

**Pathology Stage**
- Node negative, (T1-T2, N0)
- One positive node without other adverse features
- Positive node; Adverse features: positive margins
- Adverse features: extracapsular nodal spread
- Node negative, (T3-T4a, N0)

**Adjuvant Treatment**
- Consider RT\(^b\)
- Re-excision or RT\(^b\) or Consider chemo/RT\(^b,c\) (category 2B)
- Chemo/RT\(^b,c\) (category 1) or RT\(^b\) (category 2B for select patients)

**Follow-up**
- Follow-up (See FOLL-A)
- Recurrence (See ADV-2)

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

\(^a\) See Principles of Surgery (SURG-A).
\(^b\) See Principles of Radiation Therapy (SUPRA-A).
\(^c\) See Principles of Systemic Therapy (CHEM-A).
TREATMENT OF PRIMARY AND NECK

Primary site:
Complete clinical response

Primary site:
residual tumor

Salvage surgery + neck dissection as indicated

N0 or one positive node without adverse features

RT\(^b\) optional

Laryngectomy, ipsilateral thyroidectomy with ipsilateral or bilateral neck dissection

RT\(^b\) if patient not medical candidate for concurrent systemic therapy/RT

Induction chemotherapy\(^c\) (category 3)

Extracapsular spread and/or positive margin

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

Other risk features

RT\(^b\) or Consider chemo/RT\(^b,c\)

See Response Assessment (SUPRA-7)

CLINICAL STAGING

- Requiring total laryngectomy
- T3, N0

ADJUVANT TREATMENT

Follow-up (See FOLL-A)

Recurrence (See See ADV-2)

\(^a\) See Principles of Surgery (SURG-A).
\(^b\) See Principles of Radiation Therapy (SUPRA-A).
\(^c\) See Principles of Systemic Therapy (CHEM-A).
\(^d\) Adverse features: extracapsular nodal spread, positive margins, pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism.

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

### Clinical Staging

- Not requiring total laryngectomy
- T1-2, N+ and selected T3, N1

### Treatment of Primary and Neck

- Concurrent systemic therapy/RT cisplatin (category 1) preferred \(^b,c\)
- Definitive RT \(^b\)
- Partial supraglottic laryngectomy and neck dissection(s) \(^a\)
- Induction chemotherapy \(^c\) (category 3)

### Adjuvant Treatment

- Residual tumor in neck
- Complete clinical response
- Post-treatment evaluation \(^e\)
- Neck dissection \(^a\)
- Negative → Observe
- Positive → Neck dissection \(^a\)
- Observation or RT \(^b\)
- Recurrence (See ADV-2)

### Adverse Features

- Extracapsular spread and/or positive margin
  - Chemo/RT \(^b,c\) (category 1)
- Other risk features
  - RT \(^b\)
  - Consider chemo/RT \(^b,c\)

### Additional Notes

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

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\(^a\) See Principles of Surgery (SURG-A).
\(^b\) See Principles of Radiation Therapy (SUPRA-A).
\(^c\) See Principles of Systemic Therapy (CHEM-A).
\(^d\) Adverse features: extracapsular nodal spread, positive margins, pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism.
\(^e\) See Post Chemoradiation Neck Evaluation (SURG-A 6 of 6).
**CLINICAL STAGING**
- Requiring total laryngectomy
- Most T3, N2-N3

**TREATMENT OF PRIMARY AND NECK**

- **Residual tumor in neck**
  - **Complete clinical response**
  - **Concurrent systemic therapy/RT** \(b, c\)
   - **Cisplatin (category 1) preferred**
   - *or* **Primary site: residual tumor**
   - **Salvage surgery + neck dissection as indicated** \(a\)

- **No adversefeatures** \(d\)
  - **Laryngectomy, ipsilateral thyroidectomy with neck dissection** \(a\)
  - **Induction chemotherapy** \(c\)
    - **Followed by chemo/RT** (category 2B)
    - *in selected T3, N2-N3 patients*

- **Complete clinical response of neck**
  - **Post-treatment evaluation** \(e\)
  - **Positive**
    - **Neck dissection** \(a\)
  - **Negative**
    - **Observe**

**ADJUVANT TREATMENT**

- **Recurrence** (See ADV-2)
- Follow-up (See FOLL-A)

---

*a* See Principles of Surgery (SURG-A).

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

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

*d* Adverse features: extracapsular nodal spread, positive margins, pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism.

*e* See Post Chemoradiation Neck Evaluation (SURG-A 6 of 6).

---

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

**Primary site: Complete response (CR)**
- Definitive RT (category 1) or Consider chemo/RT (category 2B)
  - Complete clinical response of neck
    - Post-treatment evaluation
      - Negative → Observe
      - Positive → Neck dissection

**Primary site: Partial response (PR)**
- Chemo/RT (category 2B)
  - Residual disease
    - Salvage surgery
  - CR
    - Observe

**Primary site: < Partial response**
- Surgery
  - No adverse features
    - RT
  - Adverse features
    - Extracapsular spread and/or positive margin
      - Chemo/RT (category 1)
    - Other risk features
      - RT or Consider chemo/RT

---

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

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

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Materials included in this document are not intended to be the primary source of information for clinical decision-making. Please consult current editions of the NCCN Clinical Practice Guidelines in Oncology for the most up-to-date information.

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

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

See Principles of Surgery (SURG-A 6 of 6).

See Post Chemoradiation Neck Evaluation (SURG-A 6 of 6).
**CLINICAL STAGING**

T4a, N0-N3

**TREATMENT OF PRIMARY AND NECK**

- Laryngectomy, ipsilateral thyroidectomy with ipsilateral or bilateral neck dissection

**ADJUVANT TREATMENT**

- Extracapsular spread and/or positive margin
  - Chemo/RT (category 1)

- Other risk features
  - RT or
  - Consider chemo/RT

**TREATMENT OF PRIMARY AND NECK CLINICAL STAGING**

- T4a, N0-N3 patients who decline surgery
  - Consider concurrent chemoradiation or Clinical trial or Induction chemotherapy followed by chemo/RT (category 2B)

**ADJUVANT TREATMENT**

- Residual tumor in neck
  - Complete clinical response of neck
    - Post-treatment evaluation
      - Negative → Neck dissection
      - Positive → Neck dissection

- Salvage surgery + neck dissection as indicated

**Follow-up**

- (See FOLL-A)

**Recurrence**

- (See ADV-2)

---

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

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

**T1-2, N0:** ≥ 66 Gy conventional (2.0 Gy/fraction)

**T2-3, N0-1:**
- 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)
- Altered fractionation:
  - 6 fractions/week accelerated; 66-74 Gy to gross disease, 44-64 Gy to subclinical disease.
  - Concomitant boost accelerated RT:
    - 72 Gy/6 weeks (1.8 Gy/fraction, large field; 1.5 Gy boost as second daily fraction during last 12 treatment days)
  - Hyperfractionation: 81.6 Gy/7 weeks (1.2 Gy/fraction BID)
  - Neck
    - Uninvolved nodal stations: 44-64 Gy (1.6-2.0 Gy/fraction)

### Chemoradiation

Concurrent platinum plus 70 Gy/7 weeks conventional

### Postoperative RT

- Indicated for pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism.
- Preferred interval between resection and postoperative RT is ≤ 6 weeks.
- 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

- Indicated for extracapsular nodal spread and/or positive margins²-⁴
- Consider for other risk features: pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism.
- Concurrent single agent cisplatin at 100 mg/m² every 3 wks is recommended.

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1. See Radiation Techniques (RAD-A).

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

- **H&P including a complete head and neck exam; mirror and fiberoptic examination as clinically indicated**
- **CT and/or MRI**
- **Chest imaging**

### Clinical Presentation

- Unresected mass or incompletely resected mass

### Pathology

- Squamous cell carcinoma
- Adenocarcinoma
- Minor salivary gland tumor
- Sarcoma (non-rhabdomyosarcoma)
- Esthesioneuroblastomas[^1]
- Undifferentiated carcinoma (SNUC, small cell neuroendocrine)[^1]
- Mucosal melanoma ([See Mucosal Melanoma Guidelines MM-1](#))

[^1]: For sinonasal undifferentiated carcinoma (SNUC), esthesioneuroblastoma, and small cell neuroendocrine histologies, systemic therapy should be a part of the overall treatment.

---

[^1]: For sinonasal undifferentiated carcinoma (SNUC), esthesioneuroblastoma, and small cell neuroendocrine histologies, systemic therapy should be a part of the overall treatment.
### CLINICAL PRESENTATION

<table>
<thead>
<tr>
<th>Newly diagnosed; T1, T2</th>
<th>PRIMARY TREATMENT</th>
<th>ADJUVANT TREATMENT</th>
<th>FOLLOW-UP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Complete surgical resection(^b) (preferred)</td>
<td>RT or Observation(^d) for T1 only (category 2B) or Consider Chemo/RT(^c) (category 2B) if adverse features(^e)</td>
<td>Follow-up (See FOLL-A)</td>
</tr>
<tr>
<td></td>
<td>or Definitive RT</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Newly diagnosed; T3, T4a</th>
<th></th>
<th>RT or Consider chemo/RT(^c) (category 2B) if adverse features(^e)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Complete surgical resection(^b)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>or RT</td>
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<td></td>
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<tr>
<td></td>
<td>or Surgery (preferred), if feasible</td>
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</tr>
<tr>
<td></td>
<td>or RT</td>
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<td></td>
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<tr>
<td></td>
<td>or Chemo/RT(^c)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Newly diagnosed, T4b</th>
<th></th>
<th>RT or Consider chemo/RT(^c) (category 2B) if adverse features(^e)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diagnosed after incomplete excision (eg, polypectomy, endoscopic procedure) and gross residual disease</td>
<td>Surgery(^b) (preferred), if feasible or RT or Chemo/RT(^c)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>or RT</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>or Chemo/RT(^c)</td>
<td></td>
</tr>
</tbody>
</table>

| Diagnosed after incomplete excision (eg, polypectomy, endoscopic procedure) and no residual disease on physical exam, imaging, and/or endoscopy | RT \(^b\) if feasible (See newly diagnosed T1,T2) | RT or Observation\(^d\) for T1 only (category 2B) |          |

\(^b\) See Principles of Surgery (SURG-A).
\(^c\) See Principles of Systemic Therapy (CHEM-A).
\(^d\) Pathologic features: Negative margins, favorable histology, central tumors, low grade tumors.
\(^e\) Adverse features include positive margins and intracranial extension.

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

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

- H&P including a complete head and neck exam; mirror and fiberoptic examination as clinically indicated
- Complete head and neck CT with contrast and/or MRI
- Dental/prosthetic consultation as indicated
- Chest imaging

PATHOLOGY

- Squamous cell carcinoma
- Adenocarcinoma
- Minor salivary gland tumor
- Sarcoma (non-rhabdomyosarcoma)
- Esthesioneuroblastoma
- Undifferentiated carcinoma (SNUC, small cell neuroendocrine)
- Mucosal melanoma

For sinonasal undifferentiated carcinoma (SNUC), esthesioneuroblastoma, and small cell neuroendocrine histologies, systemic therapy should be a part of the overall treatment. Consider referral to a major medical center that specializes in this disease.

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

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

**Maxillary Sinus Tumors**

**STAGING**

**T1-2, N0**
- All histologies except adenoid cystic
  - Complete surgical resection

**T1-2, N0 Adenoid cystic**
- Complete surgical resection
  - Suprastructure
  - Infrastructure

**PRIMARY TREATMENT**

**Margin negative**
- Complete surgical resection
- Perineural invasion
- Margin positive
- Surgical resection

**Margin positive**
- Surgical reresection, if possible
- Consider RT (category 2B)

**ADJUVANT TREATMENT**

**Margin negative**
- Consider RT (category 2B)

**Margin positive**
- Chemo/RT (category 2B)

**FOLLOW-UP**

- Follow-up (See FOLL-A)
- Recurrence (See ADV-2)

---

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

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See Principles of Surgery (SURG-A).
See Principles of Radiation Therapy (MAXI-A).
See Principles of Systemic Therapy (CHEM-A).
### STAGING

- **T3-T4a, N0 squamous cell**
  - Complete surgical resection\(^c\)
  - Adverse features\(^f\)
  - Chemo/RT\(^e\) to primary and neck (category 2B)

- **T4b, any N, squamous cell**
  - Clinical trial or Definitive RT\(^d\) or Chemo/RT\(^e\)
  - Follow-up (See FOLL-A)

- **T1-T4a, N+, squamous cell**
  - Surgical excision + neck dissection\(^c\)
  - Adverse features\(^f\)
  - Chemo/RT\(^e\) to primary and neck (category 2B)

\(^{c}\) **See Principles of Surgery (SURG-A).**
\(^{d}\) **See Principles of Radiation Therapy (MAXI-A).**
\(^{e}\) **See Principles of Systemic Therapy (CHEM-A).**
\(^{f}\) *Adverse features include positive margins or extracapsular nodal spread.*

---

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

PRINCIPLES OF RADIATION THERAPY

Definitive RT
- Primary and gross adenopathy:
  - Conventional fractionation: 66-74 Gy (2.0 Gy/fraction; daily Monday-Friday)
  - Altered fractionation:
    - 6 fractions/week accelerated; 66-74 Gy to gross disease,
      44-64 Gy to subclinical disease.
    - Concomitant boost accelerated RT: 72 Gy/6 weeks (1.8 Gy/fraction, large field; 1.5 Gy boost as second daily fraction during last 12 treatment days)
    - Hyperfractionation: 81.6 Gy/7 weeks (1.2 Gy/fraction, twice daily)
- Neck
  - Uninvolved nodal stations:
    - 44-64 Gy (1.6-2.0 Gy/fraction)

Postoperative RT
- 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)

IMRT is a preferred technique for maxillary sinus or paranasal sinus tumors to minimize dose to critical structures.

---

1 See Radiation Techniques (RAD-A).

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

Newly diagnosed (M0); T4b, any N, or unresectable nodal disease

- Clinical trial preferred
- Standard therapy

**PS 0-1**
- Concurrent cisplatin chemotherapy^{a,b} + RT^{c} (category 1)
- Induction chemotherapy^{b} followed by chemoradiation (category 3)

**PS 2**
- Definitive RT^{c} ± concurrent systemic therapy^{b}

**PS 3**
- Definitive RT^{c} or Best supportive care

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

**Follow-up** (See FOLL-A)

**Recurrence** (See ADV-2)

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

^{b} See Principles of Systemic Therapy (CHEM-A).

^{c} See Principles of Radiation Therapy (ADV-A).
TREATMENT OF HEAD AND NECK CANCER

Recurrent/Persistent Head and Neck Cancer

Locoregional recurrence without prior RT

- Resectable
- Unresectable

Locoregional recurrence or Second primary with prior RT

- Resectable
- Unresectable

Distant metastases

- Clinical trial preferred
  - PS 0-1
    - Combination chemotherapy
      - or
      - Single-agent chemotherapy
    - or
      - Best supportive care
  - PS 2
    - Standard therapy
  - PS 3
    - Best supportive care

No adverse features

- Extracapsular spread and/or positive margin
  - Chemo/RT (category 1)
  - or
  - Consider chemotherapy

Adverse features

- Other risk features
  - RT
  - or Consider chemotherapy

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

Salvage therapy for persistent disease as indicated

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

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

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

See Principles of Systemic Therapy (CHEM-A).
See Principles of Radiation Therapy (ADV-A).
See Principles of Surgery (SURG-A).

*Adverse features: extracapsular nodal spread, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism.*
PRINCIPLES OF RADIATION THERAPY

Definitive RT

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

Concurrent chemoradiation (preferred)

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)

Chemoradiation

Based on published data, concurrent chemoradiation typically uses conventional fractionation at 2.0 Gy/fraction to ≥ 70 Gy in 7 wks with single agent cisplatin given every 3 wks at 100 mg/m² x 3 doses. Use of other fraction sizes (eg, 1.8 Gy, conventional), multiagent chemotherapy or altered fractionation with chemotherapy has been evaluated with no consensus on the optimal approach. In general, the use of concurrent chemoradiation carries a high toxicity burden—altered fractionation or multiagent chemotherapy will likely further increase toxicity burden. For any chemoradiation approach, close attention should be paid to published reports for the specific chemotherapy agent, dose and schedule of administration. Chemoradiation should be performed by an experienced team and include substantial supportive care.

1 See Radiation Techniques (RAD-A).

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

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

**Neck mass**

H&P: Complete head and neck exam with attention to skin; mirror and fiberoptic examination as indicated to visualize nasopharynx, oropharynx, hypopharynx, and larynx

**WORKUP**

- Neck mass
  - Fine-needle aspiration\(^a\) (preferred) or Open biopsy\(^a\)
  - Squamous cell carcinoma, adenocarcinoma, and anaplastic epithelial tumors\(^b\)
  - Lymphoma
    - See NCCN Non-Hodgkin’s Lymphoma Guidelines
  - Thyroid
    - See NCCN Thyroid Carcinoma Guidelines
  - Melanoma
    - Skin exam, note regressing lesions
    - Systemic work-up per NCCN Melanoma Guidelines

\(^a\) Repeat FNA, core, or open biopsy may be necessary for uncertain or non-diagnostic histologies. Patient should be prepared for neck dissection at time of open biopsy, if indicated.

\(^b\) Determined with appropriate immunohistochemical stains.

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

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

**Node level I, II, III, upper V**
- Examination under anesthesia (EUA)
- Palpation and inspection
- Biopsy of areas of clinical concern and tonsillectomy
- Direct laryngoscopy and nasopharynx survey

**Node level IV, lower V**
- EUA including direct laryngoscopy, esophagoscopy
- Chest/abdominal/pelvic CT

**DEFINITIVE TREATMENT**

Primary found

- Adenocarcinoma of neck node, thyroglobulin negative
  - Levels I-III
  - Neck dissection + parotidectomy, if indicated
    - RT\(^d\) to neck ± parotid bed

- Levels IV, V
  - Neck dissection
  - Evaluate for infraclavicular primary

Poorly differentiated or nonkeratinizing squamous cell or NOS or anaplastic (not thyroid) of neck node or Squamous cell carcinoma of neck node

- See Definitive Treatment (OCC-3)

\(^c\)See Principles of Surgery (SURG-A).
\(^d\)See Principles of Radiation Therapy (OCC-A).

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

#### HISTOLOGY

- Poorly differentiated or nonkeratinizing squamous cell or NOS or anaplastic (not thyroid) or Squamous cell carcinoma

#### DEFINITIVE TREATMENT

**Surgery**

- Neck dissection

**Chemotherapy/RT** (category 2B)

- Complete clinical response
- Post-treatment evaluation
  - Negative → Observe
  - Positive → Neck dissection

**RT** (category 3)

- Residual tumor in neck → Neck dissection

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

- N1 without extracapsular spread → See OCC-4
- or
- N2, N3 without extracapsular spread → See OCC-5
- or
- Extracapsular spread → See OCC-6

---

See Principles of Surgery (SURG-A).

See Principles of Radiation Therapy (OCC-A).

See Principles of Systemic Therapy (CHEM-A).

See Post Chemoradiation Neck Evaluation (SURG-A 6 of 6).

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**Note:** All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
RT$^d$ to oral cavity, Waldeyer’s ring, oropharynx, bilateral neck (block RT to the larynx)
or RT$^d$ to neck only (category 3)

RT$^d$ to oropharynx and bilateral neck or RT$^d$ to neck only (category 3)

RT$^d$ to Waldeyer’s ring, larynx, hypopharynx, bilateral neck or RT$^d$ to neck only (category 3)

RT$^d$ to larynx, hypopharynx, bilateral neck or RT$^d$ to neck only (category 3)

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

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

See Principles of Radiation Therapy (OCC-A).
See Principles of Systemic Therapy (CHEM-A).
Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

See Principles of Radiation Therapy (OCC-A).
See Principles of Systemic Therapy (CHEM-A).

Level I only
- Chemotherapy/RT (category 1) with
  - RT to oral cavity, Waldeyer’s ring, oropharynx, both sides of the neck (block RT to the larynx) or
  - RT to neck only (category 3)

Level II, III, upper level V
- Chemotherapy/RT (category 1) with
  - RT to nasopharynx, both sides of the neck, hypopharynx, larynx, oropharynx or
  - RT to neck only (category 3)

Level IV only
- Chemotherapy/RT (category 1) with
  - RT to Waldeyer’s ring, larynx, hypopharynx, both sides of the neck or
  - RT to neck only (category 3)

Lower level V
- Chemotherapy/RT (category 1) with
  - RT to larynx, hypopharynx, both sides of the neck or
  - RT to neck only (category 3)
PRINCIPLES OF RADIATION THERAPY

Gross Adenopathy:
Altered fractionation:
- 6 fractions/week accelerated; 66-74 Gy to gross disease, 44-64 Gy to subclinical disease.
- Concomitant boost accelerated RT:
  - 72 Gy/6 weeks (1.8 Gy/fraction, large field; 1.5 Gy boost as second daily fraction during last 12 treatment days)
- Hyperfractionation: 81.6 Gy/7 weeks (1.2 Gy/fraction, twice daily)

Mucosal dosing:
- 50-66 Gy (2.0 Gy/fraction) to mucosa, depending on field size and use of chemotherapy. Consider higher dose to 60-66 Gy to particularly suspicious areas

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

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

1 For squamous cell carcinoma, adenocarcinoma, and poorly differentiated carcinoma.
2 See Radiation Techniques (RAD-A)
CLINICAL PRESENTATION

Unresected salivary gland mass
- Parotid
- Submandibular
- Minor salivary gland

or

Incompletely resected salivary gland mass

WORKUP

- H&P including a complete head and neck exam; mirror and fiberoptic examination as clinically indicated
- CT/MRI, if clinically indicated
- Chest imaging
- Open biopsy or consider fine-needle aspiration (may not be necessary in incompletely resected patients)

CLINICALLY BENIGN OR CARCINOMA

- See SALI-2

LYMPHOMA

- See NCCN Non-Hodgkin’s Lymphoma Guidelines

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

### Pathology Result

**Benign or Low grade**
- Adenoid cystic; indeterminate or high grade
  - Consider RT (category 2B for T1)

- Complete surgical excision

**Benign**
- Parotid gland
  - Surgical evaluation
  - Cancer site
  - Other salivary glands

**T3, T4a**
- Surgical evaluation

**T4b**
- No surgical resection possible or surgical resection not recommended

**Follow-up as clinically indicated**

**Pathology Result**

- No surgical resection possible or surgical resection not recommended
- Definitive RT or Chemo/RT (category 2B)

**Follow-up (See FOLL-A) → Recurrence (See SALI-4)**

**Benign**
- Follow-up as clinically indicated

**Surgical excision**
- See Principles of Radiation Therapy (SALI-A).

**Clinical Trials**

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

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

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

---

**Notes:**

- All recommendations are category 2A unless otherwise indicated.
- Characteristics of benign tumor include mobile superficial lobe, slow growth, painless, VII intact, and no neck nodes.
- Surgical excision of clinically benign tumor: no enucleation of lateral lobe, intraoperative communication with pathologist if indicated.

---

**References:**

See Principles of Radiation Therapy (SALI-A).
**CANCER SITE**

**Parotid lobe**
- **Clinical N0**
  - Parotidectomy with complete excision of tumor
- **Clinical N+**
  - Parotidectomy + neck dissection

**Other salivary gland sites**
- **Clinical N0**
  - Complete tumor resection
- **Clinical N+**
  - Complete tumor resection and lymph node dissection

**TREATMENT**

- **Completely excised**
  - Adenoid cystic
    - Adverse features:
      - Intermediate or high grade
      - Close or positive margins
      - Neural/perineural invasion
      - Lymph node metastases
      - Lymphatic/vascular invasion
  - RT (category 2B)
  - Adjuvant RT or Consider chemo/RT (category 2B)

- **Incompletely excised, gross residual disease**
  - Surgical resection, if possible
  - No further surgical resection possible
  - Definitive RT or Chemo/RT (category 2B)

- **Follow-up** (See FOLL-A)
- **Recurrence** (See SALI-4)

---

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

*The facial nerve should be preserved if possible.*

*See Principles of Surgery (SURG-A).*

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

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

No adverse features → Follow-up, (See FOLL-A)

Locoregional recurrence without prior RT

Resectable → Completely excised

Adenoid cystic

Adverse features:
• Intermediate or high grade
• Close or positive margins
• Neural/perineural invasion
• Lymph node metastases
• Lymphatic/vascular invasion

RT\textsuperscript{e} (category 2B)

Adjuvant RT\textsuperscript{e} or Consider chemo/RT (category 2B)

Unresectable

Locoregional recurrence or second primary with prior RT

Resectable

Surgery\textsuperscript{g} (preferred)

or Reirradiation ± chemotherapy, clinical trial preferred

Unresectable

Reirradiation ± chemotherapy, clinical trial preferred or Chemotherapy (see Distant metastases pathway below)

Locoregional recurrence or second primary with prior RT

Distant metastases

Clinical trial preferred

PS 0-2

Standard therapy

PS 3

Best supportive care

Locoregional recurrence or second primary with prior RT

Resectable

Surgery\textsuperscript{g} (preferred)

or Reirradiation ± chemotherapy, clinical trial preferred

Unresectable

Reirradiation ± chemotherapy, clinical trial preferred or Chemotherapy (see Distant metastases pathway below)

Distant metastases

Clinical trial preferred

PS 0-2

Standard therapy

PS 3

Best supportive care

Recurrence

Follow-up (See FOLL-A)

Distant metastases

Clinical trial preferred

PS 0-2

Standard therapy

PS 3

Best supportive care

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

\textsuperscript{e} See Principles of Radiation Therapy (SALI-A).
\textsuperscript{g} See Principles of Surgery (SURG-A).
Definitive RT
T4b disease or gross residual disease
- Photon or photon/electron therapy or neutron therapy
- Dose
  - Primary and gross adenopathy:
    - $\geq 70$ Gy (1.8-2.0 Gy/fraction)\(^2\) or
    - $19.2$ nGy (1.2 nGy/fraction)
  - Uninvolved nodal stations:
    - $44-64$ Gy (1.6-2.0 Gy/fraction)\(^2\) or
    - $13.2$ nGy (1.2 nGy/fraction)

Postoperative RT
- Photon or photon/electron therapy or neutron therapy
- Dose
  - Primary: $\geq 60$ Gy (1.8-2.0 Gy/fraction)\(^2\)
    - or $18$ nGy (1.2 nGy/fraction)
  - Uninvolved nodal stations:
    - $44-64$ Gy (1.6-2.0 Gy/fraction)\(^2\)
    - or $13.2$ nGy (1.2 nGy/fraction)

---

1 See Radiation Techniques (RAD-A).
2 Range based on grade/natural history of disease (eg, 1.8 Gy fraction may be used for slower growing tumors).

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

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

Presentation/Workup

Sinus or nasal cavity mucosal melanoma

See Primary Treatment (MM-2)

Oral cavity, oropharynx, larynx, or hypopharynx mucosal melanoma

See Primary Treatment (MM-3)

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

### Stage III
- T4a, N0 → Wide surgical resection of primary
- T3-T4a, N1 → Wide surgical resection + neck dissection of positive neck
- Stage IVB → Wide surgical resection of primary
- Stage IVC → Wide surgical resection of primary

### ADJUVANT TREATMENT
- Strongly consider postoperative RT to primary site
- Postoperative RT to primary site and neck
- Clinical trial (preferred) or Primary RT or Biologic therapy
- Clinical trial (preferred) or Best supportive care or Primary RT or Biologic therapy

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**Follow-up**

**Recurrence,** [See NCCN Melanoma Guidelines](#)

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

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See Principles of Surgery (SURG-A).
See Principles of Radiation Therapy (MM-A).
See Principles of Systemic Therapy for Advanced or Metastatic Melanoma page ME-D from the NCCN Melanoma Guidelines.
**Mucosal Melanoma**

**Head and Neck Cancers**

**PRIMARY TREATMENT**

- **Stage III**
  - Wide surgical resection, elective neck dissection

- **Stage IVA**
  - Wide surgical resection + neck dissection

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

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

**ADJUVANT TREATMENT**

- Strongly consider postoperative RT

- Postoperative RT

**FOLLOW-UP**

- Follow-up (See FOLL-A)

**Recurrence**

See NCCN Melanoma Guidelines

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*a See Principles of Surgery (SURG-A).

b See Principles of Radiation Therapy (MM-A).

c See Principles of Systemic Therapy for Advanced or Metastatic Melanoma page ME-D from the NCCN Melanoma Guidelines.

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

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
PRIMARY THERAPY FOR OCCULT PRIMARY- MELANOMA

Level V, occipital node → Posterior lateral node dissection

All other nodal sites → Neck dissection

± RT to nodal bed\textsuperscript{d,e} → ± Adjuvant systemic therapy, per NCCN Melanoma Guidelines

\textsuperscript{a}See Principles of Surgery (SURG-A).


\textsuperscript{e}RT is indicated for satellitosis, positive nodes, or extracapsular spread.

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

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

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

Dose and Fractionation:
- Primary and neck (high-risk sites): 60-66 Gy (2.0 Gy/fraction)
- Low risk, undissected, or uninvolved portions of neck: 50-60 Gy (2 Gy/fraction)

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

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

---

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

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

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

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

All patients should be evaluated by a head and neck surgical oncologist prior to 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 behaviors 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 upon any response observed before therapy except in instances of tumor progression that mandates a more extensive procedure in order 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 (ie, unresectable based on technical ability to obtain clear margins).

- Significant involvement of pterygopalatine fossa, severe trismus due to tumor infiltration into the pterygoid muscles;
- Gross extension of tumor to the skull base (i.e. erosion of the pterygoid plates or sphenoid bone, widening of the foramen ovale, etc.);
- 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 270 degrees or greater;
- Direct extension of neck disease to involve the external skin;*
- Direct extension to mediastinal structures, prevertebral fascia or cervical vertebrae.*

*In selected cases, surgery might still be considered.

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

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
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 upon the extent of the primary tumor as ascertained by clinical examination and careful interpretation of appropriate radiographic images.
- Perineural invasion should be suspected when tumors are adjacent to motor or sensory nerves. When invasion is suspected, the nerve should be dissected both proximally and distally and should be resected to obtain clearance of disease. Frozen section determination of the proximal and distal nerve margins may prove helpful to facilitate tumor clearance.
- Partial or segmental resection of the mandible may be necessary to encompass adequately the cancer with adequate tumor free margins. Adequate resection may require partial, horizontal, or sagittal resection of the mandible for tumors involving or adherent to mandibular periosteum. Segmental resection should be considered in tumors that grossly involve mandibular periosteum (as determined by tumor fixation to the mandible) or show evidence of direct tumor involvement of the bone at the time of operation or through preoperative imaging. The extent of mandibular resection will depend on the degree of involvement accessed clinically and in the operating room.
- For tumors of the larynx, the decision to perform either total laryngectomy or conservation laryngeal surgery (ie, laser resection, hemilaryngectomy, supraglottic laryngectomy, etc.) 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.
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 resection margins with at least 2 cm clearance from gross tumor or clear frozen section margins. 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 (i.e., 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.
Neck Management

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

- Tumor sites that frequently have bilateral lymphatic drainage (i.e., 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 effect adequate tumor resection.

- The type of neck dissection (radical, modified, 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:

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>Selective or modified radical neck dissection</td>
</tr>
<tr>
<td></td>
<td>- Oral cavity at least Levels I-III</td>
</tr>
<tr>
<td></td>
<td>- Oropharynx at least Levels I-IV</td>
</tr>
<tr>
<td></td>
<td>- Larynx at least Levels II-IV and level VI when appropriate</td>
</tr>
<tr>
<td></td>
<td>- Hypopharynx at least Levels II-IV and level VI when appropriate</td>
</tr>
<tr>
<td>N1</td>
<td>Selective neck dissection or modified radical neck dissection</td>
</tr>
<tr>
<td>N2a-b</td>
<td>Selective or modified radical neck dissection</td>
</tr>
<tr>
<td>N2c</td>
<td>Bilateral modified (selective) radical neck dissection or combined with a unilateral selective neck dissection</td>
</tr>
<tr>
<td>N3</td>
<td>Modified or radical neck dissection</td>
</tr>
</tbody>
</table>

- Level VI neck dissections are performed for certain primary sites (such as thyroid and larynx) 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 and thyroid malignancies 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 undergo surgical salvage, as well. Neck disease in an untreated neck should be addressed by formal neck dissection or modification depending on the clinical situation. Non-surgical therapy may also be utilized 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 [FOLL-A]).
- Post chemoradiation or RT neck evaluation (See Principles of Surgery-Neck Evaluation SURG-A 6 of 6)


**PRINCIPLES OF SURGERY**

*(POST CHEMORADIATION OR RT NECK EVALUATION)*

- If suspected progression
  - CT and/or MRI with contrast (4-8 weeks)
    - Clinically negative
      - See stable disease pathway below
    - Clinically positive
      - Neck dissection
  - PET-CT (suggest full dose CT + IV contrast) minimum 12 weeks
    - Lymph node < 1 cm; PET positive
      - Individual decision: Observe or Neck dissection Consider ultrasound FNA
    - Lymph node > 1 cm; PET negative
      - Neck dissection
    - Lymph node > 1 cm; PET positive
      - Neck dissection

- After chemo/RT or RT
  - 4-8 wks clinical assessment as appropriate
    - If stable disease or response
      - CT and/or MRI with contrast 6-12 weeks (if PET unavailable)
        - Clinically negative
          - Observe
        - Clinically positive
          - Neck dissection

1 Adapted with permission from Kutler DI, Patel SG, Shah JP. The role of neck dissection following definitive chemoradiation. Oncology 2004;18:993-998; discussion 999, 1003-4, 1007. Review

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

3 PET negative = No or low-grade uptake, felt not suspicious for disease

4 PET positive = PET suspicious for disease

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

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

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

**IMRT and Fractionation**
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/week) and the “6 fractions/week accelerated” schedule. The Sequential (SEQ) IMRT technique typically delivers the initial (lower dose) phase (weeks 1-5) followed by the high-dose boost volume phase (weeks 6-7) using 2-3 separate dose plans, and is commonly applied in standard fractionation and hyperfractionation. The Concomitant Boost Accelerated schedule may utilize a “Modified SEQ” dose plan by delivering the dose to the subclinical targets once a day for 6 weeks, and a separate boost dose plan as a second daily fraction for the last 12 treatment days.

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

### Squamous Cell Cancers

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

- **Primary Systemic Therapy + concurrent RT**
  - Cisplatin alone\(^1-3\) (preferred) (category 1)
  - Cetuximab\(^4\) (category 1)
  - 5-FU/hydroxyurea\(^5\)
  - Cisplatin/paclitaxel\(^5\)
  - Cisplatin/infusional 5-FU\(^6\)
  - Carboplatin/infusional 5-FU\(^7\)
  - Carboplatin/taxol\(^8\) (category 2B)

- **Postoperative Chemoradiation**
  - Cisplatin alone\(^9-11\) (category 1 for high risk)

- **Induction*/Sequential chemotherapy**
  - Docetaxel/cisplatin/5-FU\(^12-14\) (category 1 if induction is chosen)
  - Following 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-FU\(^16\) (category 1)

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

- **Combination therapy**
  - Cisplatin or carboplatin + 5-FU + cetuximab\(^17\) (category 1)
  - Cisplatin or carboplatin + docetaxel\(^18\) or paclitaxel\(^19\)
  - Cisplatin/cetuximab\(^20\)
  - Cisplatin + 5-FU\(^19,21\)

- **Single agents**
  - Cisplatin
  - Carboplatin
  - Paclitaxel
  - Docetaxel
  - 5-FU
  - Methotrexate
  - Ifosfamide
  - Bleomycin
  - Gemcitabine\(^22\) (nasopharyngeal)
  - Cetuximab\(^23\)

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

---

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


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

**Table 1**

**American Joint Committee on Cancer (AJCC)**

**TNM Staging Classification for the Lip and Oral Cavity**

(7th ed., 2010)

(Nonepithelial tumors such as those of lymphoid tissue, soft tissue, bone, and cartilage are not included)

<table>
<thead>
<tr>
<th>Primary Tumor (T)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor 2 cm or less in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor more than 2 cm but not more than 4 cm in greatest dimension</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor more than 4 cm in greatest dimension</td>
</tr>
<tr>
<td>T4a</td>
<td>Moderately advanced local disease* (lip)</td>
</tr>
<tr>
<td>T4b</td>
<td>Very advanced local disease</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Regional Lymph Nodes (N)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension</td>
</tr>
</tbody>
</table>

| N2 | Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension |
| N2a | Metastasis in single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension |
| N2b | Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension |
| N2c | Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension |
| N3 | Metastasis in a lymph node more than 6 cm in greatest dimension |

<table>
<thead>
<tr>
<th>Distant Metastasis (M)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Histologic Grade (G)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>GX</td>
<td>Grade cannot be assessed</td>
</tr>
<tr>
<td>G1</td>
<td>Well differentiated</td>
</tr>
<tr>
<td>G2</td>
<td>Moderately differentiated</td>
</tr>
<tr>
<td>G3</td>
<td>Poorly differentiated</td>
</tr>
<tr>
<td>G4</td>
<td>Undifferentiated</td>
</tr>
</tbody>
</table>

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[Continued...]
### Table 1 - Continued

**American Joint Committee on Cancer (AJCC)**

TNM Staging Classification for the Lip and Oral Cavity
(7th ed., 2010)

(Nonepithelial tumors such as those of lymphoid tissue, soft tissue, bone, and cartilage are not included)

<table>
<thead>
<tr>
<th>Anatomic Stage/Prognostic Groups</th>
<th>Tis</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage I</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage II</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>T4a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVA</td>
<td>T4a</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4a</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVB</td>
<td>Any T</td>
<td>N3</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4b</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVC</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

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### Table 2: American Joint Committee on Cancer (AJCC) TNM Staging System for the Pharynx (7th ed., 2010)

(Nonepithelial tumors such as those of lymphoid tissue, soft tissue, bone, and cartilage are not included)

#### Primary Tumor (T)

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

**Nasopharynx**

<table>
<thead>
<tr>
<th>T</th>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>T1</td>
<td>Tumor confined to the nasopharynx, or tumor extends to oropharynx and/or nasal cavity without parapharyngeal extension*</td>
</tr>
<tr>
<td>T2</td>
<td>T2</td>
<td>Tumor with parapharyngeal extension*</td>
</tr>
<tr>
<td>T3</td>
<td>T3</td>
<td>Tumor involves bony structures of skull base and/or paranasal sinuses</td>
</tr>
<tr>
<td>T4</td>
<td>T4</td>
<td>Tumor with intracranial extension and/or involvement of cranial nerves, hypopharynx, orbit, or with extension to the infratemporal fossa/masticator space</td>
</tr>
</tbody>
</table>

*Note: Parapharyngeal extension denotes posterolateral infiltration of tumor.

**Oropharynx**

<table>
<thead>
<tr>
<th>T</th>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>T1</td>
<td>Tumor 2 cm or less in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>T2</td>
<td>Tumor more than 2 cm but not more than 4 cm in greatest dimension</td>
</tr>
<tr>
<td>T3</td>
<td>T3</td>
<td>Tumor more than 4 cm in greatest dimension or extension to lingual surface of epiglottis</td>
</tr>
<tr>
<td>T4a</td>
<td>T4a</td>
<td>Moderately advanced local disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible*</td>
</tr>
<tr>
<td>T4b</td>
<td>T4b</td>
<td>Very advanced local disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery</td>
</tr>
</tbody>
</table>

*Note: Mucosal extension to lingual surface of epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of larynx.

**Hypopharynx**

<table>
<thead>
<tr>
<th>T</th>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>T1</td>
<td>Tumor limited to one subsite of hypopharynx and/or 2 cm or less in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>T2</td>
<td>Tumor invades more than one subsite of hypopharynx or an adjacent site, or measures more than 2 cm but not more than 4 cm in greatest diameter without fixation of hemilarynx</td>
</tr>
<tr>
<td>T3</td>
<td>T3</td>
<td>Tumor more than 4 cm in greatest dimension or with fixation of hemilarynx or extension to esophagus</td>
</tr>
<tr>
<td>T4a</td>
<td>T4a</td>
<td>Moderately advanced local disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, or central compartment soft tissue**</td>
</tr>
<tr>
<td>T4b</td>
<td>T4b</td>
<td>Very advanced local disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tumor invades prevertebral fascia, encases carotid artery, or involves mediastinal structures</td>
</tr>
</tbody>
</table>

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

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### Table 2 - Continued

**American Joint Committee on Cancer (AJCC)**

**TNM Staging System for the Pharynx (7th ed., 2010)**

(Nonepithelial tumors such as those of lymphoid tissue, soft tissue, bone, and cartilage are not included)

**Regional Lymph Nodes (N):**

**Nasopharynx**

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

<table>
<thead>
<tr>
<th>NX</th>
<th>Regional lymph nodes cannot be assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Unilateral metastasis in cervical lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa, and/or unilateral or bilateral, retropharyngeal lymph nodes, 6 cm or less, in greatest dimension*</td>
</tr>
<tr>
<td>N2</td>
<td>Bilateral metastasis in cervical lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa*</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in a lymph node(s)* &gt; 6 cm and/or to supraclavicular fossa</td>
</tr>
<tr>
<td>N3a</td>
<td>More than 6 cm in dimension</td>
</tr>
<tr>
<td>N3b</td>
<td>Extension to the supraclavicular fossa**</td>
</tr>
</tbody>
</table>

*Note: Midline nodes are considered ipsilateral nodes.

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

**Regional Lymph Nodes (N)†:**

**Oropharynx and Hypopharynx**

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

†Note: Metastases at level VII are considered regional lymph node metastases.

**Distant Metastasis (M)**

<table>
<thead>
<tr>
<th>M0</th>
<th>No distant metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

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Continued...
<table>
<thead>
<tr>
<th>Anatomic Stage/Prognostic Groups: Nasopharynx</th>
<th>Anatomic Stage/Prognostic Groups: Oropharynx, Hypopharynx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0 Tis N0 M0</td>
<td>Stage 0 Tis N0 M0</td>
</tr>
<tr>
<td>Stage I T1 N0 M0</td>
<td>Stage I T1 N0 M0</td>
</tr>
<tr>
<td>Stage II T1 N1 M0</td>
<td>Stage II T2 N0 M0</td>
</tr>
<tr>
<td>T2 N0 M0</td>
<td>Stage III T3 N0 M0</td>
</tr>
<tr>
<td>T2 N1 M0</td>
<td>T1 N1 M0</td>
</tr>
<tr>
<td>Stage III T1 N2 M0</td>
<td>T2 N1 M0</td>
</tr>
<tr>
<td>T2 N2 M0</td>
<td>T3 N1 M0</td>
</tr>
<tr>
<td>T3 N0 M0</td>
<td>Stage IVA T4a N0 M0</td>
</tr>
<tr>
<td>T3 N1 M0</td>
<td>T4a N0 M0</td>
</tr>
<tr>
<td>T3 N2 M0</td>
<td>T4a N1 M0</td>
</tr>
<tr>
<td>Stage IVA T4 N0 M0</td>
<td>T4a N2 M0</td>
</tr>
<tr>
<td>T4 N1 M0</td>
<td>T4b Any N M0</td>
</tr>
<tr>
<td>T4 N2 M0</td>
<td>Any T Any N M1</td>
</tr>
<tr>
<td>Stage IVB Any T N3 M0</td>
<td>Stage IVB T4b Any N M0</td>
</tr>
<tr>
<td>Stage IVC Any T Any N M1</td>
<td>Any T N3 M0</td>
</tr>
</tbody>
</table>

### Histologic Grade (G)
- GX Grade cannot be assessed
- G1 Well differentiated
- G2 Moderately differentiated
- G3 Poorly differentiated
- G4 Undifferentiated

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### Table 3

**American Joint Committee on Cancer (AJCC)**

**TNM Staging System for the Larynx (7th ed., 2010)**

(Nonepithelial tumors such as those of lymphoid tissue, soft tissue, bone, and cartilage are not included)

<table>
<thead>
<tr>
<th>Glottis</th>
<th>Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>Tumor limited to one vocal cord</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumor involves both vocal cords</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor involves vocal cord fixation and/or invasion of subglottis or glottis or region outside the supraglottis (eg, mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor limited to larynx with vocal cord fixation and/or invasion of subglottis or glottis or region outside the supraglottis (eg, mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx</td>
</tr>
<tr>
<td>T4a</td>
<td>Moderately advanced local disease</td>
</tr>
<tr>
<td>T4b</td>
<td>Very advanced local disease</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Supraglottis</th>
<th>Tumor limited to one subsite of supraglottis with normal vocal cord mobility</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>Tumor limited to one subsite of supraglottis with normal vocal cord mobility</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (eg, mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor limited to larynx with vocal cord fixation and/or invasion of subglottis or glottis or region outside the supraglottis (eg, mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx</td>
</tr>
<tr>
<td>T4a</td>
<td>Moderately advanced local disease</td>
</tr>
<tr>
<td>T4b</td>
<td>Very advanced local disease</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subglottis</th>
<th>Tumor limited to the subglottis</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>Tumor extends to vocal cord(s) with normal or impaired mobility</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor extends to vocal cord(s) with normal or impaired mobility</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor limited to larynx with vocal cord fixation</td>
</tr>
<tr>
<td>T4a</td>
<td>Moderately advanced local disease</td>
</tr>
<tr>
<td>T4b</td>
<td>Very advanced local disease</td>
</tr>
</tbody>
</table>

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Table 3 - continued
American Joint Committee on Cancer (AJCC)
TNM Staging System for the Larynx (7th ed., 2010)
(Nonepithelial tumors such as those of lymphoid tissue, soft tissue, bone, and cartilage are not included)

<table>
<thead>
<tr>
<th>Regional Lymph Nodes (N)*</th>
<th>Anatomic Stage/Prognostic Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Stage 0: Tis N0 M0</td>
</tr>
<tr>
<td>N1</td>
<td>Stage I: T1 N0 M0</td>
</tr>
<tr>
<td></td>
<td>Stage II: T2 N0 M0</td>
</tr>
<tr>
<td></td>
<td>Stage III: T3 N0 M0</td>
</tr>
<tr>
<td>N2a</td>
<td>Stage IVA: T4a N0 M0</td>
</tr>
<tr>
<td>N2b</td>
<td>Stage IVB: T4b Any N M0</td>
</tr>
<tr>
<td>N2c</td>
<td>Stage IVC: Any T Any N M1</td>
</tr>
<tr>
<td>N3</td>
<td></td>
</tr>
</tbody>
</table>

*Note: Metastases at level VII are considered regional lymph node metastases.

Distant Metastasis (M)
M0  No distant metastasis
M1  Distant metastasis

Histologic Grade (G)
GX  Grade cannot be assessed
G1  Well differentiated
G2  Moderately differentiated
G3  Poorly differentiated
G4  Undifferentiated

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### Table 4
American Joint Committee on Cancer (AJCC)
TNM Staging System for the Nasal Cavity and Paranasal Sinuses
(7th ed., 2010)
(Nonepithelial tumors such as those of lymphoid tissue, soft tissue, bone, and cartilage are not included)

<table>
<thead>
<tr>
<th>Primary Tumor (T)</th>
<th>Maxillary Sinus</th>
<th>Nasal Cavity and Ethmoid Sinus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TXT</strong></td>
<td>T1</td>
<td>Tumor limited to maxillary sinus mucosa with no erosion or destruction of bone</td>
</tr>
<tr>
<td><strong>T0</strong></td>
<td>T2</td>
<td>Tumor causing bone erosion or destruction including extension into the hard palate and/or middle nasal meatus, except extension to posterior wall of maxillary sinus and pterygoid plates</td>
</tr>
<tr>
<td><strong>Tis</strong></td>
<td>T3</td>
<td>Tumor invades any of the following: bone of the posterior wall of maxillary sinus, subcutaneous tissues, floor or medial wall of orbit, pterygoid fossa, ethmoid sinuses</td>
</tr>
<tr>
<td><strong>T1</strong></td>
<td>T4a</td>
<td>Moderately advanced local disease</td>
</tr>
<tr>
<td><strong>T2</strong></td>
<td>T4b</td>
<td>Very advanced local disease</td>
</tr>
<tr>
<td><strong>T3</strong></td>
<td>T4a</td>
<td>Tumor invades anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribiform plate, sphenoid or frontal sinuses</td>
</tr>
<tr>
<td><strong>T4a</strong></td>
<td>T4b</td>
<td>Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve (V2), nasopharynx, or clivus</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regional Lymph Nodes (N)</th>
<th>Maxillary Sinus</th>
<th>Nasal Cavity and Ethmoid Sinus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NX</strong></td>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td><strong>N1</strong></td>
<td>N1</td>
<td>Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension</td>
</tr>
<tr>
<td><strong>N2</strong></td>
<td>N2a</td>
<td>Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension</td>
</tr>
<tr>
<td><strong>N2b</strong></td>
<td>N2b</td>
<td>Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension</td>
</tr>
<tr>
<td><strong>N2c</strong></td>
<td>N2c</td>
<td>Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension</td>
</tr>
<tr>
<td><strong>N3</strong></td>
<td>N3</td>
<td>Metastasis in a lymph node, more than 6 cm in greatest dimension</td>
</tr>
</tbody>
</table>

| Distant Metastasis (M) | T4a | Moderately advanced local disease |
|------------------------| T4b | Very advanced local disease |
| **M0** | T4a | Tumor invades any of the following: anterior orbital contents, skin of nose or cheek, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid or frontal sinuses |
| **M1** | T4b | Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than (V2), nasopharynx, or clivus |

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Table 4 - Continued

American Joint Committee on Cancer (AJCC)

TNM Staging System for the Nasal Cavity and Paranasal Sinuses (7th ed., 2010)

(Non-epithelial tumors such as those of lymphoid tissue, soft tissue, bone, and cartilage are not included)

<table>
<thead>
<tr>
<th>Anatomic Stage/Prognostic Groups</th>
<th>Histologic Grade (G)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage 0</strong></td>
<td>Gx: Grade cannot be assessed</td>
</tr>
<tr>
<td>T1 N0 M0</td>
<td>G1: Well differentiated</td>
</tr>
<tr>
<td>T2 N0 M0</td>
<td>G2: Moderately differentiated</td>
</tr>
<tr>
<td>T3 N0 M0</td>
<td>G3: Poorly differentiated</td>
</tr>
<tr>
<td>T1 N1 M0</td>
<td>G4: Undifferentiated</td>
</tr>
<tr>
<td>T2 N1 M0</td>
<td></td>
</tr>
<tr>
<td>T3 N1 M0</td>
<td></td>
</tr>
<tr>
<td><strong>Stage IVA</strong></td>
<td></td>
</tr>
<tr>
<td>T4a N0 M0</td>
<td></td>
</tr>
<tr>
<td>T4a N1 M0</td>
<td></td>
</tr>
<tr>
<td>T1 N2 M0</td>
<td></td>
</tr>
<tr>
<td>T2 N2 M0</td>
<td></td>
</tr>
<tr>
<td>T3 N2 M0</td>
<td></td>
</tr>
<tr>
<td>T4a N2 M0</td>
<td></td>
</tr>
<tr>
<td><strong>Stage IVB</strong></td>
<td></td>
</tr>
<tr>
<td>T4b Any N M0</td>
<td></td>
</tr>
<tr>
<td>Any T N3 M0</td>
<td></td>
</tr>
<tr>
<td><strong>Stage IVC</strong></td>
<td></td>
</tr>
<tr>
<td>Any T Any N M1</td>
<td></td>
</tr>
</tbody>
</table>

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### Table 5

**American Joint Committee on Cancer (AJCC)**  
**TNM Staging System for the Major Salivary Glands (7th ed., 2010)**  
(Parotid, Submandibular, and Sublingual)

#### Primary Tumor (T)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor 2 cm or less in greatest dimension without extraparenchymal extension*</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor more than 2 cm but not more than 4 cm in greatest dimension without extraparenchymal extension*</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor more than 4 cm and/or tumor having extraparenchymal extension*</td>
</tr>
<tr>
<td>T4a</td>
<td>Moderately advanced disease</td>
</tr>
<tr>
<td>T4b</td>
<td>Very advanced disease</td>
</tr>
</tbody>
</table>

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

#### Regional Lymph Nodes (N)

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

#### Distant Metastasis (M)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

#### Anatomic Stage/Prognostic Groups

**Stage I**

- T1 N0 M0

**Stage II**

- T2 N0 M0
- T3 N0 M0
- T1 N1 M0
- T2 N1 M0
- T3 N1 M0

**Stage III**

- T4a N0 M0
- T4a N1 M0
- T1 N2 M0
- T2 N2 M0
- T3 N2 M0
- T4a N2 M0

**Stage IVA**

- T4a N0 M0
- T4a N1 M0
- T1 N2 M0
- T2 N2 M0
- T3 N2 M0
- T4a N2 M0

**Stage IVB**

- T4b Any N M0
- Any T N3 M0

**Stage IVC**

- Any T Any N M1

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### Table 6

American Joint Committee on Cancer (AJCC)
TNM Staging System for Mucosal Melanoma of the Head and Neck
(7th ed., 2010)

<table>
<thead>
<tr>
<th>Primary Tumor (T)</th>
<th>Anatomic Stage/Prognostic Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>T3</td>
<td>Stage III T3 N0 M0</td>
</tr>
<tr>
<td>T4a</td>
<td>Stage IVA T4a N0 M0</td>
</tr>
<tr>
<td>T4b</td>
<td>Stage IVB T4b Any N M0</td>
</tr>
<tr>
<td></td>
<td>Stage IVC Any T Any N M1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regional Lymph Nodes (N)</th>
<th>Histologic Grade (G)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Stage III T3 N0 M0</td>
</tr>
<tr>
<td>N0</td>
<td>Stage IVA T4a N0 M0</td>
</tr>
<tr>
<td>N1</td>
<td>Stage IVB T4b Any N M0</td>
</tr>
<tr>
<td></td>
<td>Stage IVC Any T Any N M1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Distant Metastasis (M)</th>
<th>TX</th>
<th>G1</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
<td>Well differentiated</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
<td>Moderately differentiated</td>
</tr>
</tbody>
</table>

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Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 05/22/08

<table>
<thead>
<tr>
<th>NCCN Categories of Evidence and Consensus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Category 1:</strong> The recommendation is based on high-level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus.</td>
</tr>
<tr>
<td><strong>Category 2A:</strong> The recommendation is based on lower-level evidence and there is uniform NCCN consensus.</td>
</tr>
<tr>
<td><strong>Category 2B:</strong> The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).</td>
</tr>
<tr>
<td><strong>Category 3:</strong> The recommendation is based on any level of evidence but reflects major disagreement.</td>
</tr>
</tbody>
</table>

All recommendations are category 2A unless otherwise noted.

Overview

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

Incidence and Etiology

Approximately 47,560 new cases of oral cavity, pharyngeal, and laryngeal cancers are estimated to occur in 2008. This accounts for about 3% of new cancer cases in the United States. An estimated 11,260 deaths from H&N cancers will occur in 2008. Alcohol and tobacco abuse are common etiologic factors in cancers of the oral cavity, oropharynx, hypopharynx, and larynx. Moreover, because the entire aerodigestive tract epithelium may be exposed to these carcinogens, patients with H&N cancer are at risk for developing second primary neoplasms of the H&N, lung, and esophagus. Human papilloma virus (HPV) infection appears to be a risk factor for some squamous cancers of the oropharynx (predominately cancers of the lingual and palatine tonsils).²⁻⁷

Staging

Stage at diagnosis is the most predictive factor of survival. The TNM staging system for the lip and oral cavity, pharynx (nasopharynx, oropharynx, and hypopharynx), larynx (glottis and supraglottis), major salivary glands (parotid, submandibular, and sublingual), and nasal cavity and paranasal sinuses were developed by the American Joint Committee on Cancer (AJCC).⁸ The 2002 AJCC staging classification was used as a basis for the NCCN's treatment recommendations for the pharynx. Definitions for regional lymph node (N) involvement and spread to distant metastatic sites (M) are uniform except for N staging of nasopharyngeal carcinoma. Definitions for staging the primary tumor (T), based on its size, are uniform for the lip, oral cavity, and oropharynx. In contrast, T stage is based on subsite involvement and is specific to each subsite for the glottic larynx, supraglottic larynx, hypopharynx, and nasopharynx.

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

Treating the patient with H&N cancer is complex. Each specific site of disease, the extent of disease, and the pathologic findings dictate the appropriate surgical procedure, radiation fields, dose and fractionation, and indications for chemotherapy. Single-modality treatment with surgery or radiotherapy is generally recommended for the approximately 40% of patients who present with early-stage disease (stage I or stage II). The 2 modalities result in similar survival in these individuals. In contrast, for the 60% of patients with locally advanced disease at diagnosis, combined modality therapy is generally recommended.

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

Multidisciplinary Team Involvement

The initial evaluation and development of a plan for treating the patient with H&N cancer require a multidisciplinary team of individuals with expertise in all aspects of the special care needs of these patients. Similarly, managing and preventing sequelae of radical surgery, radiotherapy, and chemotherapy require the involvement of various health care professionals familiar with the disease. Follow-up for these sequelae should include a comprehensive H&N examination. Adequate nutritional support can help to prevent severe weight loss in patients receiving treatment for H&N cancer. Patients should also be encouraged to stop smoking and drinking alcohol, because these habits decrease the efficacy of treatment. Programs using behavioral counseling combined with stop-smoking medications are useful for smoking cessation.

Comorbidity and Quality of Life

Comorbidity

Comorbidity refers to the presence of concomitant disease (in addition to H&N cancer) that may affect the diagnosis, treatment, and prognosis for the patient. Documentation of comorbidity is particularly important in oncology, because the failure to identify comorbid conditions (such as renal, heart, or liver failure) may result in inaccurate attribution of poor outcomes to the cancer. Comorbidity is known to be a strong independent predictor for mortality in H&N cancer patients.

Comorbidity has also been shown to influence costs of care, utilization, and quality of life. Numerous indices of comorbidity have been developed. Traditional indices include the Charlson index 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 have a tremendous effect on basic physiological functions (such as the ability to chew, swallow, and breathe), the senses (taste, smell, and hearing), and uniquely human characteristics (such as appearance and voice). In informal use, the terms health status, function, and quality of life are frequently used interchangeably; however, these terms have important distinctions. Health status describes an individual’s physical, emotional, and social capabilities and limitations. Function and performance refer to how well an...
individual is able to perform important roles, tasks, or activities. On the other hand, **quality of life** differs, because the central focus is on the **value** (determined by the patient alone) that individuals place on their health status and function. An 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 validated measures that have received the most widespread acceptance are: (1) the University of Washington Quality of Life scale (UW-QOL); (2) the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-HN35); and (3) the Functional Assessment of Cancer Therapy Head and Neck module (FACT-HN). A clinician-rated performance scale that has also achieved widespread use is the Performance Status Scale. Numerous other instruments are available to measure generic cancer issues and other aspects of H&N cancer but are beyond the scope of this discussion.

**Head and Neck Surgery**

**Resectable Versus Unresectable Disease**

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

The term “unresectable” has resisted formal definition by H&N cancer specialists for decades. No definition of surgical unresectability meets with universal approval. The experience of the surgeon and the support available from reconstructive surgeons, physiatrists, and prosthodontists often strongly influence recommendations. This is particularly common in institutions where few patients with locally advanced H&N cancer are treated. The NCCN member institutions have teams experienced in the treatment of H&N cancer and maintain the multidisciplinary infrastructure needed for reconstruction and rehabilitation. A patient's cancer is deemed unresectable if H&N surgeons at NCCN member institutions doubt their ability to remove all gross tumor on anatomic grounds or if they are certain local control will not be achieved after an operation (even with the addition of radiotherapy to the treatment approach). Typically, such tumors densely involve the cervical vertebrae, brachial plexus, deep muscles of the neck, or carotid artery. Unresectable tumors (that is, those tumors unable to be removed without imposing unacceptable morbidity) should be distinguished from those tumors in patients whose constitutional state precludes an operation (even if the cancer is readily resected with few sequelae). Additionally, a subgroup of patients will refuse surgical management, but these tumors should not be deemed unresectable. Although local and regional disease may be surgically treatable, patients with distant metastases are usually treated as though the primary tumor were unresectable. Thus, patient choice or a doctor’s expectations regarding cure and morbidity will influence or determine treatment.

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

**Cervical Lymph Node Dissections**

Historically, cervical lymph node dissections have been classified as "radical" or "modified radical" procedures. The less radical procedures preserved the sternocleidomastoid muscle, jugular vein, and spinal accessory nerve. The panel prefers to classify cervical...
lymphadenectomy differently, classifying cervical lymph node dissections as either “comprehensive” or “selective.”

A *comprehensive* neck dissection is one that removes all lymph node groups that would be included in a classic radical neck dissection. Whether the sternocleidomastoid muscle, jugular vein, or spinal accessory nerve are preserved does not affect whether the dissection is comprehensive.

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

If a complete response has been achieved after radiotherapy for N1 disease, all of the panel members are satisfied with the strategy of observing the patient. Panelists also concur that any patient with residual disease in the neck after radiotherapy should undergo a neck dissection. However, the surgeons had differing opinions regarding the management of the patient with N2 or N3 disease at initial staging who achieves a complete response to radiation. Some will observe such patients while other institutions recommend a planned neck dissection.

Many factors influence survival and locoregional tumor control in patients with H&N cancer. In most NCCN member institutions, patients with extracapsular nodal spread and/or positive surgical margins receive adjuvant chemoradiotherapy after resection. The presence of other adverse risk factors—multiple positive nodes (without extracapsular nodal spread), vascular/lymphatic/perineural invasion, T4a primary, and oral cavity primary with positive level 4 nodes—are established indications for postoperative RT. Because patients with these features were also included in the EORTC trial that showed a survival advantage for patients receiving cisplatin concurrent with postoperative radiotherapy compared to radiotherapy alone, the panel elected to add the choice to consider RT plus chemotherapy for these features.

**Postoperative Management of High-Risk Disease**

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, larynx, or hypopharynx. The US Intergroup trial R95-01 randomly assigned patients with 2 or more involved nodes, positive margins, or extracapsular spread of tumor to receive standard postoperative radiotherapy or the same radiotherapy plus cisplatin 100 mg/m² every 3 weeks for 3 doses. The European trial was designed using the same treatment but also included as high-risk factors the presence of perineural or perivascular disease and nodal involvement at levels 4 and 5 from an oral cavity or oropharynx cancer. The US trial
demonstrated statistically significant improvement in locoregional control and disease-free survival but not overall survival, whereas the European trial found significant improvement in survival and the other outcome parameters. Note that randomized trials support several schedules for cisplatin (for example, 50 mg IV weekly or 6 mg/m² daily), but most centers use high-dose cisplatin (100 mg/m² every 3 weeks).

To better define risk, a combined analysis of prognostic factors and outcome from the 2 trials was performed. This analysis demonstrated 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, there was no survival advantage. These publications form the basis for the NCCN recommendations in this updated guideline. Chemoradiation is clearly indicated for adverse risk features or extracapsular nodal spread and/or microscopic positive mucosal margins (category 1). The management of patients with multiple nodes only, without extracapsular spread or other adverse risk features, was discussed by the panel and postoperative RT was recommended; however, chemoradiation can be considered based on clinical judgment. The panel noted that the combined analysis was considered exploratory by the authors, because it was not part of the initial protocol design.

Head and Neck Radiotherapy

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

Radiation Doses

Selection of radiation doses depends on the tumor and neck node size, location of the tumor, and clinical circumstances. In general, primary and gross adenopathy require a total of 70 Gy or more at a dosage of 2.0 Gy/day. In contrast, radiation to low-risk nodal stations in the neck requires a total of 50 Gy or more, also at a dosage of 2.0 Gy/day. Postoperative irradiation is recommended based on the tumor stage, tumor histology, and surgical findings after tumor resection. In general, postoperative RT is recommended for risk features, including multiple positive nodes (without extracapsular nodal spread) or perineural/lymphatic/vascular invasion. Higher doses of radiation (60-65 Gy) are required for microscopic disease to decrease the chances of locoregional failure because of interruption of the normal vasculature, scarring, and relative hypoxia in the tumor bed. The preferred interval between resection and postoperative RT is 6 weeks.

Fractionation

No single fractionation schedule has proven to be best for all tumors. Historically, most radiation oncology departments in the United States deliver treatment once per day, 5 days per week, at 1.8 to 2.0 Gy/fraction. Data strongly indicate some squamous cancers can grow rapidly, especially in the face of cell depletion. The upper dose of 2.0 Gy/fraction, delivering 1000 cGy or greater per week, is now the most commonly used dose among the NCCN member institutions. Thus, the guidelines have been revised to indicate that the dose of 2.0 Gy/fraction is preferred, with the exception of salivary gland tumors, which may have slower cell kinetics. External radiation doses exceeding 75 Gy at conventional fractionation of 1.8 to 2.0 Gy/day may lead to unacceptable normal tissue injury.
Most of the published studies with concurrent chemoradiation have used conventional fractionation at 2.0 Gy per fraction to 70 Gy or more in 7 weeks with single-agent cisplatin given every 3 weeks at 100 mg/m². Use of other fraction sizes (for example, 1.8 Gy, conventional), multiagent chemotherapy, or altered fractionation with chemotherapy has been evaluated, but there is no consensus on the optimal approach. In general, the use of concurrent chemoradiation carries a high toxicity burden, and altered fractionation or multiagent chemotherapy will likely further increase the toxicity burden. For any chemotherapeutic approach, close attention should be paid to published reports for the specific chemotherapy agent, dose, and schedule of administration. Chemoradiation should be performed by an experienced team and should include substantial supportive care.

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

Two large, randomized clinical trials have reported improved locoregional control using altered fractionation. The European Organization for Research and Treatment of Cancer (EORTC) protocol 22791 compared hyperfractionation (1.15 Gy twice daily, or 80.5 Gy over 7 weeks) with conventional fractionation (2 Gy once daily, or 70 Gy over 7 weeks) in the treatment of T2,T3,N0-1 oropharyngeal carcinoma. At 5 years, there was a statistically significant increase in local control in the hyperfractionation arm (38% versus 56%; \( P = .01 \)) and no increase in late complications. A long-term follow-up analysis has also demonstrated a small survival advantage for hyperfractionation (\( P = .05 \)). Another EORTC protocol (22851) compared accelerated fractionation (1.6 Gy 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 did significantly better with regard to locoregional control (\( P = .02 \)) at 5 years. Disease-specific survival showed a trend (\( P = .06 \)) in favor of the accelerated fractionation arm. Acute and late toxicity were increased in this fractionation arm, however, raising questions about the net advantages of accelerated fractionation.

In the United States, the Radiation Therapy Oncology Group (RTOG) reported the initial 2-year results and subsequent mature results (after a median follow-up of 8.5 years) of a large phase III clinical trial (protocol 90-03) comparing hyperfractionation and 2 variants of accelerated fractionation with standard fractionation. 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 demonstrated in the frequency of grade 3 or worse late effects reported at 6 to 24 months after treatment start, among the various treatment groups. Long-term follow-up confirmed a statistically significant improvement in locoregional control with either AFX-C or hyperfractionation compared to standard fractionation. However, neither disease-free survival nor overall survival were significantly improved. Severe late toxicity was more frequently observed with AFX-C. A meta-analysis of updated patient data analyzing the effect of hyperfractionated or accelerated radiotherapy on survival of patients with head and neck cancer was recently published. This meta-analysis included 15 randomized trials that had standard
fractionation as the control group. An absolute survival benefit of 3.4% at 5 years (HR 0.92; 95% CI, 0.86-0.97; \( P = .003 \)) was reported. This benefit, however, was limited to patients younger than 60 years of age.\(^{63}\) Consensus regarding altered fractionation schedules with concomitant boost or hyperfractionation for stage III or IV oral cavity, oropharynx, supraglottic larynx, and hypopharyngeal squamous cell cancers has not yet emerged among NCCN member institutions.\(^{63-65}\)

**Brachytherapy**

Brachytherapy is used less often because of improved local control obtained with concurrent chemo/RT. However, brachytherapy still has a role primarily for lip cancer, cancer of the oral cavity, and oropharynx. Several European and North American medical centers have had extensive experience with brachytherapy.\(^{66-74}\) The success of brachytherapy techniques is partly dependent on the training, experience, and skills of the implant team.

**Intensity-Modulated Radiation Therapy**

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

Several institutions have conducted phase II studies to explore the use of beam modulation in H\&N cancer. The objective data from these institutions consistently show a decrease in acute and late toxicities without compromising tumor control.\(^{75-82}\) However, no phase III studies have been done to substantiate the results from phase II studies.

RTOG 0022 and RTOG 0225 are single-arm studies exploring the feasibility of IMRT in the treatment of oropharyngeal and nasopharyngeal cancer.\(^{83,84}\) These trials are currently ongoing. At present, IMRT is not the standard of care for the treatment of H\&N cancers; however, selected patients may benefit from this new technology if they are treated in centers that have expertise in IMRT.

Three-dimensional conformal techniques may be used depending on the stage, tumor location, physician training/experience, and available physics support. IMRT techniques are an area of active investigation among the NCCN institutions and others.\(^{85-88}\) Target delineation and optimal dose distribution require special training in H\&N imaging, a thorough understanding of patterns of disease spread, and special training in IMRT techniques. Standards for target definition, dose specification, fractionation (with and without concurrent chemotherapy), and normal tissue constraints should emerge within the next few years.

**Paranasal Tumors (Maxillary and Ethmoid Sinus Tumors)**

Tumors of the paranasal sinuses are rare and often asymptomatic until late in the course of their disease. Although the most common histology for these tumors is squamous cell carcinoma, multiple histologies have been reported including sarcoma (excluding rhabdomyosarcoma), lymphoma, adenocarcinoma, esthesioneuroblastoma (also known as olfactory neuroblastoma), small cell neuroendocrine and undifferentiated carcinoma (sinonasal undifferentiated carcinoma [SNUC]).\(^{89-91}\) Locoregional control and incidence of distant metastasis are dependent on both T stage and tumor histology. However, T stage remains the most reliable predictor of survival and local regional control.
Management of Ethmoid Sinus Cancer

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

Treatment of Maxillary Sinus Tumors

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

Salivary Gland Tumors

Salivary gland tumors can arise in the major salivary glands (parotid, submaxillary, or sublingual salivary glands) or in one of the minor salivary glands, which are widely spread throughout the aerodigestive tract. Many minor salivary gland tumors are located on the hard palate. Even though many salivary gland tumors are generally benign, approximately 20% of the parotid gland tumors are malignant; the incidence of malignancy in submandibular and minor salivary gland tumors is approximately 50% and 80%, respectively. These malignant tumors constitute a broad spectrum of histologic types, including mucoepidermoid, acinic, adenocarcinoma, adenoid cystic carcinoma, malignant myoepithelial tumors, and squamous carcinoma. The primary diagnosis of squamous carcinoma of the parotid gland is rare; however, the parotid is a frequent site of metastasis from skin cancer.

Prognosis and tendency to metastasize vary among these histologic types. Major prognostic factors are histologic grade, tumor size, and local invasion.

Treatment

The major therapeutic approach for salivary gland tumors is adequate and appropriate surgical resection. Surgical intervention requires careful planning and execution, particularly in parotid tumor surgery because of the presence of the facial nerve within the gland, which should be preserved if the nerve is not directly involved by the tumor. Most of the parotid gland tumors are located in the superficial lobe, and if the facial nerve is functioning preoperatively, the nerve can be preserved in most patients. The facial nerve should be sacrificed if there is preoperative facial nerve involvement with facial palsy or if there is direct invasion of the tumor into the nerve where the tumor
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Head and Neck Cancers

Carcinoma of the Lip

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

Workup and Staging

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

Treatment of the Primary

The treatment of lip cancer is governed by the stage of the disease. The choice of a local treatment modality is based on the expected functional and cosmetic outcome. In early-stage cancers, surgery and radiation are equivalent options in terms of local control. Some very small or superficial cancers are managed more expeditiously with a surgical excision without resultant functional deformity or an undesired cosmetic result. On the other hand, a superficial cancer that occupies most of the lower lip, for example, would be best managed with RT. Some advanced lip cancers can cause a great deal of tissue destruction and secondary deformity. Surgery is a more viable option in this clinical setting. Surgery is also the local modality of choice for...
advanced cancers with extension into the bone. Patients with resectable T3, N0; T4a, N0; or any T, N1-3 disease who are a poor surgical risk can be treated with definitive RT (with or without brachytherapy) or with chemotherapy/RT.

**Management of the Neck**

The management of the neck is also governed by stage, but the location of the tumor should also be taken into account. For example, the lymphatics of the upper lip are very extensive. Thus, tumors in this location are more apt to spread to deep superior jugular nodes. The position of the tumor along the lip also can be helpful in predicting the pattern of lymph node spread. A midline location can place a patient at higher risk for contralateral disease. For patients with advanced disease (T3, T4a) and an N0 neck, a unilateral or bilateral selective neck dissection should be considered. When a patient presents with palpable disease, care is taken to ensure all appropriate nodal levels are dissected.

**Radiation**

Radiotherapy, when used as definitive treatment, may consist of external-beam RT or brachytherapy alone or in combination, depending on the size of the tumor. The dose required also depends on tumor size, but doses of 66 Gy or more are adequate to control the disease. For T1-2, N0 lesions, the total dose of external-beam RT may be decreased to 50 Gy or more when given in conjunction with brachytherapy. In the adjuvant setting, doses of 60 Gy or more are required, depending on the pathologic features. In both definitive and adjuvant settings, the neck is treated with doses that address adverse features, such as positive margins or invasion (perineural, vascular, and/or lymphatic).

**Follow-up/Surveillance**

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

**Cancer of the Oral Cavity**

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

Regional node involvement at presentation is evident in approximately 30% of patients, but the risk varies according to subsite. For example, primaries of the alveolar ridge and hard palate infrequently involve the neck, whereas occult neck metastasis is common (50% to 60%) in patients with anterior tongue cancers. In general, all patients undergo treatment of the neck with either unilateral or bilateral selective neck dissection or if primary RT is chosen for treatment of T1-2, N0 disease, at least 50 Gy is given to the neck at risk.

**Workup and Staging**

Imaging studies to evaluate mandibular involvement and a careful dental evaluation (including Panorex, as indicated) are particularly important for staging and planning therapy for oral cavity cancers in addition to a physical examination, biopsy, and chest imaging.

**Treatment**

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

Postoperative chemotherapy/RT is recommended (category 1) for all patients with resected oral cavity cancers with the adverse pathologic features of extracapsular nodal spread and/or a positive mucosal margin.\textsuperscript{45-47} (category 1). 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 embolism—clinical judgment should be utilized in the consideration of adding chemotherapy to RT or treating with RT alone. The concept of organ preservation using chemotherapy in the initial management of locally advanced resectable disease has not been studied in trials specifically designed for this site.

**Follow-up/Surveillance**

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

**Cancer of the Oropharynx**

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

**Workup and Staging**

A multidisciplinary consultation is encouraged. Accurate staging depends on a thorough physical examination coupled with appropriate imaging studies. CT with contrast or MRI is recommended for the primary and the neck; chest imaging is also recommended. Examination of the H&N region should include an examination under anesthesia with endoscopy. Bronchoscopy and esophagoscopy are also recommended because of the relative frequency of simultaneous second primaries. A dental evaluation is recommended, with Panorex studies as indicated. Speech and swallowing evaluation may be useful, as indicated. Testing for high-risk oncogenic HPV types (HPV 16, -18, -31, -33, -35) is recommended (using either polymerase chain reaction [PCR] or in situ hybridization [ISH]) because of the strong association with oropharyngeal squamous cell carcinoma and the increasing incidence of cancers of the lingual and palatine tonsils.\textsuperscript{4,98,99} In patients with oropharyngeal carcinoma, recent data indicate that those with HPV-associated cancers have improved response to treatment and improved survival when compared with HPV-negative tumors.\textsuperscript{100}

**Treatment**

The treatment algorithm has been divided into 3 staging categories: (1) T1-2, N0-1; (2) T3-4a, N0; and (3) T3-4a, N+ or any T, N2-3. Early-stage (T1-2, N0-1) oropharyngeal cancers may be treated with primary surgery including neck dissection, as indicated, or with definitive radiotherapy (category 2B). The panel members strongly disagreed about the third option of RT plus systemic therapy (category 3). Surgery is also indicated for salvage in cases of residual or recurrent disease after definitive radiotherapy. Radiotherapy alone is appropriate management for patients with a T1 or T2 primary and N1 disease. For patients treated surgically who have adverse pathologic features that warrant post-operative RT, the optimal time interval between resection and RT is not more than 6 weeks. Adjuvant chemotherapy/RT is recommended (category 1) for adverse pathologic features of
extracapsular nodal spread and/or 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 embolism—clinical judgment should be utilized in the consideration of adding chemotherapy to RT or treating with RT alone.

For advanced resectable disease (T3-4a, any N or any T, N2-3), there are 3 treatment approaches in the algorithms, in addition to enrollment in a multimodality clinical trial that includes function evaluation. The three approaches are: (1) concurrent systemic therapy/RT (for example, cisplatin [category 1] preferred) (salvage surgery is used for managing residual or recurrent disease); (2) surgery with neck dissection and reconstruction, as indicated, followed by radiotherapy with or without chemotherapy as dictated by the presence of pathologic adverse features; or (3) induction chemotherapy followed by chemo/RT (category 3) for which there was strong disagreement among panel members.

For the concurrent systemic therapy/RT approach, all patients are evaluated at completion of treatment for response in the primary site and in the neck. For patients with nodal involvement at initial staging who achieve a complete response in the primary and the neck, subsequent management is based on initial nodal stage. Patients who had N1 disease are observed, while patients who had N2 or N3 disease can be either observed or undergo a planned neck dissection. This is an area of controversy among NCCN institution surgeons. However, if residual neck disease is present (and the primary is controlled), there is uniform agreement to proceed to neck dissection. Patients with residual tumor in the primary should be offered salvage surgery with neck dissection as indicated.

Concurrent systemic therapy/RT with cisplatin (category 1) is preferred for treatment of locally advanced (T3-4a or N2-3) cancer of the oropharynx. The use of induction chemotherapy added to chemoradiotherapy (termed sequential therapy) is an area of controversy among the NCCN panelists. Most randomized trials of induction chemotherapy followed by radiotherapy or surgery (which were published in the 1980s and 1990s) did not demonstrate a survival advantage. Induction chemotherapy had no effect on local control; however, in many trials, it did reduce the distant metastatic rate. A rationale for reevaluating induction chemotherapy added to concurrent chemotherapy/RT is to reduce distant metastases as a site of failure now that improved local control can be achieved with concurrent chemotherapy/RT. Results from 3 phase III trials—that compared induction cisplatin plus infusional 5-FU with or without the addition of a taxane (docetaxel or paclitaxel)—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 to those receiving 2 drugs (cisplatin plus 5-FU). Taken together, these results show that a more effective triplet combination has been identified compared to the standard of cisplatin plus 5-FU used in the induction trials of the 1980s and 1990s. However, a survival advantage over concurrent chemoradiation has yet to be demonstrated. The NCCN panel uniformly agreed that clinical trials should be performed to directly answer the question of whether or not induction chemotherapy added to systemic therapy/RT improves survival in patients with locally advanced cancer of the oropharynx and other specified sites. Such trials are in progress, and the panel members uniformly agreed that patients should be enrolled in these trials. The panel members differed in their opinion as to whether or not this treatment should be considered a standard treatment option. A small minority of panel members do advocate this approach. This disagreement is reflected by a category 3 recommendation in the algorithms.

Altered fractionation is preferred when radiotherapy is used definitively for selected T1, N1 or T2, N0-1 tumors. For patients not receiving
concurrent chemoradiation, altered fractionation is preferred. The recommended schedules are: (1) concomitant boost accelerated radiotherapy consisting of 72 Gy delivered over 6 weeks using 1.8 Gy/fractions to the large volume and 1.5 Gy boost as the second daily fraction 6 hours later during the last 12 treatments to a smaller volume; or (2) hyperfractionation consisting of 81.6 Gy given in 7 weeks with 1.2 Gy/fractions twice daily 6 hours apart. This change from standard radiotherapy for large lesions was made on the basis of the results of the RTOG 9003 protocol, which detected a local control advantage for patients who were treated with hyperfractionation and concomitant boost versus those treated with standard fractionation or accelerated fractionation with a break in the treatment schedule. Increased acute toxicity was demonstrated in both altered fractionation schedules when compared with standard radiotherapy. The concomitant boost schedule resulted in prolongation of acute symptoms 6 to 24 months after the initiation of treatment, but no significant difference was demonstrated in the frequency of late effects among schedules. In addition to the RTOG trial, 4 other randomized trials have demonstrated improved outcomes with hyperfractionation.\(^{58,108}\)

**Salvage Surgery**

Patients with advanced carcinoma of the oropharynx who undergo nonsurgical treatment, such as concurrent chemotherapy and RT, need very close follow-up both to evaluate for local recurrence and to assess for ipsilateral or contralateral neck recurrence. The patients who do not respond completely to chemotherapy/RT require salvage surgery to the primary and the neck. However, all panelists emphasized that it may be difficult to detect local or regional recurrence due to radiation-related tissue changes and, this may result in a delayed diagnosis of persistent or recurrent disease. The panelists also emphasized the increased risk of complications when salvage surgery is attempted. Additionally, laryngectomy is occasionally required to obtain clear surgical margins or to prevent aspiration in patients with advanced oropharyngeal cancer. Some of these patients may require microvascular free flap reconstruction to cover the defects at the primary site. The patients undergoing neck dissection may develop complications related to delayed wound healing, skin necrosis, or carotid exposure. The patients requiring salvage laryngectomy may have high incidence of pharyngocutaneous fistula and may require either a free flap reconstruction of the laryngopharyngeal defect or if the pharynx can be closed primarily, buttressing the suture line with myocutaneous flap.

**Follow-up/Surveillance**

The follow-up of patients treated for oropharyngeal cancer continues to rely on physical examination. Chest imaging is recommended as clinically indicated as surveillance for second primary tumors. Post-treatment baseline imaging (3-6 months) of the primary and neck is recommended for disease that is difficult to follow (ie, patients who have had chemoradiation not surgery); repeat imaging if indicated by signs/symptoms on physical examination. If PET is used for follow-up, the first scan should be performed at not less than 12 weeks after treatment to reduce the false-positive rate. Patients whose thyroid gland has been irradiated should have TSH levels monitored every 6 to 12 months. Speech, hearing, & swallowing evaluation and rehabilitation and dental evaluation should be done as indicated. Smoking cessation counseling is also recommended.

**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 postcricoid area.
Workup and Staging

A multidisciplinary consultation is encouraged. Accurate staging depends on a thorough physical examination coupled with appropriate imaging studies, such as CT with contrast or MRI of the primary and neck and chest imaging. Examination of the H&N region should include an examination under anesthesia with endoscopy. Bronchoscopy and esophagoscopy are also recommended because of the relative frequency of simultaneous second primaries. A dental evaluation is recommended. Speech and swallowing evaluation should be performed in most patients.

At the time of diagnosis, approximately 60% of patients with cancer of the hypopharynx have locally advanced disease with spread to regional nodes. Furthermore, autopsy series have shown a high rate of distant metastases (60%) involving virtually every organ. Thus, the prognosis for patients with cancer of the hypopharynx is quite poor. Despite standard radical surgery and radiotherapy, the persistent or recurrent locoregional disease and distant dissemination contribute to the poor outcome for these patients.

Treatment

Patients with resectable disease are divided into 2 groups: those patients with early-stage cancer (T1, N0; small T2, N0) who do not require a total laryngectomy and those patients with advanced resectable cancer (T1, N+; T2-4a, any N) who do require laryngectomy. The surgery and radiotherapy options for the former group represent a consensus among the panel members. For patients treated initially with definitive RT (without chemotherapy), surgery is indicated for residual neck disease. For patients with a complete response of the neck, observation is recommended.

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 in addition to enrollment in a multimodality clinical trial that includes function evaluation: (1) induction chemotherapy followed by definitive RT if a complete response was achieved at the primary site (category 1) or followed by concurrent chemoradiation if a partial response was achieved at the primary site (category 2B) or followed by surgery if the response to induction chemotherapy was less than partial; (2) surgery with neck dissection and post-operative radiation or chemoradiation as dictated by pathologic risk features; or (3) concurrent chemotherapy/RT cisplatin preferred (category 2B). Note that the panel uniformly supports the recommendation of induction chemotherapy (category 1) followed either by definitive RT (category 1) or by chemoradiation (category 2B) based upon the response achieved at the primary site for patients with (1) T1, N+, or (2) T2-3, any N disease. The standard induction regimen is docetaxel, cisplatin, and 5-FU (TPF). The recommendation of the induction chemotherapy (cisplatin and 5-FU)/definitive radiotherapy option is based on the results of an EORTC randomized trial. This trial enrolled 194 eligible patients with stage II, stage III, or stage IV resectable squamous cell carcinoma of the pyriform sinus (152 patients) and aryepiglottic fold (42 patients), excluding patients with T1 or N2c disease. Patients were randomly assigned either to laryngopharyngectomy and postoperative radiotherapy, or to chemotherapy with cisplatin and 5-FU for a maximum of 3 cycles, followed by definitive radiotherapy. In contrast to a similar regimen used for laryngeal cancer, a complete response to induction chemotherapy was required in order to proceed with definitive radiotherapy. The published results showed equivalent survival, with median survival duration and 3-year survival rate of 25 months and 43%, respectively, for the surgery group versus 44 months and 57%, respectively, for the induction chemotherapy group. A functioning larynx
was preserved in 42% of patients who did not undergo surgery. Local or regional failure rates did not differ between the surgery-treated patients and chemotherapy-treated patients, although the chemotherapy recipients did demonstrate a significant reduction in distant metastases as a site of first failure \((P=.041)\). Adherence to the requirements for complete response to chemotherapy and for inclusion of only patients with the specified TN-stage are emphasized.

As noted in the algorithm, surgery is recommended if less than a partial response occurs after 3 cycles of induction chemotherapy. In this situation, or when primary surgery is the selected management path, postoperative chemotherapy/RT is recommended (category 1) for adverse pathologic features of extracapsular nodal spread and/or 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 embolism—clinical judgment should be utilized in the consideration of adding chemotherapy to RT or treating with RT alone.

Options for patients with T4a, any N disease include (1) surgery plus comprehensive neck dissection (preferred) followed by adjuvant chemotherapy/RT (category 1); (2) multimodality clinical trials that include function evaluation; (3) concurrent systemic therapy/RT (category 3); or induction chemotherapy followed by chemotherapy/RT or RT (category 3).

**Follow-up/Surveillance**

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

**Occult Primary Cancer**

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

Most patients older than 40 years who present with a neck mass prove to have metastatic cancer. The source of the lymphadenopathy is almost always discovered in the course of a complete H&N examination, which should be performed on all patients with neck masses before other studies are initiated. The following should be assessed during office evaluation: 1) antecedent history of malignancy and 2) prior excision, destruction, or regression of cutaneous lesions.

**Workup**

When patients present with a neck mass, fine-needle aspiration (FNA) should be the first study undertaken. Needle aspiration generally guides management and treatment planning. Core or open biopsy should be avoided, because it may alter or interfere with subsequent treatment.

When a needle biopsy demonstrates squamous cell carcinoma, adenocarcinoma, or anaplastic epithelial cancer and no primary site has been found, additional studies are needed. HPV-16 and Epstein
Barr Virus encoded RNA (EBER) testing are suggested for squamous cell or undifferentiated histology.98,99,112-114

Nasopharyngolaryngoscopy, chest imaging, and either CT scan with contrast or MRI with gadolinium should be performed. A fused PET/CT scan should only be done if other tests do not reveal a primary. PET can be used to confirm clinical impressions, detect an unknown primary, and for surveillance. Other imaging studies have very low yield and should not be undertaken.

If the FNA proves nondiagnostic, then repeat FNA, core biopsy, or open biopsy may be needed. Open biopsy should not be performed unless the patient is prepared for definitive surgical management of the malignancy documented in the operating room. This management may entail a formal neck dissection. Therefore, an open biopsy of an undiagnosed neck mass should not be undertaken lightly, and patients should be thoroughly apprised of the potential sequelae.

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

Treatment

Comprehensive neck dissection (including level I-III) is recommended for all patients with adenocarcinoma. If the metastatic adenocarcinoma presents high in the neck, parotidectomy may be included with the neck dissection. NCCN member institutions have major disagreements about the management of patients with poorly differentiated or nonkeratinizing squamous cell, anaplastic cancer of unknown primary site, or other uncommon histologies. Some members believe such patients should be managed with comprehensive neck dissection (levels I-V), whereas others believe the following options can be used (all the following are category 3): (1) chemoradiation; (2) primary RT; or (3) induction chemotherapy followed by chemoradiation.

If an N1 node was excised in an open biopsy, then most NCCN institutions recommend radiation that encompasses the potential primary sites as determined by the neck node levels involved and both necks. Some institutions would radiate the neck only (category 3). When a neck dissection is performed, postoperative radiation and concurrent chemotherapy are recommended by all institutions if extracapsular nodal spread was present or if the patient presented with N2 or N3 disease. Some NCCN institutions would radiate the neck only (category 3), whereas most institutions would also radiate the likely occult primary sites based on the level of nodes involved; chemotherapy/RT to the likely primary site and the neck is also an option (category 2B). Extending the radiation field to encompass all possible mucosal primary sites is controversial and the source of much disagreement. There is little evidence to support a survival benefit from radiation to all possible primary sites.

Cancer of the Larynx

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

**Workup and Staging**

The evaluation of the patient to determine tumor stage is similar for glottic and supraglottic primaries. In both sites, the algorithms now explicitly recommend CT scan with contrast and thin cuts through the larynx, or MRI of the primary and neck; chest imaging is also recommended. These imaging tests are considered particularly important for accurate staging. Examination under anesthesia with endoscopy is also recommended. A barium esophagram is recommended for patients with subglottic tumors. Speech, swallowing, and dental evaluation should be done if indicated. Multidisciplinary consultation is particularly important for both sites because of the potential for loss of speech and, in some instances, for swallowing dysfunction.

**Treatment**

The treatment of patients with laryngeal cancer is divided into 3 categories: (1) tumors of the glottic larynx, (2) tumors of the supraglottic larynx without positive nodes (N0), and (3) tumors of the supraglottic larynx with positive nodes (N+). For patients with carcinoma in situ of the larynx, recommended treatment options include endoscopic removal (stripping, laser) or RT. NCCN also encourages participation in clinical trials. For invasive cancer, surgery (partial laryngectomy through either endoscopic or open approaches) and radiotherapy are equally effective for early-stage glottic or supraglottic cancers. The choice of treatment modality depends on functional outcome, the patient’s wishes, reliability of follow-up, and general medical condition.

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

Patients with locally advanced disease who desire laryngeal preservation should receive treatment with concurrent chemotherapy consisting of cisplatin 100 mg/m² on days 1, 22, and 43 (category 1) preferred and radiotherapy; the second option is definitive RT (without chemotherapy) for patients who are medically unfit or refuse chemotherapy. Surgery is reserved for managing the neck as indicated, for those patients whose disease persists after radiotherapy, or those patients who develop a subsequent locoregional recurrence.

The NCCN recommendations for managing locally advanced, resectable glottic and supraglottic cancers requiring laryngectomy reflect the results of Intergroup trial R91-11. Before 2002, either
induction chemotherapy with cisplatin/5-FU followed by radiotherapy or definitive radiotherapy alone (without chemotherapy) were the standard of care options recommended in the NCCN H&N guidelines based on the results of the Veterans Administration (VA) Laryngeal Cancer Study Group trial published in 1991. In the 2002-2008 versions of the guidelines, concurrent radiotherapy and cisplatin 100 mg/m² is the recommended option for achieving laryngeal preservation. R91-11 was a successor trial to the Veterans Administration trial and compared 3 non-surgical regimens: (1) induction cisplatin/5-FU followed by RT (control arm and identical to that in the VA trial); (2) concurrent RT and cisplatin 100 mg/m² days 1, 22, and 43; and (3) RT alone. Radiotherapy was uniform in all 3 arms, 70 Gy/7 wks, 2 Gy/fx.

Laryngectomy was used for salvage of treatment failures in all arms. Stage III and IV (M0) patients were eligible, excluding T1 primaries and high-volume T4 primaries (tumor extending more than 1 cm into the base of tongue or tumor penetrating through cartilage). The key findings of the trial were a statistically significant higher 2-year laryngeal preservation (local control) rate for concurrent RT with cisplatin of 88%, compared to 74% with induction chemotherapy and to 69% with RT alone; no significant difference in laryngeal preservation between induction and RT alone treatments; and similar survival for all treatment groups. These R91-11 results changed the standard of care to concurrent RT and cisplatin (category 1) preferred for achieving laryngeal preservation for T3, N0 and T4a, N0 supraglottic cancers and for most T3, any N glottic cancers. In contrast, the recommended options for those with high-volume T4a, N+ disease (for example, cartilage destruction, skin involvement, massive invasion of the base of the tongue) are either (1) laryngectomy, ipsilateral thyroidectomy with ipsilateral or bilateral neck dissection followed by chemotherapy/RT (category 1 for chemo/RT); or (2) a clinical trial. Definitive radiotherapy alone (without chemotherapy) is reserved for patients in the poor medical risk category.

**Follow-up/Surveillance**

It is particularly important for nonsurgically treated patients to have careful and regular follow-up examinations by a trained H&N surgical oncologist so that any local or regional recurrence is detected early, and salvage surgery (and neck dissection as indicated) is performed. Post-treatment baseline imaging (3-6 months) of the primary and neck is recommended for disease that is difficult to follow; repeat imaging if indicated by signs/symptoms on physical examination. If PET is used for follow-up, the first scan should not be performed sooner than 12 weeks after treatment. Follow-up examinations in many of these patients need to be supplemented with serial endoscopy or high-resolution, advanced radiologic imaging techniques because of the scarring, edema, and fibrosis that occur in the laryngeal tissues and neck after high-dose radiation. Speech, hearing, & swallowing evaluation and rehabilitation may be useful, as indicated. Smoking cessation counseling is recommended.

For patients with glottic T4a tumors, the standard approach is a laryngectomy with ipsilateral thyroidectomy and neck dissection as indicated. For selected patients with glottic T4a tumors, the panel recommends 1) considering concurrent chemoradiation, or 2) clinical trials testing function-preserving surgical or nonsurgical approaches.
Carcinoma of the Nasopharynx

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

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

Workup and Staging

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

Treatment

Treatment options are subdivided according to T, N, and M status, rather than by stage alone. Patients with early-stage nasopharyngeal tumors (T1, N0, M0, and T2a, N0, M0 tumors) may be treated with definitive RT alone (without chemotherapy) to the nasopharynx, with elective radiation to the neck. For early-stage cancer, radiation doses of at least 70 Gy given with standard fractions are necessary for control of gross tumor. The local control rate for these tumors ranges from 80% to 90%, whereas T3-4 tumors have a control rate of 30% to 65%.

The combination of RT and platinum-based chemotherapy has been shown to increase the local control rate from 54% to 78%. The Intergroup trial 0099, which randomly assigned patients to chemotherapy plus external-beam RT versus external radiation alone, closed early when an interim analysis disclosed a significant survival and progression-free survival advantage favoring the combined chemotherapy and radiation group. The addition of chemotherapy also decreased local, regional, and distant recurrence rates. A similar randomized study conducted in Singapore, which was modeled after the Intergroup treatment regimen, continued to show the benefit of the addition of chemotherapy to radiation therapy. Adjuvant chemotherapy after combined chemotherapy and radiation was also given in this trial. In addition, the administration of the cisplatin dose was spread out over several days, and this regimen appeared to reduce toxicity while still providing a beneficial antitumor effect.
The guidelines recommend combined chemotherapy (cisplatin) plus radiotherapy for T1-T2a, N1-3; and for T2b-T4, any N lesions (stages IIIB, III, IVA, IVB). The scheduling and doses of chemotherapy are those used in the intergroup trial 0099. Although an unusual occurrence, a patient with residual disease in the neck and a complete response at the primary should undergo a neck dissection. Initial therapy for patients who present with metastatic disease (stage IV) should consist of a platinum-based combination chemotherapy regimen. If a complete response is achieved, definitive RT alone (without chemotherapy) should be administered to the primary tumor and neck area. For early-stage cancer, radiation doses of at least 70 Gy given with standard fractions are necessary for control of gross tumor. In patients with metastatic carcinoma who have failed platinum-based therapy, a triplet-based combination using paclitaxel, carboplatin, and gemcitabine may be useful. Likewise, cetuximab plus carboplatin may be useful for patients with recurrent or metastatic nasopharyngeal cancer who have failed platinum-based therapy. Gemcitabine monotherapy or in combination with cisplatin may also be useful.

Follow-up/Surveillance
For patients whose nasopharyngeal cancer has been treated, the recommended follow-up includes periodic physical examination and an assessment of thyroid function (that is, the TSH level should be determined every 6 to 12 months). Increased TSH levels have been detected in 20% to 25% of patients who received neck irradiation. Post-treatment baseline imaging of the primary and neck is recommended; repeat imaging if indicated by signs/symptoms on physical examination. Speech, hearing, & swallowing evaluation and rehabilitation and dental evaluation may be useful, as indicated. Smoking cessation counseling is recommended.

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

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

Unresectable Disease
For patients with a performance status (PS) of 0 or 1, the standard treatment of newly diagnosed, unresectable disease is concurrent cisplatin (single agent) or carboplatin-based chemotherapy and radiotherapy (category 1). The panel disagreed regarding whether induction chemotherapy (cisplatin) followed by chemoradiation should be used (category 3) for patients with a PS of 0 or 1. For those with a PS of 2, the recommended treatment is generally radiotherapy with or without concurrent chemotherapy; again, the panel disagreed about using induction chemotherapy followed by RT (category 3). For those with PS of 3, the recommended treatment is generally radiotherapy alone or, in some cases, best supportive care.
Many randomized trials and meta-analyses of clinical trials demonstrate significantly improved overall survival, disease-free survival, and local control when concomitant or alternating chemotherapy and radiation is compared with radiotherapy alone. All combined chemoradiotherapy regimens are associated with various degrees of enhanced mucosal toxicities, which require close patient monitoring, ideally provided by a team experienced in treating H&N cancer patients. The various single-agent chemoradiotherapy regimens have not been directly compared in randomized trials. Therefore, no optimal standard regimen is defined. Single-agent cisplatin plus RT is effective and relatively easy to administer. In a phase III randomized trial, cetuximab-based chemoradiotherapy improved locoregional control and overall survival in patients with stage III/IV head and neck cancer; however, there have been concerns about the method used to assess locoregional control. A randomized phase II study in patients with advanced H&N (oral cavity, oropharynx, or hypopharynx) suggested that cisplatin plus paclitaxel and RT may yield better overall survival than either cisplatin plus 5-FU and RT or hydroxyurea, 5-FU and RT, although statistical comparisons were not possible.

Based on published data, concurrent chemoradiation typically uses conventional fractionation at 2.0 g per fraction to 70 Gy or more in 7 weeks with single-agent cisplatin given every 3 weeks at 100 mg/m². Use of other fraction sizes (for example, 1.8 Gy, conventional), multiagent chemotherapy, or altered fractionation with chemotherapy has been evaluated, but there is no consensus on the optimal approach. In general, the use of concurrent chemoradiation carries a high toxicity burden, and altered fractionation or multiagent chemotherapy will likely further increase the toxicity burden. For any chemoradiation approach, close attention should be paid to published reports for the specific chemotherapy agent, dose, and schedule of administration. Chemoradiation should be performed by an experienced team and should include substantial supportive care.

Bonner and colleagues have randomly assigned 424 patients with locally advanced and measurable squamous cell carcinomas of the H&N to receive definitive radiotherapy with or without cetuximab. Locoregional control and survival (49 months versus 29.3 months, \( P = .03 \)) were significantly improved in patients treated with radiotherapy and cetuximab compared to radiotherapy alone. Radiotherapy and cetuximab may provide a therapeutic option for patients not considered medically fit for standard chemoradiotherapy regimens. However, more study is needed.

### Recurrent Disease

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

A study in patients with metastatic or recurrent H&N cancer found no significant difference in survival when comparing cisplatin plus 5-FU with cisplatin plus paclitaxel. Other combination regimens used in this patient population include carboplatin plus 5-FU and cetuximab plus cisplatin. These regimens are all listed as treatment options for this patient population.

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

In phase II trials, cetuximab was combined with cisplatin in treating patients with recurrent disease that was refractory to platinum-based chemotherapy.\textsuperscript{158-160} Objective tumor response was observed in 12% to 14% of patients. Vermorken and colleagues reported response in 13% of platinum refractory patients, treated with cetuximab administered as a single agent.\textsuperscript{161} Burtness and colleagues\textsuperscript{156} did a direct comparison of cisplatin plus cetuximab versus cisplatin plus placebo as first-line treatment of recurrent disease; they reported a significant improvement in response rate (26% versus 10%, respectively). Taken together, this data indicates that cetuximab does not overcome platinum resistance, the single-agent response rate is on the order of 12% to 14%. In combination with cisplatin as first-line treatment, a synergistic effect is observed. Moreover, the preliminary results of a phase III 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 when compared to the standard chemotherapy doublet (10.1 months versus 7.4 months, $P=.036$).\textsuperscript{162} Other recent phase II trials using either cisplatin/docetaxel/erlotinib or paclitaxel/cetuximab also suggest benefit from EGFR inhibition.\textsuperscript{163,164}

Randomized trials assessing a combination of cisplatin plus 5-FU versus single-agent therapy with cisplatin, 5-FU, or methotrexate have demonstrated significantly higher response rates for the combination regimen. No difference in overall survival, however, is demonstrable.\textsuperscript{154,155,165-167} The median survival with chemotherapy is approximately 6 months, and the 1-year survival rate is approximately 20%. Achievement of a complete response is associated with longer survival and, although infrequent, has been reported more often with combination regimens.

The standard treatment of patients with incurable, recurrent, or metastatic H&N cancer should be dictated, in large part, by the patient’s PS. Individuals with a good PS (0-1) may be offered combination or single-agent chemotherapy. Patients should be fully informed about the goals of treatment, cost of combination chemotherapy, and potential for added toxicity. For patients with a PS of 2, single-agent chemotherapy or best supportive care is most appropriate. For patients with a good PS who relapse after first-line chemotherapy, second-line treatment in a clinical trial or best supportive care is appropriate. For patients with a PS of 3, best supportive care is appropriate.
**Figure 1**
Anatomic sites and subsites of the head and neck

**Figure 2**
Level designation for cervical lymphatics in the right neck

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