NCCN National Comprehensive Cancer Network®

NCCN

Head and Neck Cancers

Clinical Practice Guidelines in Oncology

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Overview

This shortened version of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Head and Neck (H&N) Cancers addresses tumors arising in the oral cavity, oropharynx, hypopharynx, and nasopharynx (see Figure 1).[1] Other types of H&N cancer (e.g., lip, larynx, paranasal sinus, salivary gland, mucosal melanoma, and occult primary cancer) are included in the complete version of the H&N guidelines available on the NCCN Web site

NCCN Clinical Practice Guidelines in Oncology for Head and Neck Cancers

Key Words

NCCN Clinical Practice Guidelines, NCCN Guidelines, head and neck cancer, chemotherapy, radiotherapy, surgery, oral cavity, oropharynx, hypopharynx, nasopharynx, glottic, supraglottic, larynx *(JNCCN* 2011;9:596–650)

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g., randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

The full NCCN Clinical Practice Guidelines in Oncology for Head and Neck Cancers are not printed in this issue of *JNCCN*, but can be accessed online at www.NCCN.org.

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

Please Note

Disclosures for the NCCN Guidelines Panel for Head and Neck Cancers

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

Individual disclosures for the NCCN Guidelines for Head and Neck Cancers panel members can be found on page 650. (The most recent version of these guidelines and accompanying disclosures, including levels of compensation, are available on the NCCN Web site at www.NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit www.NCCN.org.

(www.NCCN.org). A brief overview of the epidemiology and management of H&N cancer is provided.

By definition, the NCCN Guidelines cannot incorporate all possible clinical variations and are not intended to replace good clinical judgment or individualization of treatments. Exceptions to the rule were discussed among the members of the panel while developing these guidelines. A 5% rule (i.e., omitting clinical scenarios that comprise < 5% of all cases) was used to eliminate uncommon clinical occurrences or conditions from these guidelines.

Incidence and Etiology

An estimated 36,500 new cases of and 7900 deaths from oral cavity and pharyngeal cancers occurred in 2010 in the United States.[2,3] Squamous cell carcinoma or a variant is the histologic type in more than 90% of these tumors. Alcohol and tobacco abuse are common etiologic factors in cancers of the oral cavity, oropharynx, and hypopharynx. Because the entire aerodigestive tract epithelium may be exposed to these carcinogens, patients with H&N cancer are at risk for developing second primary neoplasms of the H&N, lung, esophagus, and other sites that share these risk factors.

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

Text continues on p. 628

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KEY:

*Writing Committee Member

Subcommittees: [a]Principles of Surgery; [b]Principles of Radiation Therapy; [c]Principles of Systemic Therapy (Please note: underlining denotes the lead of the subcommittee)

Specialties: †Medical Oncology; ÞInternal Medicine; §Radiation Oncology; ¶Surgery/Surgical Oncology; ζOtolaryngology

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 patients with head and neck cancer may involve the following:

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

*To view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.

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

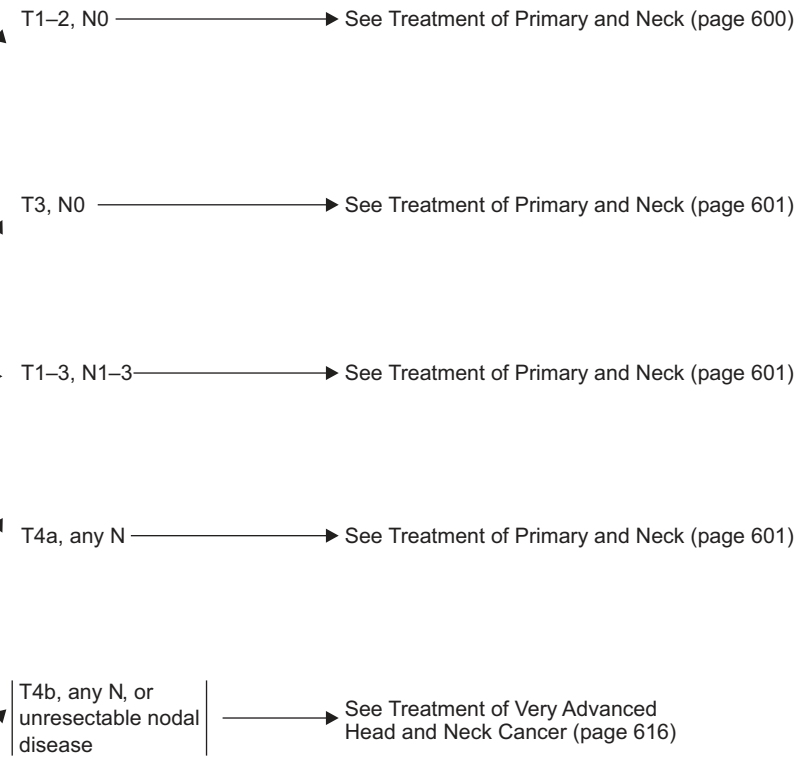
Buccal mucosa, floor of mouth, anterior tongue, alveolar ridge, retromolar trigone, hard palate

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[a]
- Examination under anesthesia with endoscopy, if indicated
- Preanesthesia studies
- Dental/prosthodontic evaluation, including jaw imaging as indicated
- Nutrition, speech & swallowing evaluation/therapy as indicated

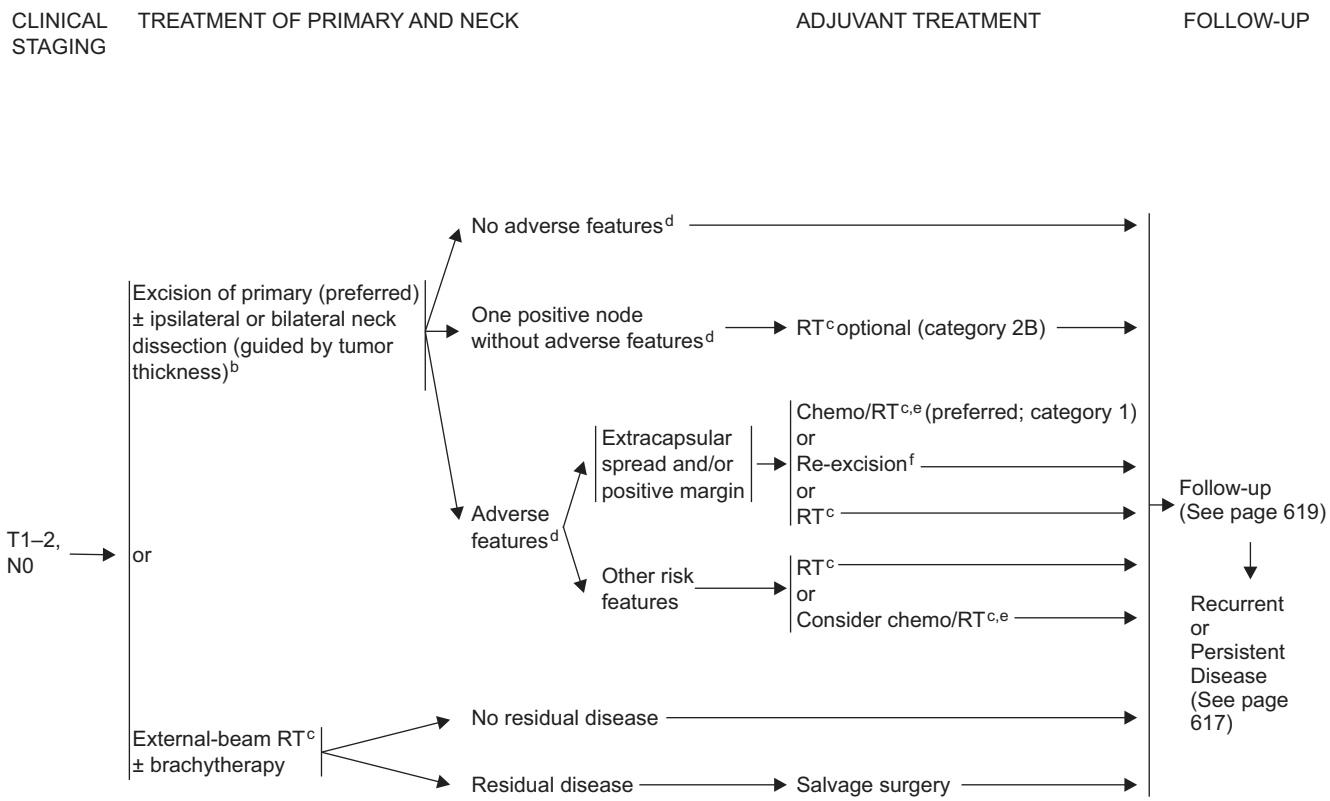
Multidisciplinary consultation as indicated

CLINICAL STAGING



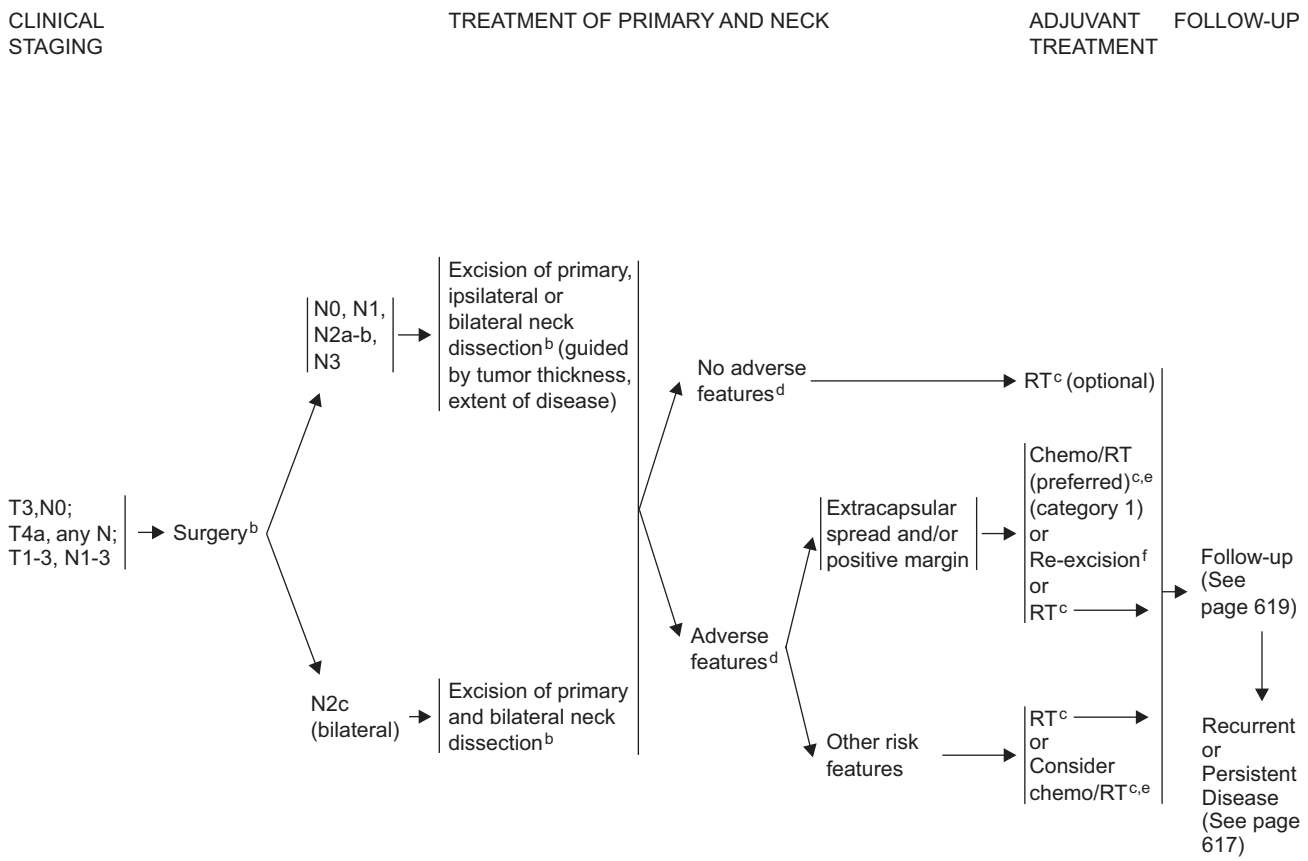
[a]See Discussion.

Buccal mucosa, floor of mouth, anterior tongue, alveolar ridge, retromolar trigone, hard palate



[b] See Principles of Surgery (pages 620-624).
[c] See Principles of Radiation Therapy (page 602).
[d] Adverse risk features: extracapsular nodal spread, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, nodal disease in levels IV or V, perineural invasion, vascular embolism (see Discussion).
[e] See Principles of Systemic Therapy (pages 626 and 627).
[f] Consider re-excision to achieve negative margins, if feasible.

Buccal mucosa, floor of mouth, anterior tongue, alveolar ridge, retromolar trigone, hard palate



[b] See Principles of Surgery (pages 620-624).
[c] See Principles of Radiation Therapy (page 602).
[d] Adverse risk features: extracapsular nodal spread, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, nodal disease in levels IV or V, perineural invasion, vascular embolism (see Discussion).
[e] See Principles of Systemic Therapy (pages 626 and 627).
[f] Consider re-excision to achieve negative margins, if feasible.

PRINCIPLES OF RADIATION THERAPY[1]

DEFINITIVE:

RT

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

For unresectable disease (See page 616)

POSTOPERATIVE:

RT

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

Postoperative chemoradiation

- Concurrent single agent cisplatin at 100 mg/m^2 every 3 wk is recommended[2-4]

[1] See Radiation Techniques (page 625) and Discussion.

[2] Bernier J, Domenge C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med 2004;350:1945-1952.

[3] Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med 2004;350:1937-1944.

[4] Bernier J, Cooper JS, Pajuk TF, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (#9501). Head Neck 2005;27:843-850.

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[a]
- Chest imaging
- CT with contrast and/or MRI with contrast of primary and neck
- Consider PET-CT[b] for stage III-IV disease
- Dental evaluation, including panorex as indicated
- Nutrition, speech & swallowing evaluation/therapy and audiogram as indicated
- Examination under anesthesia with endoscopy as indicated
- Preanesthesia studies

Multidisciplinary consultation as indicated

CLINICAL STAGING

T1-2, N0-1 → See Treatment of Primary and Neck (page 604)

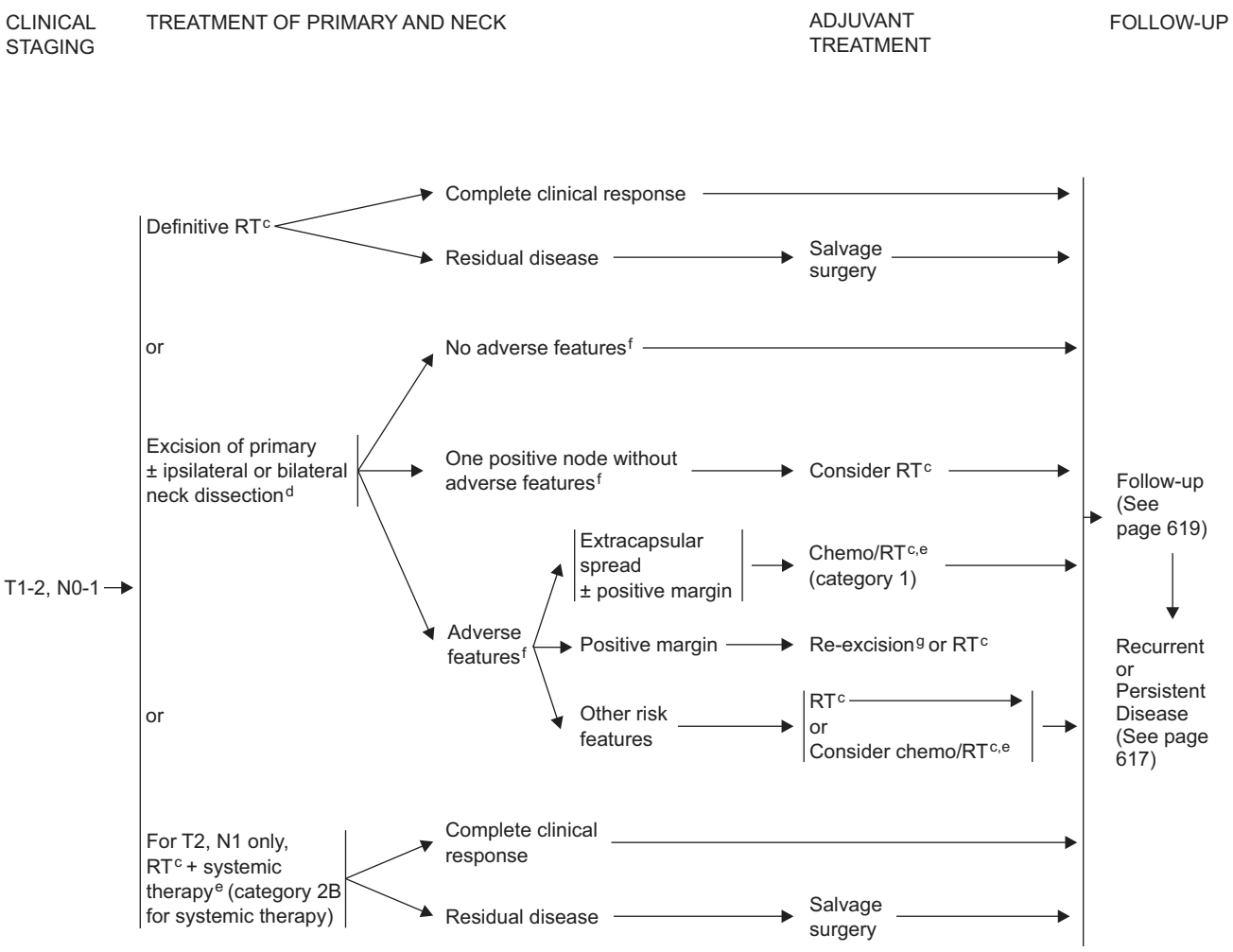
T3-4a, N0-1 → See Treatment of Primary and Neck (page 605)

Any T, N2-3 → See Treatment of Primary and Neck (page 606)

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

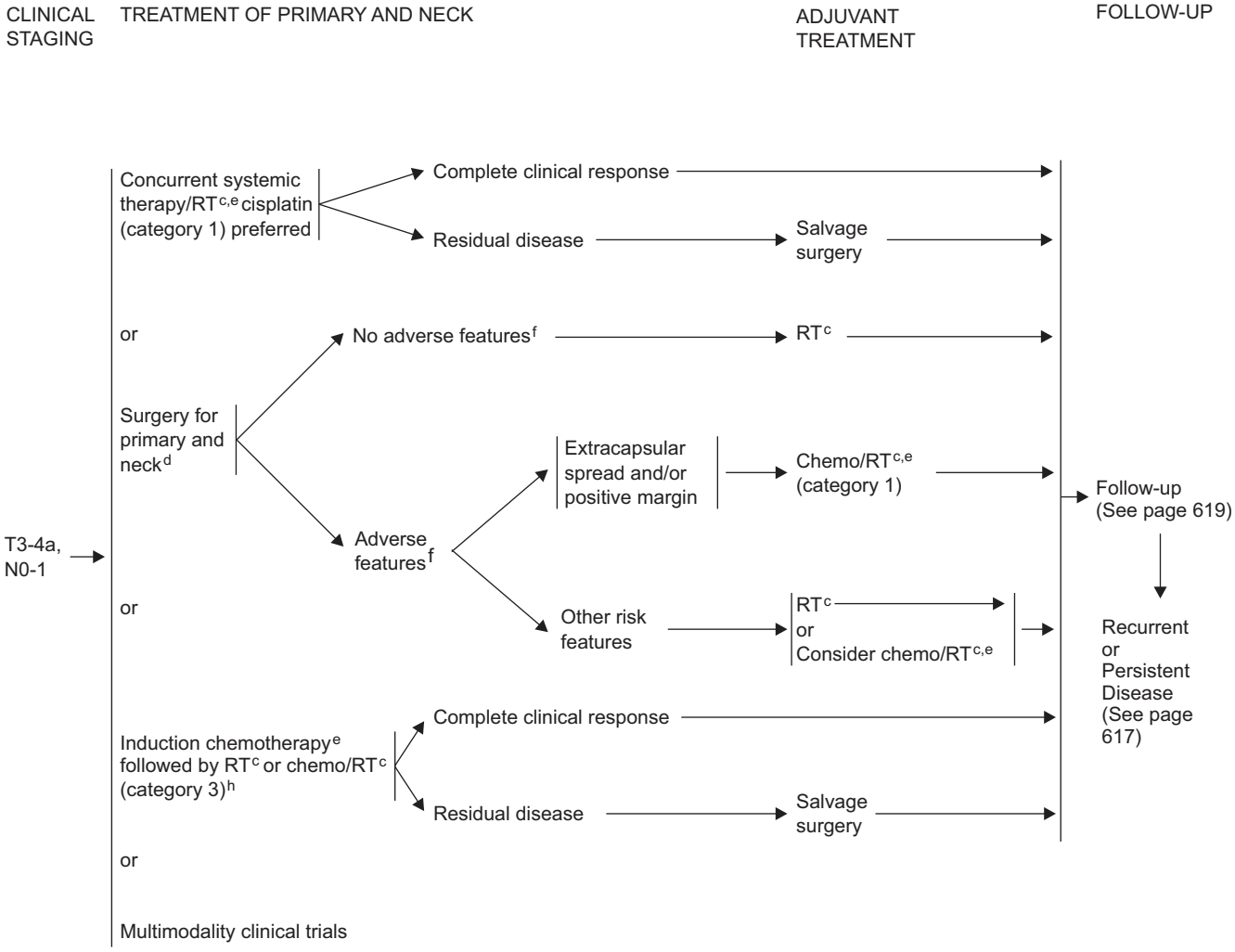
[a] Immunohistochemical staining for p16 is recommended. Although not used to guide treatment, HPV testing is valuable prognostically. The results of HPV testing should not change management decisions except in the context of a clinical trial.
[b] Anatomical imaging is also recommended.

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



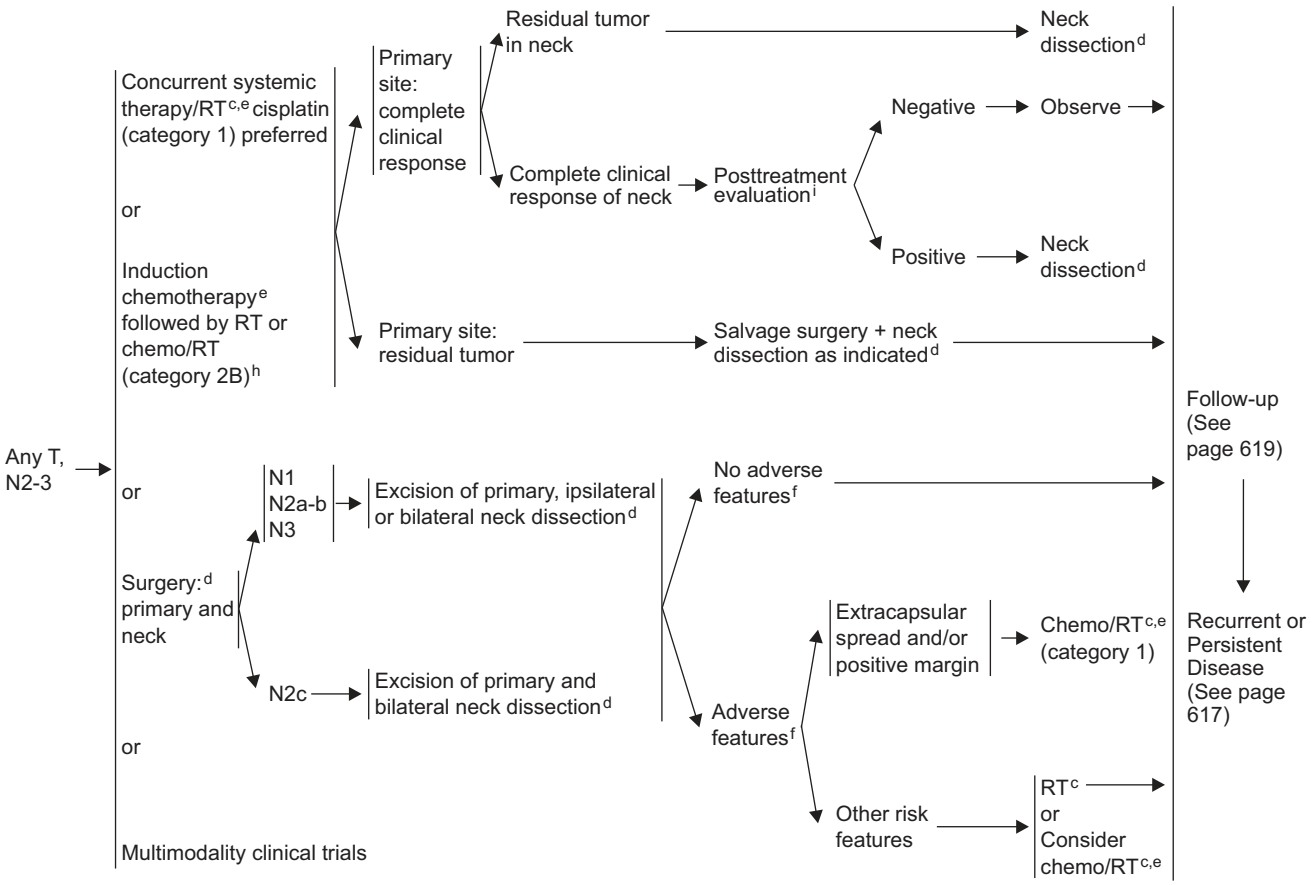
[c] See Principles of Radiation Therapy (page 607).
[d] See Principles of Surgery (pages 620-624).
[e] See Principles of Systemic Therapy (pages 626 and 627).
[f] Adverse features: extracapsular nodal spread, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, nodal disease in levels IV or V, perineural invasion, vascular embolism (see Discussion).
[g] Consider re-excision to achieve negative margins, if feasible.

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



[c] See Principles of Radiation Therapy (page 607).
[d] See Principles of Surgery (page 620-624).
[e] See Principles of Systemic Therapy (pages 626 and 627).
[f] Adverse features: extracapsular nodal spread, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, nodal disease in levels IV or V, perineural invasion, vascular embolism (see Discussion).
[h] See Discussion on induction chemotherapy.

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



[c] See Principles of Radiation Therapy (page 607).
[d] See Principles of Surgery (pages 620-624).
[e] See Principles of Systemic Therapy (pages 626 and 627).
[f] Adverse features: extracapsular nodal spread, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, nodal disease in levels IV or V, perineural invasion, vascular embolism (see Discussion).
[h] See Discussion on induction chemotherapy.
[i] See Post Chemoradiation or RT Neck Evaluation (page 624).

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

PRINCIPLES OF RADIATION THERAPY[1]

DEFINITIVE

RT

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

Concurrent chemoradiation

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

POSTOPERATIVE

RT

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

Postoperative chemoradiation

- Concurrent single agent cisplatin at 100 mg/m^2 every 3 wk x 3 doses is recommended[3-5]

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

[1] See Radiation Techniques (page 625) and Discussion.

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

[3] Bernier J, Domenge C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med 2004;350:1945-1952.

[4] Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med 2004;350:1937-1944.

[5] Bernier J, Cooper JS, Pajak TF, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (#9501). Head Neck 2005;27:843-850.

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
- Consider PET-CT[a] for stage III-IV disease
- Examination under anesthesia with endoscopy
- Preanesthesia studies
- Nutrition, speech & swallowing evaluation/ therapy and audiogram as indicated
- Dental evaluation
- Consider videostrobe for select patients

Multidisciplinary consultation as indicated

CLINICAL STAGING

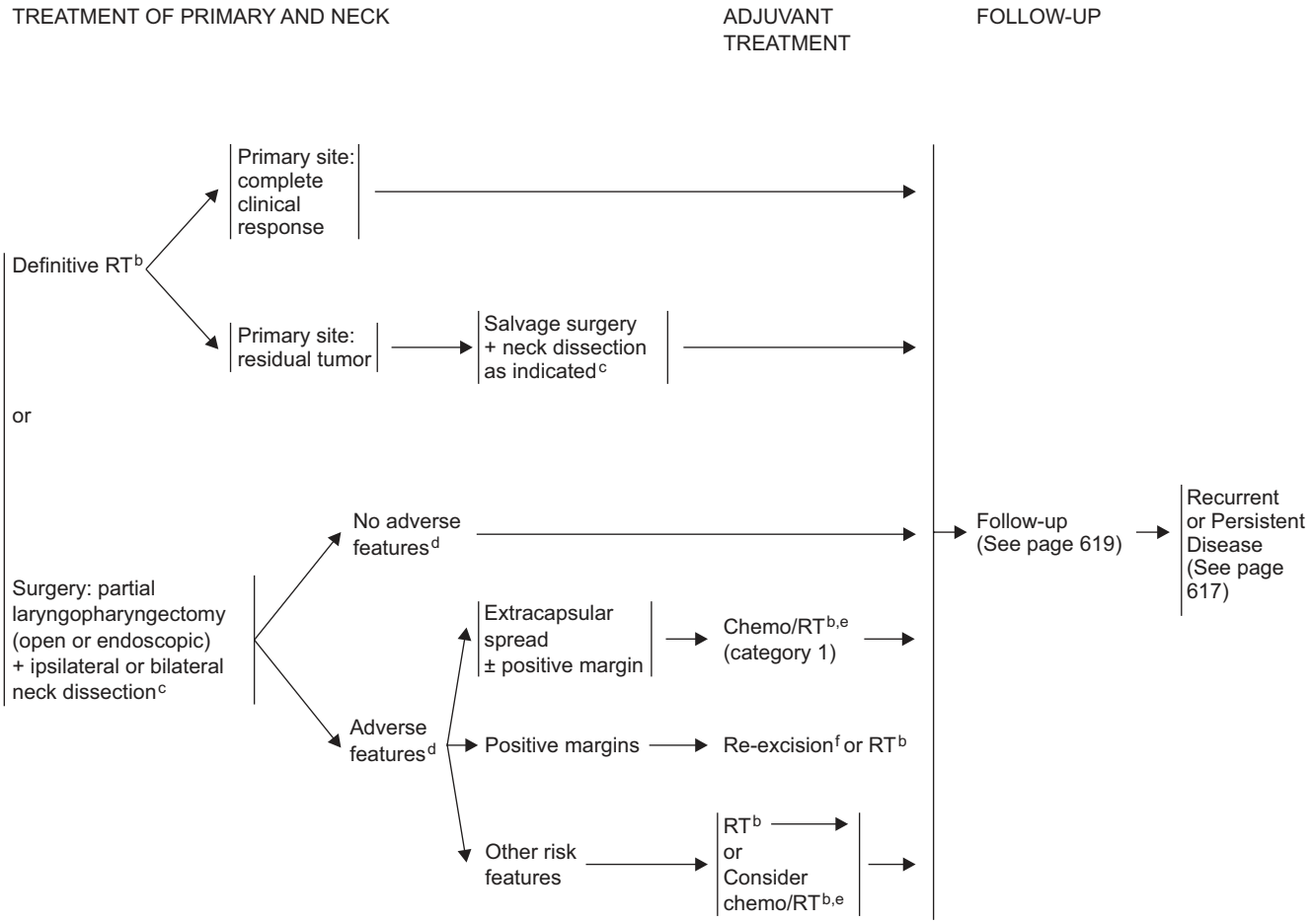
Most T1, N0, selected T2, N0 (not requiring total laryngectomy) →

Advanced cancer requiring total laryngectomy

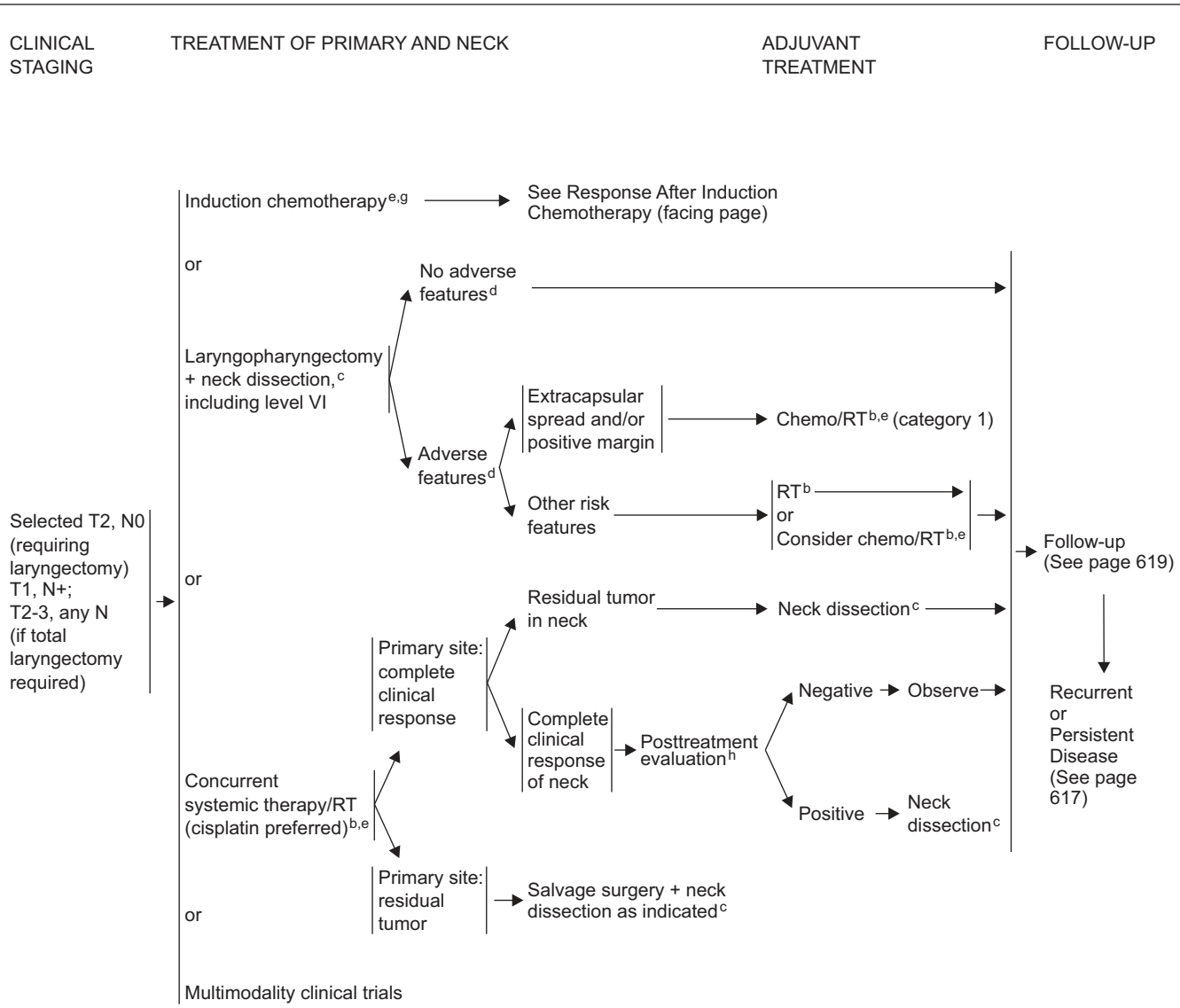
- T1, N+; T2-3, any N → See Treatment of Primary and Neck (page 610)
- T4a, any N → See Treatment of Primary and Neck (page 612)

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

[a]Anatomical imaging is also recommended.

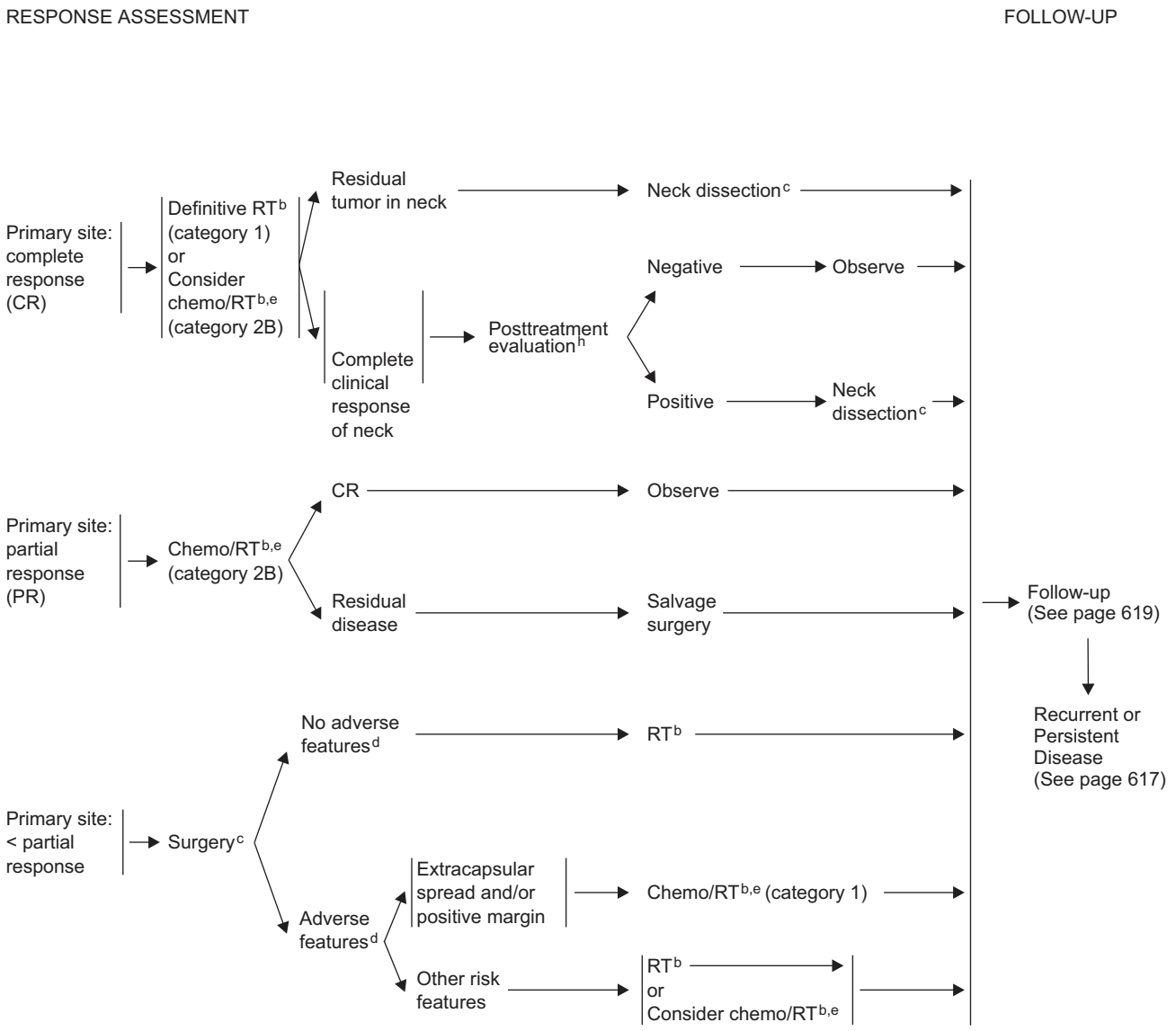


[b] See Principles of Radiation Therapy (page 613).
[c] See Principles of Surgery (pages 620-624).
[d] Adverse features: extracapsular nodal spread, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism (see Discussion).
[e] See Principles of Systemic Therapy (pages 626 and 627).
[f] Consider re-excision to achieve negative margins, if feasible.



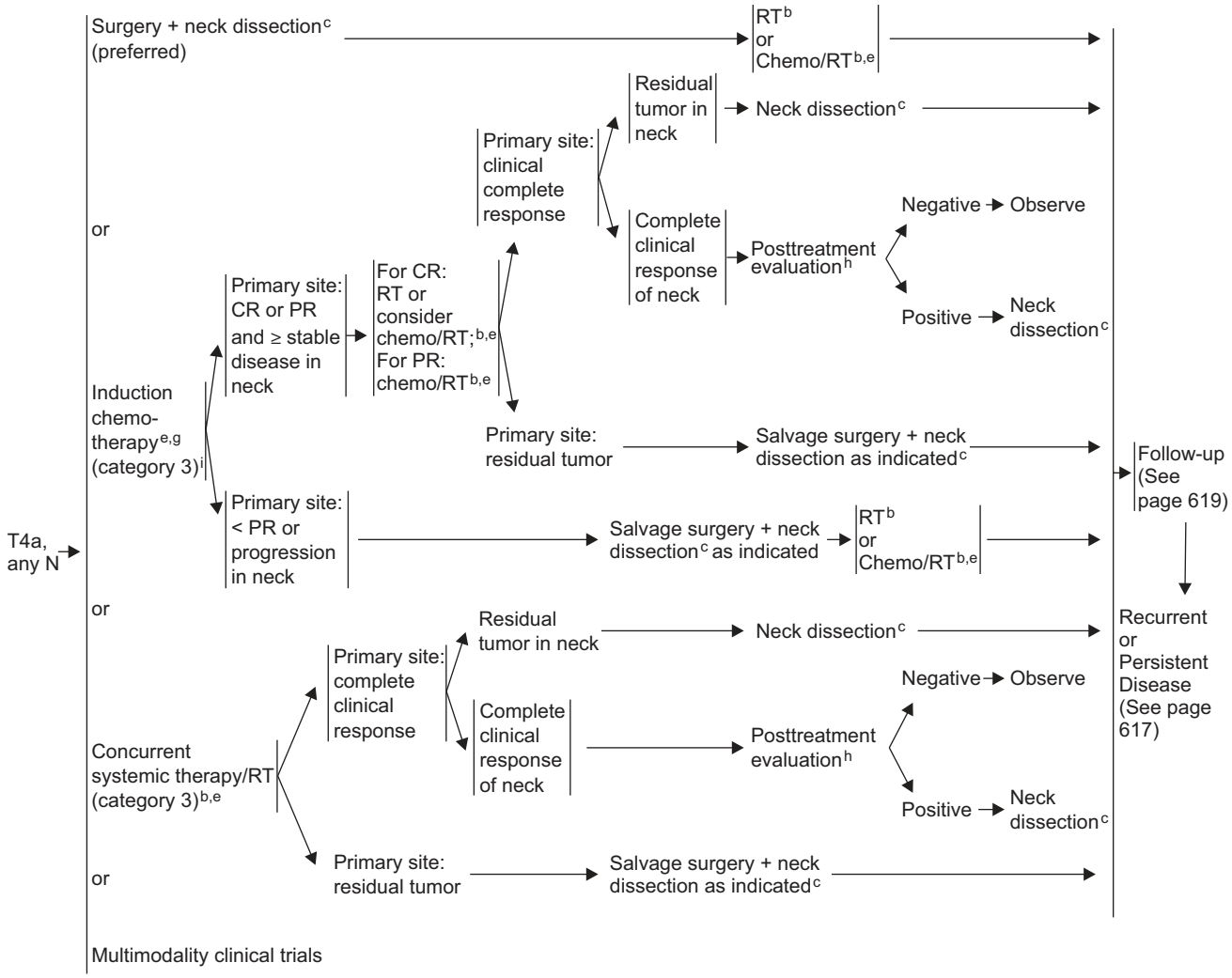
[b] See Principles of Radiation Therapy (page 613).
[c] See Principles of Surgery (pages 620-624).
[d] Adverse features: extracapsular nodal spread, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism (see Discussion).
[e] See Principles of Systemic Therapy (pages 626 and 627).
[g] In randomized clinical trials, assessment of response has been done after 2 or 3 cycles.
[h] See Post Chemoradiation or RT Neck Evaluation (page 624).

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



[b] See Principles of Radiation Therapy (page 613).
[c] See Principles of Surgery (pages 620-624).
[d] Adverse features: extracapsular nodal spread, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism (See Discussion).
[e] See Principles of Systemic Therapy (pages 626 and 627).
[g] In randomized clinical trials, assessment of response has been done after 2 or 3 cycles.
[h] See Post Chemoradiation or RT Neck Evaluation (page 624).

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



[b] See Principles of Radiation Therapy (page 613).
[c] See Principles of Surgery (pages 620-624).
[e] See Principles of Systemic Therapy (pages 626 and 627).
[g] In randomized clinical trials, assessment of response has been done after 2 or 3 cycles.
[h] See Post Chemoradiation or RT Neck Evaluation (page 624).
[i] See Discussion on induction chemotherapy.

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

PRINCIPLES OF RADIATION THERAPY[1,2]

DEFINITIVE

RT

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

Concurrent chemoradiation

- Conventional fractionation[3]
  - Primary and gross adenopathy: ≥ 70 Gy (2.0 Gy/fraction)
  - Neck
    Uninvolved nodal stations: 44-64 Gy (1.6-2.0 Gy/fraction)

POSTOPERATIVE

RT

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

Postoperative chemoradiation

- Concurrent single agent cisplatin at 100 mg/m^2 every 3 wk is recommended[4-6]

[1] See Radiation Techniques (page 625) and Discussion.

[2] Particular attention to speech and swallowing needs during therapy.

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

[4] Bernier J, Domenge C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med 2004;350:1945-1952.

[5] Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med 2004;350:1937-1944.

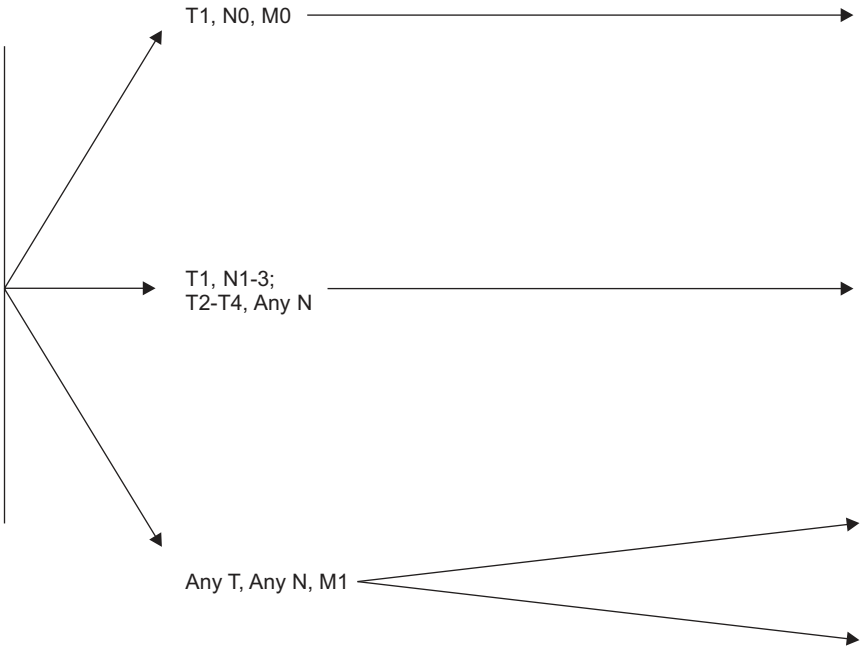
[6] Bernier J, Cooper JS, Pajak TF, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (#9501). Head Neck 2005;27:843-850.

WORKUP

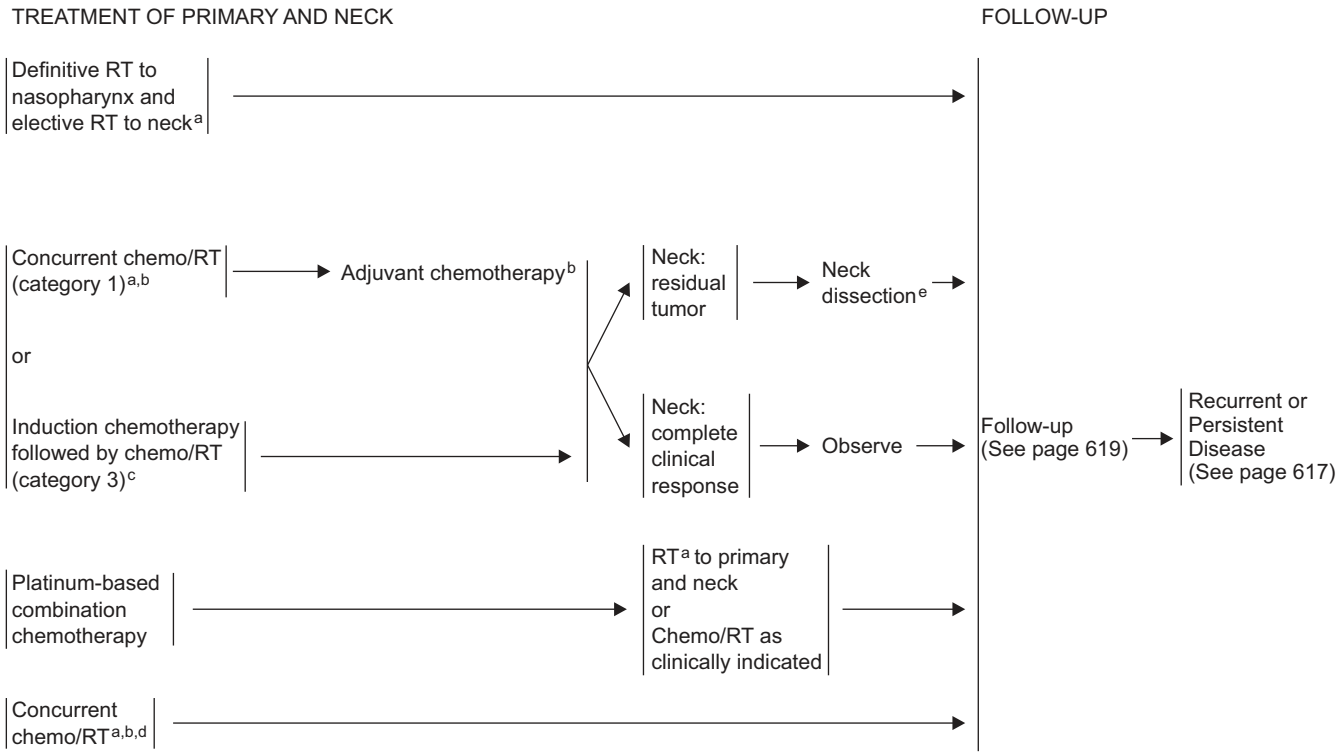
- H&P including a complete head and neck exam; mirror and fiberoptic examination as clinically indicated
- Nasopharyngeal exam and biopsy
- Chest imaging
- MRI with gadolinium of nasopharynx and base of skull to clavicles and CT (as indicated) with contrast
- Consider PET-CT for stage III-IV disease
- Dental evaluation as indicated
- Nutrition, speech & swallowing evaluation/therapy, and audiogram as indicated
- Imaging for distant metastases (chest, liver, bone) for WHO class 2-3/N2-3 disease (may include PET scan and/or CT)

Multidisciplinary consultation as indicated

CLINICAL STAGING



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



[a] See Principles of Radiation Therapy (below).
[b] See Principles of Systemic Therapy (pages 626 and 627).
[c] See Discussion on induction chemotherapy.
[d] Can be used for select patients with distant metastasis in limited site or with small tumor burden, or for patients with symptoms in the primary or any nodal site.
[e] See Principles of Surgery (pages 620-624).

PRINCIPLES OF RADIATION THERAPY[1]

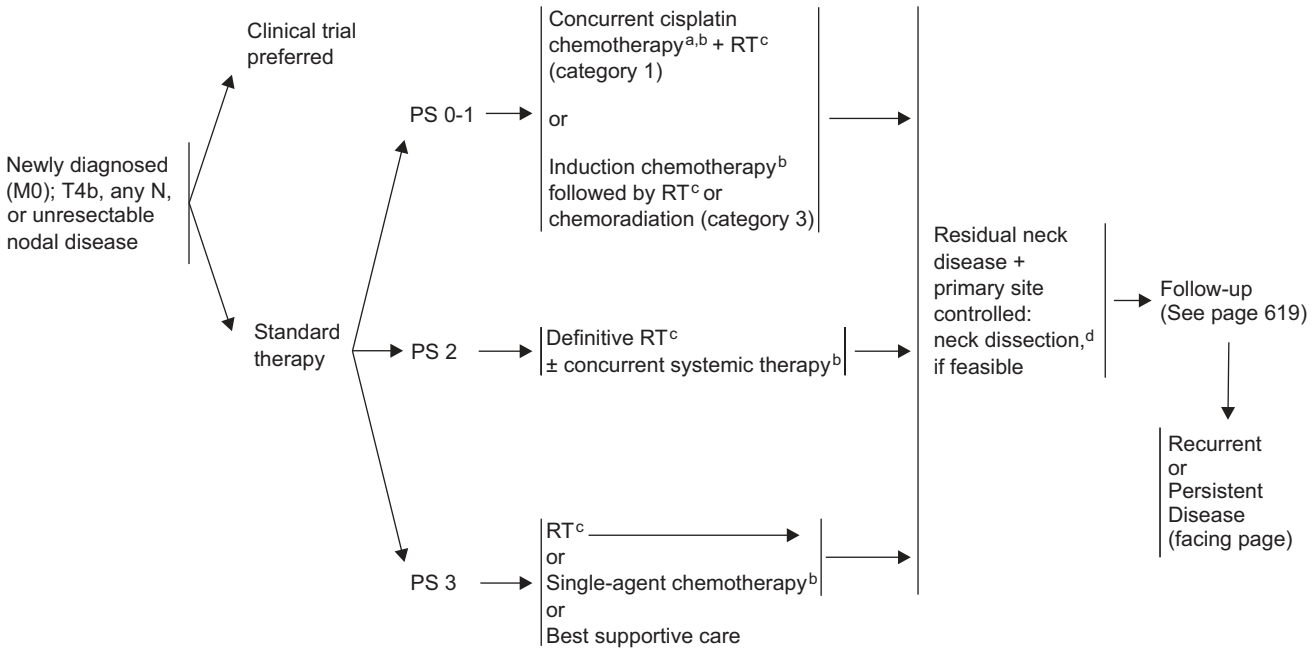
Definitive RT
- Primary and gross adenopathy: 66-70 Gy (2.0 Gy/fraction; daily Monday-Friday) in 7 wk
- Neck
  - Uninvolved nodal stations: 44-64 Gy (1.6-2.0 Gy/fraction)

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

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

[1] See Radiation Techniques (page 625) and Discussion.

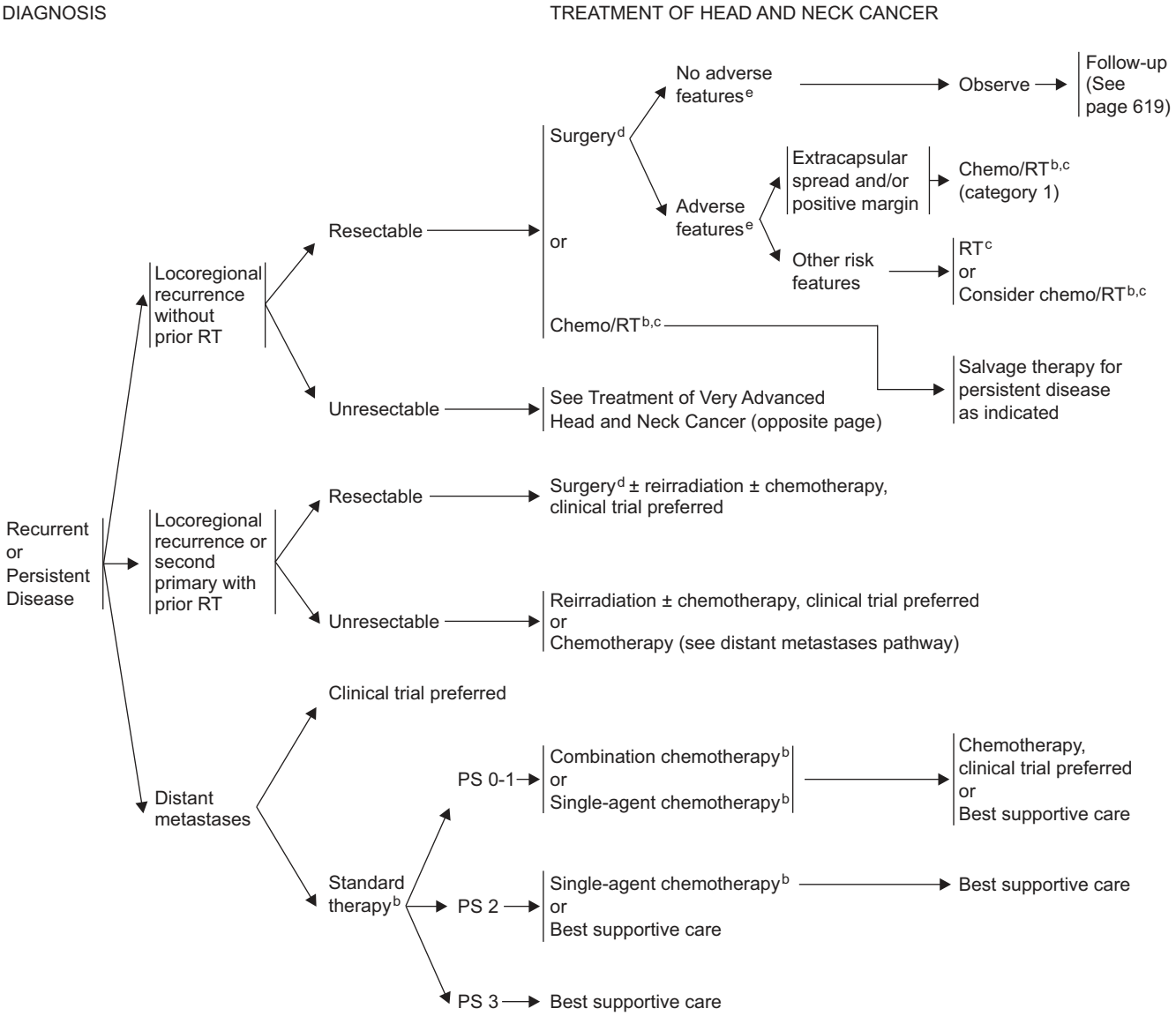
DIAGNOSIS TREATMENT OF HEAD AND NECK CANCER



PS = Performance Status (ECOG)

[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 (pages 626 and 627).
[c] See Principles of Radiation Therapy (page 618).
[d] See Principles of Surgery (pages 620-624).

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



PS = Performance Status (ECOG)

[b] See Principles of Systemic Therapy (pages 626 and 627).
[c] See Principles of Radiation Therapy (page 618).
[d] See Principles of Surgery (pages 620-624).
[e] Adverse features: extracapsular nodal spread, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism (see Discussion).

PRINCIPLES OF RADIATION THERAPY[1]

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

Definitive RT
- Conventional fractionation:
  - Primary and gross adenopathy: 70-74 Gy (2.0 Gy/fraction; daily Monday-Friday) in 7 wk
  - Neck
    Uninvolved nodal stations:
    44-64 Gy (1.6-2.0 Gy/fraction)
- Altered fractionation:
  - 6 fractions/wk accelerated; 70 Gy to gross disease, ≥ 50 Gy to subclinical disease
  - Concomitant boost accelerated RT:
    72 Gy/6 wk (1.8 Gy/fraction, large field; 1.5 Gy boost as second daily fraction during last 12 treatment days)
  - Hyperfractionation:
    81.6 Gy/7 wk (1.2 Gy/fraction, twice daily)
  - Modified fractionation total dose > 70 Gy and treatment course < 7 wk

[1] See Radiation Techniques (page 625) and Discussion.

FOLLOW-UP RECOMMENDATIONS

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

[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.

PRINCIPLES OF SURGERY

Evaluation

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

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

Integration of Therapy

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

Assessment of Resectability

Tumor involvement of the following sites is associated with poor prognosis[1] or with T4b cancer (i.e., unresectable based on technical ability to obtain clear margins):

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

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[1] In selected cases, surgery might still be considered.

PRINCIPLES OF SURGERY (Cont.)

Primary Tumor Resection

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

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

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PRINCIPLES OF SURGERY (Cont.)

Margins

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

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

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

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

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

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PRINCIPLES OF SURGERY (Cont.)

Neck Management

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

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

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

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

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

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

N3 Comprehensive neck dissection

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

Management of Recurrences

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

Surveillance

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

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

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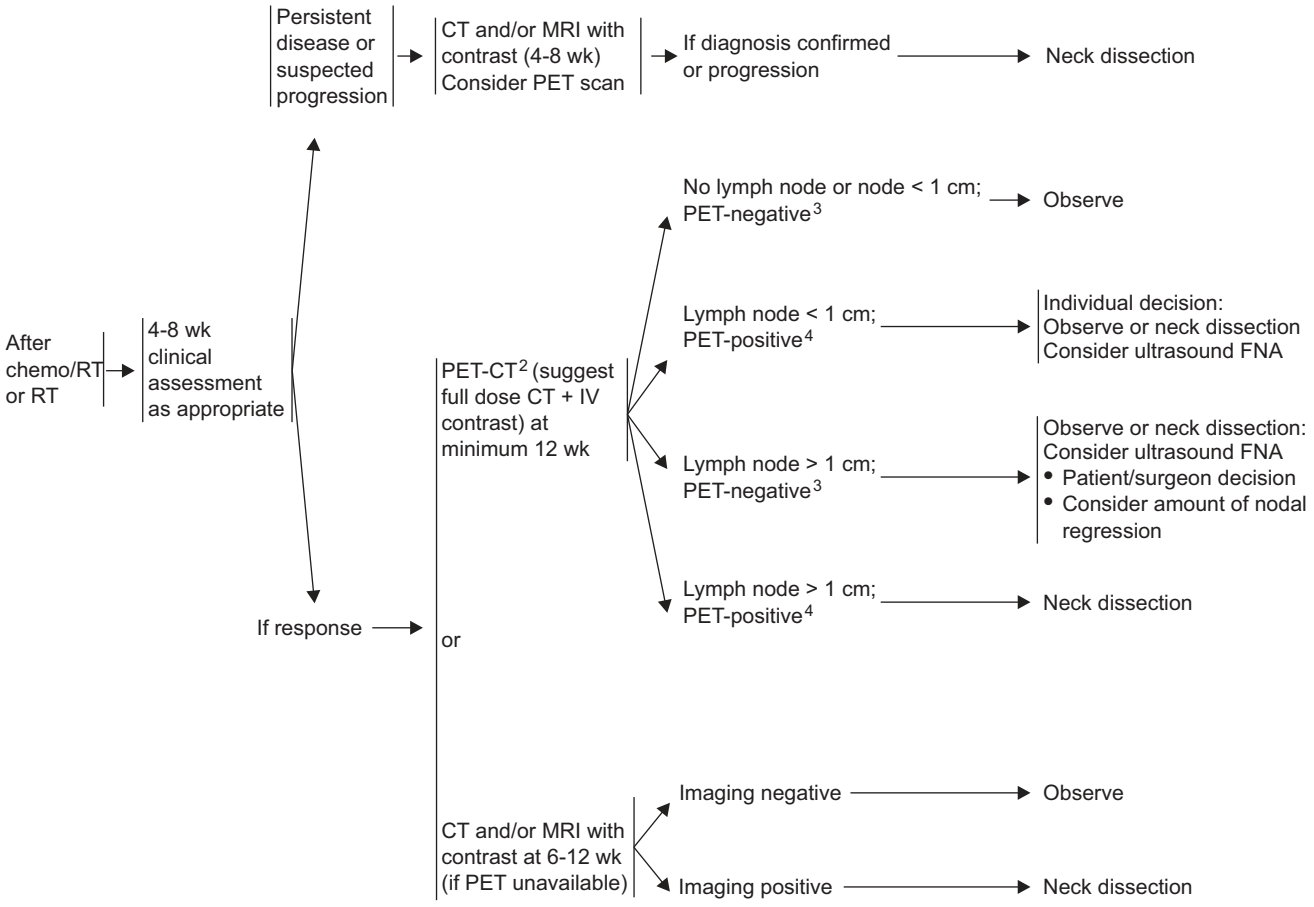
PRINCIPLES OF SURGERY
(POST CHEMORADIATION OR RT NECK EVALUATION)[1]



[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, 1003-1004, 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.

RADIATION TECHNIQUES[1-8]

Target delineation and optimal dose distribution require experience in head and neck imaging, and a thorough understanding of patterns of disease spread. Standards for target definition, dose specification, fractionation (with and without concurrent chemotherapy), and normal tissue constraints are still evolving. IMRT, 3D, and 2D conformal techniques may be used as appropriate depending on the stage, tumor location, physician training/experience, and available physics support. Close interplay exists between radiation technology, techniques, fractionation, and chemotherapy options resulting in a large number of combinations that may impact toxicity or tumor control. Close cooperation and interdisciplinary management are critical to treatment planning and radiation targeting, especially in the postoperative setting or after induction chemotherapy.[9]

Intensity-Modulated Radiotherapy

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

IMRT and Fractionation[10,11]

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

[1] Dogan N, King S, Emami B, et al. Assessment of different IMRT boost delivery methods on target coverage and normal-tissue sparing. Int J Radiat Oncol Biol Phys 2003;57:1480-1491.
[2] Lee NY, de Arruda FF, Puri DR, et al. A comparison of intensity-modulated radiation therapy and concomitant boost radiotherapy in the setting of concurrent chemotherapy for locally advanced oropharyngeal carcinoma. Int J Radiat Oncol Biol Phys 2006;66:966-974.
[3] Lee NY, O'Meara W, Chan K, et al. Concurrent chemotherapy and intensity-modulated radiotherapy for locoregionally advanced laryngeal and hypopharyngeal cancers. Int J Radiat Oncol Biol Phys 2007;69:459-468.
[4] Mohan R, Wu Q, Morris M, et al. "Simultaneous Integrated Boost" (SIB) IMRT of advanced head and neck squamous cell carcinomas—dosimetric analysis. Int J Radiat Oncol Biol Phys 2001;51:180–181.
[5] Overgaard J, Hansen HS, Specht L, et al. Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6 and 7 randomised controlled trial. Lancet 2003;362:933-940.
[6] Schoenfeld GO, Amdur RJ, Morris CG, et al. Patterns of failure and toxicity after intensity-modulated radiotherapy for head and neck cancer. Int J Radiat Oncol Biol Phys 2008;71:377-385.
[7] Wolden SL, Chen WC, Pfister DG, et al. Intensity-modulated radiation therapy (IMRT) for nasopharynx cancer: update of the Memorial Sloan-Kettering experience. Int J Radiat Oncol Biol Phys 2006;64:57-62.
[8] Wu Q, Manning M, Schmidt-Ullrich R, Mohan R. The potential for sparing of parotids and escalation of biologically effective dose with intensity-modulated radiation treatments of head and neck cancers: a treatment design study. Int J Radiat Oncol Biol Phys 2000;46:195-205.
[9] Salama JK, Haddad RI, Kies MS, et al. Clinical practice recommendations for radiotherapy planning following induction chemotherapy in locoregionally advanced head and neck cancer. Int J Radiat Oncol Biol Phys 2009;75:725-733.
[10] Hartford AC, Palisca MG, Eichler TJ, et al. American Society for Therapeutic Radiology and Oncology (ASTRO) and American College of Radiology (ACR) practice guidelines for intensity-modulated radiation therapy (IMRT). Int J Radiat Oncol Biol Phys 2009;73:9-14.
[11] IMRT Documentation Working Group, Holmes T, Das R, Low D, et al. American Society of Radiation Oncology recommendations for documenting intensity-modulated radiation therapy treatments. Int J Radiat Oncol Biol Phys. 2009;74:1311-1318.

PRINCIPLES OF SYSTEMIC THERAPY

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

Squamous Cell Cancers

Oral Cavity, Oropharynx, Hypopharynx:

Primary Systemic Therapy + Concurrent RT
- Cisplatin alone[1,2] (preferred) (category 1)
- Cetuximab[3] (category 1)
- 5-FU/hydroxyurea[4]
- Cisplatin/paclitaxel[4]
- Cisplatin/infusional 5-FU[5]
- Carboplatin/infusional 5-FU[6]
- Carboplatin/paclitaxel[7] (category 2B)

Postoperative Chemoradiation
- Cisplatin alone[8-11] (category 1 for high risk)

Induction*/Sequential Chemotherapy
- Docetaxel/cisplatin/5-FU[12-14] (category 1 if induction is chosen)
- After induction, agents to be used with concurrent chemoradiation typically include weekly platinums, weekly taxanes, or cetuximab.[15]

Nasopharynx

Chemoradiation Followed by Adjuvant Chemotherapy
- Cisplatin + RT followed by cisplatin/5-FU[16,17] (category 1)

Recurrent, Unresectable, or Metastatic (Incurable)

Combination Therapy
- Cisplatin or carboplatin + 5-FU + cetuximab (non-nasopharyngeal)[18] (category 1)
- Cisplatin or carboplatin + docetaxel[19] or paclitaxel[20]
- Cisplatin/cetuximab (non-nasopharyngeal)[21]
- Cisplatin + 5-FU[20,22]

Single Agents
- Cisplatin
- Carboplatin
- Paclitaxel
- Docetaxel
- 5-FU
- Methotrexate
- Ifosfamide
- Bleomycin
- Gemcitabine[23] (nasopharyngeal)
- Cetuximab (non-nasopharyngeal)[24]

See references on facing page

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

PRINCIPLES OF SYSTEMIC THERAPY - REFERENCES

[1]Forastiere A, Maor M, Weber R, et al. Long term results of Intergroup RTOG 91-11: a phase III trial to preserve the larynx - induction cisplatin/5-FU and radiation therapy versus concurrent cisplatin and radiation therapy versus radiation therapy [abstract]. J Clin Oncol 2006;24:Abstract 5517.
[2]Adelstein DJ, Li Y, Adams GL, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. J Clin Oncol 2003;21:92-98.
[3]Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. Lancet Oncol 2010;11:21-28.
[4]Garden AS, Harris J, Vokes EE, et al. Preliminary results of Radiation Therapy Oncology Group 97-03: a randomized phase II trial of concurrent radiation and chemotherapy for advanced squamous cell carcinomas of the head and neck. J Clin Oncol 2004;22:2856-2864.
[5]Taylor S, Murthy A, Vannetzel J, et al. Randomized comparison of neoadjuvant cisplatin and fluorouracil infusion followed by radiation versus concomitant treatment in advanced head and neck cancer. J Clin Oncol 1994;12:385-395.
[6]Denis F, Garaud P, Bardet E, et al. Final results of the 94-01 French Head and Neck Oncology and Radiotherapy Group randomized trial comparing radiotherapy alone with concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. J Clin Oncol 2004;22:69-76.
[7]Suntharalingam M, Haas ML, Conley BA, et al. The use of carboplatin and paclitaxel with daily radiotherapy in patients with locally advanced squamous cell carcinomas of the head and neck. Int J Radiat Oncol Biol Phys 2000;47:49-56.
[8]Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med 2004;350:1937-1944.
[9]Bernier J, Domenge C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med 2004;350:1945-1952.
[10]Bernier J, Cooper JS, Pajak TF, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). Head Neck 2005;27:843-850.
[11]Bachaud JM, Cohen-Jonathan E, Alzieu C, et al. Combined postoperative radiotherapy and weekly cisplatin infusion for locally advanced head and neck carcinoma: final report of a randomized trial. Int J Radiat Oncol Biol Phys 1996;36:999-1004.
[12]Vermorken JB, Remenar E, van Herpen C, et al. EORTC 24971/TAX 323 Study Group. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. N Engl J Med 2007;357:1695-1704.
[13]Posner MR, Hershock DM, Blajman CR, et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. N Engl J Med 2007;357:1705-1715.
[14]Pointreau Y, Garaud P, Chapet S, et al. Randomized trial of induction chemotherapy with cisplatin and 5-fluorouracil with or without docetaxel for larynx preservation. J Natl Cancer Inst 2009;101:498-506.
[15]Chitapanarux I, Lorvidhaya V, Kamnerdsupaphon P, et al. Chemoradiation comparing cisplatin versus carboplatin in locally advanced nasopharyngeal cancer: randomised, non-inferiority, open trial. Eur J Cancer 2007;43:1399-1406.
[16]Al-Sarraf M, LeBlanc M, Giri PG, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. J Clin Oncol 1998;16:1310-1317.
[17]Chan AT, Leung SF, Ngan RK, et al. Overall survival after concurrent cisplatin-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma. J Natl Cancer Inst 2005;97:536-539.
[18]Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 2008;359:1116-1127.
[19]Samlowski WE, Moon J, Kuebler JP, et al. Evaluation of the combination of docetaxel/carboplatin in patients with metastatic or recurrent squamous cell carcinoma of the head and neck (SCCHN): a Southwest Oncology Group phase II study. Cancer Invest 2007;25:182-188.
[20]Gibson MK, Li Y, Murphy B, et al. Randomized phase III evaluation of cisplatin plus fluorouracil versus cisplatin plus paclitaxel in advanced head and neck cancer (E1395): an Intergroup Trial of the Eastern Cooperative Oncology Group. J Clin Oncol 2005;23:3562-3567.
[21]Burtness B, Goldwasser MA, Flood W, et al. Phase III randomized trial of cisplatin plus placebo versus cisplatin plus cetuximab in metastatic/recurrent head and neck cancer: an Eastern Cooperative Oncology Group study. J Clin Oncol 2005;23:8646-8654.
[22]Forastiere AA, Metch B, Schuller DE, et al. Randomized comparison of cisplatin plus flurouracil and carboplatin plus fluorouracil versus methotrexate in advanced squamous cell carcinoma of the head and neck: a Southwest Oncology Group study. J Clin Oncol 1992;10:1245-1251.
[23]Zhang L, Zhang Y, Huang PY, et al. Phase II clinical study of gemcitabine in the treatment of patients with advanced nasopharyngeal carcinoma after the failure of platinum-based chemotherapy. Cancer Chemother Pharmacol 2008;61:33-38.
[24]Vermorken JB, Trigo J, Hitt R, et al. Open-label, uncontrolled, multicenter phase II study to evaluate the efficacy and toxicity of cetuximab as a single agent in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck who failed to respond to platinum-based therapy. J Clin Oncol 2007;25:2171-2177.

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

Staging

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

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

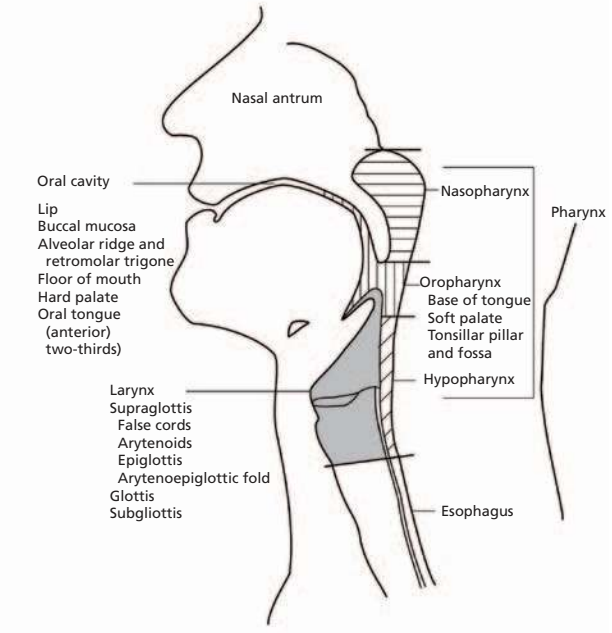

Figure 1 Anatomic sites and subsites of the head and neck
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In general, stage I or II disease defines a relatively small primary tumor with no nodal involvement. Stage III or IV cancers include larger primary tumors, which may invade underlying structures and/or spread to regional nodes. Distant metastases are uncommon at presentation. More advanced TNM stages are associated with worse survival.

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

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

Minor changes were made in the T staging categories for the nasopharynx in the 7th edition of the AJCC (see Table 2, available online, in these guidelines, at www.NCCN.org [ST-3]).[12] Thus, former T2a lesions are now designated T1; therefore, former stage IIA is now stage I. Lesions previously staged as T2b are now T2; therefore, former stage IIB is now

stage II. Regardless of unilateral or bilateral location, retropharyngeal lymph nodes are considered N1.

Management Approaches

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

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

Multidisciplinary Team Involvement

The initial evaluation and treatment plan for patients with H&N cancer require a multidisciplinary team of health care providers with expertise in caring for these patients. Similarly, managing and preventing sequelae of radical surgery, radiotherapy, and chemotherapy (e.g., pain, xerostomia, speech and swallowing problems, depression) require professionals who are familiar with the disease. Follow-up for these sequelae should include a comprehensive H&N examination. Adequate nutritional support can help to prevent severe weight loss in patients undergoing treatment for H&N cancer; thus, patients should be encouraged to see a dietician.[14] Patients should also be encouraged to stop smoking and modify alcohol consumption if excessive, because these habits may decrease the efficacy of treatment and adversely affect other health outcomes.[15,16] Programs using behavioral counseling combined with FDA-approved medications that promote smoking cessation can be very useful (http://www.ahrq.gov/path/tobacco.htm). Specific components of patient support and follow-up are listed in the algorithm on page 598. The panel also recommends referring to the NCCN Guidelines for Palliative Care (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).

Comorbidity and Quality of Life

Comorbidity

Comorbidity refers to the presence of concomitant disease (in addition to H&N cancer) that may affect the diagnosis, treatment, and prognosis for the patient.[17–19] Documentation of comorbidity is particularly important in oncology to facilitate optimal treatment selection and estimates of prognosis. Comorbidity is known to be a strong independent predictor for mortality in patients with H&N cancer,[19–26] and comorbidity also influences costs of care, use, and quality of life.[27–29] Traditional indices of comorbidity include the Charlson index[18] and the Kaplan-Feinstein index and its modifications.[19,30] The Adult Comorbidity Evaluation-27 (ACE-27) is specific for H&N cancer and has excellent emerging reliability and validity.[31,32]

Quality of Life

Health-related quality-of-life issues are paramount in H&N cancer. These tumors affect basic physiologic functions (e.g., the ability to chew, swallow, and breathe), the senses (taste, smell, and hearing), and uniquely human characteristics (e.g., appearance and voice). *Health status* describes an individual's physical, emotional, and social capabilities and limitations. *Function* and *performance* refer to how well an individual is able to perform important roles, tasks, or activities. *Quality of life* differs, because the central focus is on the *value* (determined by the patient alone) that individuals place on their health status and function.[33]

A National Institutes of Health (NIH)–sponsored conference[34] recommended the use of patient-completed scales to measure quality of life. For H&N cancer–specific issues, the 3 most widely accepted validated measures are: 1) the University of Washington Quality of Life scale (UW-QOL)[35]; 2) the

EORTC Quality of Life Questionnaire (EORTC-HN35)[36]; and 3) the Functional Assessment of Cancer Therapy-Head and Neck module (FACT-HN).[37] The Performance Status scale for patients with H&N cancer is a clinician-rated performance scale—with a narrower focus than the previously mentioned scales—that is also widely used.[38]

Head and Neck Surgery

Principles of Surgery

All patients should be evaluated by an H&N surgical oncologist before treatment. In addition, multidisciplinary evaluation and treatment must be well coordinated. Evaluation, integration of therapy, assessment of resectability, primary tumor resection, margins, surgical management of cranial nerves (VII, X–XII), neck management, management of recurrences, and surveillance (including posttreatment neck evaluation) are discussed in Principles of Surgery, pages 620–624.[1,39] Resectable disease, neck dissection, postoperative management, and salvage surgery of high-risk disease are discussed in the following sections.

Resectable Versus Unresectable Disease

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

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

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

Neck Dissection

Historically, cervical lymph node (i.e., neck) dissections have been classified as "radical" or "modified radical" procedures. The less radical procedures preserved the sternocleidomastoid muscle, jugular vein, spinal accessory nerve, or selective lymph node levels. The panel prefers to classify cervical lymphadenectomy using contemporary nomenclature, thus classifying cervical lymph node dissections as either "comprehensive" or "selective."[40] A comprehensive neck dissection is one that removes all lymph node groups that would be included in a classic radical neck dissection. Whether the sternocleidomastoid muscle, jugular vein, or spinal accessory nerve is preserved does not affect whether the dissection is classified as comprehensive. Depending on the site, comprehensive neck dissection is often recommended for N3 disease (see specific site guidelines in the algorithm and Neck Management, pages 623 and 624).

Selective neck dissections were developed based on an understanding of the common pathways for spread of H&N cancers to regional nodes (see Figure 2).[41,42] Depending on the site, selective neck dissection is often recommended for N0 disease (see specific

site guidelines in the algorithm, and pages 623 and 624). To remove the nodes most commonly involved with metastases from the oral cavity, a selective neck dissection is recommended, which includes the nodes found above the omohyoid muscle (levels I–III and sometimes the superior parts of level V).[40,43] Similarly, to remove the nodes most commonly involved with metastases from the pharynx, a selective neck dissection is recommended, which includes the nodes in levels II through IV and level VI when appropriate.[40] 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).[44–46]

The chief role of selective neck dissections in these NCCN Guidelines for H&N Cancers is to select patients for possible adjuvant therapy (i.e., chemo/RT or RT), although selective neck dissections may be used as treatment when neck tumor burden is low.[47] In general, patients undergoing selective neck dissection should not have clinical nodal disease; however, selective neck dissection may prevent morbidity in patients with nodal disease and may be appropriate in certain patients with N1 to N2 disease.[48–50] In the guidelines, patients with cervical node metastases who undergo operations with therapeutic intent are generally treated with comprehensive neck dissections, because often they have disease outside the bounds of selective neck dissections. Determining whether an ipsilateral or bilateral neck dissection is needed depends on tumor thickness, the extent of the tumor, and tumor site.[39] For example, bilateral neck dissection is often recommended for tumors at or near the midline and/or for tumor sites with bilateral drainage.

It is particularly important for patients treated nonsurgically to have careful and regular follow-up examinations by a trained H&N surgical oncologist so that any local or regional recurrence is detected early and salvage surgery (and neck dissection as indicated) can be performed. After either RT or chemoradiation, posttreatment evaluation with imaging (e.g., CT and/or MRI with contrast, PET-CT) guides the use of neck dissection (see Post Chemoradiation or RT Neck Evaluation, page 624).[51–54] If PET-CT is used for follow-up, the first scan should be performed at approximately 12 weeks after treatment to reduce the false-positive rate.[52,55]

Note that a complete clinical response (i.e., clinically negative) may be defined as no visible or palpable neck disease and no radiographic findings (i.e., the absence of either focally abnormal lymph nodes or large nodes [> 1.5 cm])[51,56]; a complete pathologic response requires pathologic confirmation. If a complete clinical response is seen in patients who were N0 at initial staging, all panel members recommend observation.[51,56,57] In patients who have a clinically negative neck, a negative PET-CT is 90% reliable and further imaging is optional.[58–60] Panelists also concur that any patient with residual disease or suspected progression in the neck after radiotherapy or chemoradiation should undergo a neck dissection.[51]

Postoperative Management of High-Risk Disease

Many factors influence survival and locoregional tumor control in patients with H&N cancer. The role of chemotherapy in the postoperative management of the patient with adverse prognostic risk factors has been clarified by 2 separate multicenter randomized trials[61,62] and a combined analysis of data from the 2 trials for patients with high-risk cancers of the oral cavity, oropharynx, or hypopharynx.[63]

The US Intergroup trial RTOG 95-01 randomly assigned patients with 2 or more involved nodes,

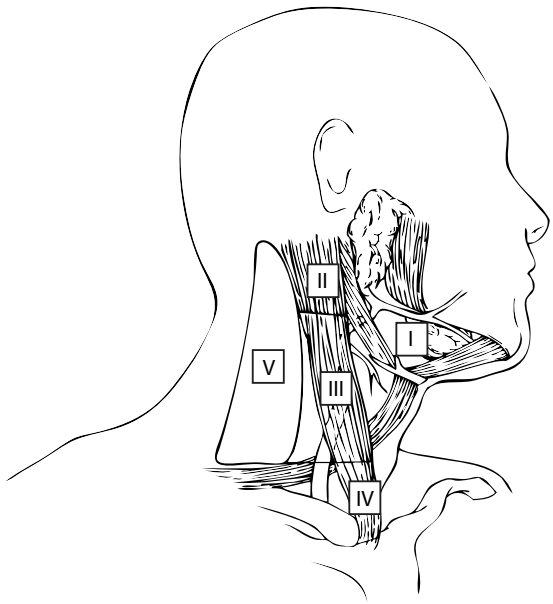

Figure 2 Level designation for cervical lymphatics in the right neck.
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positive margins, or extracapsular nodal spread of tumor to undergo standard postoperative radiotherapy or the same radiotherapy plus cisplatin 100 mg/m^2 every 3 weeks for 3 doses.[62] The European trial EORTC 22931 was designed using the same chemotherapy treatment and similar radiotherapy dosing, but also included as high-risk factors the presence of perineural or perivascular disease and nodal involvement at levels IV and V from an oral cavity or oropharynx cancer.[61] The RTOG trial showed statistically significant improvement in locoregional control and disease-free survival but not overall survival, whereas the EORTC trial found significant improvement in survival and the other outcome parameters. A schedule using cisplatin at 50 mg intravenously weekly has also shown improved survival in this setting.[64]

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

In NCCN Member Institutions, patients with extracapsular nodal spread and/or positive surgical margins undergo adjuvant chemoradiotherapy after resection.[64–70] The presence of other adverse risk factors—multiple positive nodes (without extracapsular nodal spread), vascular/lymphatic/perineural invasion, pT3 or pT4 primary, and oral cavity or oropharynx primary cancers with positive level IV or V nodes—are established indications for postoperative radiotherapy. Because patients with these other adverse features were also included in the EORTC 22931 trial that showed a survival advantage for patients receiving cisplatin concurrent with postoperative radiotherapy compared with radiotherapy alone, the panel added "consider chemoradiation" for these features.[61]

Salvage Surgery

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

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

H&N Radiotherapy

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

Radiation Doses

Selection of radiation total dose depends on the primary tumor and neck node size, fractionation, and clinical circumstances, including whether to use concurrent chemotherapy (see page 625 and the in-

dividual Principles of Radiation Therapy guidelines for each primary site). In general, the primary tumor and gross adenopathy require a total of 66 to 74 Gy (2.0 Gy/fraction) and up to 81.6 Gy (1.2 Gy/fraction) in hyperfractionation. External radiation doses exceeding 75 Gy using conventional fractionation (2.0 Gy/fraction) may lead to unacceptable rates of normal tissue injury.

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

Fractionation in Radiotherapy Alone

No single fractionation schedule has proven to be best for all tumors. Data strongly indicate squamous cancers of the H&N can grow rapidly, and may compensate for radiotherapy-induced cell loss through the mechanism of accelerated repopulation.[71–73] Especially in radiotherapy-alone settings, schedules delivering at least 1000 cGy/wk are recommended.[74–78]

Two large, randomized clinical trials from Europe have reported improved locoregional control using altered fractionation. The EORTC protocol 22791 compared hyperfractionation (1.15 Gy twice daily, or 80.5 Gy over 7 weeks) with conventional fractionation (2 Gy once daily, or 70 Gy over 7 weeks) in the treatment of T2, T3, N0–1 oropharyngeal carcinoma excluding base of tongue primaries. At 5 years, a statistically significant increase was seen in local control in the hyperfractionation arm (38% vs. 56%; P = .01) and no increase in late complications.[79] A long-term follow-up analysis has also shown a small survival advantage for hyperfractionation (P = .05).[80] Another EORTC protocol (22851) compared accelerated fractionation (1.6 Gy 3 times daily, or 72 Gy over 5 weeks) with conventional fractionation (1.8–2.0 Gy once daily, or 70 Gy over 7–8 weeks) in various intermediate to advanced H&N cancers (excluding cancers of the hypopharynx). Patients in the accelerated fractionation arm had significantly better locoregional control at 5 years (P = .02). Disease-specific survival showed a trend favoring the accelerated fractionation arm (P = .06). Acute and late toxicity were increased with acceleration, however, raising questions about the net advantages of accelerated fractionation.[81]

The RTOG reported the initial 2-year results and subsequent mature results (after a median follow-up of 8.5 years) of a 4-armed phase III randomized clinical trial (protocol 90-03) comparing hyperfractionation and 2 variants of accelerated fractionation against standard fractionation.[82,83] After 2 years of follow-up, both accelerated fractionation with a concomitant boost (AFX-C) and hyperfractionation were associated with improved locoregional control and disease-free survival compared with standard fractionation. However, acute toxicity was increased. No significant difference was seen among the various treatment groups in the frequency of grade 3 or worse late effects reported at 6 to 24 months after treatment initiation. Long-term follow-up confirmed a statistically significant improvement in locoregional control with either AFX-C or hyperfractionation compared with standard fractionation. However, neither disease-free survival nor overall survival was significantly improved.

A meta-analysis of updated individual patient data from 15 randomized trials analyzing the effect of hyperfractionated or accelerated radiotherapy on survival of patients with H&N cancer has been published.[84] Standard fractionation constituted the control arm in all of the trials in this meta-analysis. An absolute survival benefit of 3.4% at 5 years (hazard ratio [HR], 0.92; 95% CI, 0.86–0.97; P = .003) was reported. This benefit, however, was limited to patients younger than 60 years.[84] Consensus regarding altered fractionation schedules with concomitant boost or hyperfractionation for stage III or IV oral cavity and oropharyngeal cancers has not yet emerged among NCCN Member Institutions.[83–86]

Fractionation in Concurrent Chemoradiation

No consensus exists regarding the optimal radiation dose-fractionation scheme when administered with concurrent chemotherapy. Most published studies have used conventional fractionation at 2.0 Gy per fraction to 70 Gy or more in 7 weeks with single-

agent cisplatin given every 3 weeks at 100 mg/m^2. Other fraction sizes (e.g., 1.8 Gy, conventional), other dosing schedules of cisplatin, other single agents, multiagent chemotherapy, and altered fractionation with chemotherapy have been evaluated alone or in combination. Numerous trials have shown that modified fractionation and concurrent chemotherapy are more efficacious than modified fractionation alone.[86–89] However, whether modified fractionation with concurrent chemotherapy is superior to standard fractionation and concurrent chemotherapy is currently unknown. RTOG 0129 is assessing accelerated fractionation versus standard fractionation with concurrent cisplatin. Preliminary results suggest that accelerated fractionation does not improve survival over standard fractionation.[90]

Concurrent chemoradiation increases acute toxicity compared with radiation alone, although an increase in late toxicity beyond that caused by radiotherapy alone is less clear.[91–93] Altered fractionation and/or multiagent chemotherapy may further increase the toxicity burden.[94] For any chemotherapeutic approach, close attention should be paid to published reports for the specific chemotherapy agent, dose, and schedule of administration. Chemoradiation should be performed by an experienced team and should include substantial supportive care.

Radiation Techniques and IMRT

The intensity of the radiation beam can be modulated to decrease doses to normal structures without compromising the doses to the cancer targets (http://www.icru.org/index.php?option=com_content&task=view&id=171).[95,96] IMRT is an advanced form of conformal radiotherapy permitting more precise targeting of cancer while reducing dose to normal tissues.[97–100] Xerostomia is a common long-term side effect of radiotherapy, which can be reduced with IMRT, drug therapy (e.g., pilocarpine, cevimeline), and other novel approaches (e.g., acupuncture).[101–105]

IMRT dose painting refers to the method of assigning different dose levels to different structures within the same treatment fraction (e.g., 2.0 to gross tumor, 1.7 to microscopic tumor, and < 1.0 Gy to parotid gland), resulting in different total doses to different targets (e.g., 70 Gy, 56 Gy, < 26 Gy).[106] Although dose painting has been used to simplify radiation planning, hot spots associated with higher toxicity can occur.[106,107] Alternatively, separate dose plans for the low versus higher dose targets can be delivered sequentially ("reduce target size and boost") or on the same day as separate fractions in twice-daily schemes (see Radiation Techniques, page 625).[99,108]

IMRT is now widely used in H&N cancer and is the predominant technique used at NCCN Member Institutions. It is useful in reducing long-term toxicity in oropharyngeal and nasopharyngeal cancers through reducing the dose to one or more major salivary glands, temporal lobes, mandible, auditory structures (including cochlea), and optic structures.[101,102,109–115] However, overall survival is similar among patients treated with IMRT and those receiving conventional RT.[109,116,117] In-field recurrences, low-grade mucositis in areas away from the cancer targets, and posterior neck hair loss can occur with IMRT.[118,119] The application of IMRT to other sites (e.g., oral cavity, hypopharynx) is evolving and may be used at the discretion of treating physicians.[120,121]

Numerous phase II studies show a decrease in late toxicity (xerostomia) without compromising tumor control for nasopharyngeal and other sites. More recently, 3 randomized trials have supported the clinical benefits of IMRT in H&N cancer with regard to the reduction in xerostomia. Pow et al.[101] evaluated treatment of early-stage nasopharyngeal carcinoma with conventional radiotherapy techniques versus IMRT. The results showed a statistical improvement in salivary flow and patient-reported quality-of-life parameters.[101] In the study by Kam et al.,[102] patients with nasopharyngeal carcinoma were randomized to either IMRT or conventional 2-dimensional radiotherapy. At 1 year after treatment, patients in the IMRT arm had significantly lower rates of clinician-rated severe xerostomia than patients in the 2-dimensional radiotherapy arm (39.3% vs. 82.1%; P = .001). Salivary flow rates were also higher with IMRT. The mean parotid dose was 32 Gy in the IMRT group and 62 Gy in the conventional group. Although a trend for improvement in patient-reported dry mouth was observed after IMRT, recovery was incomplete and no significant difference was seen in patient-reported outcomes between the arms. The authors concluded that other salivary glands may also be important and merit protection.

Recent data from the PARSPORT phase III randomized trial indicate that IMRT decreases xerostomia compared with conventional radiotherapy in patients with non-nasopharyngeal carcinoma.[122,123] In this trial, patients with T1–T4, N0–N3, M0 disease were treated

with either conventional radiotherapy (i.e., parallel opposed technique) or IMRT to a total dose of 60 or 65 Gy in 30 fractions; 80 patients with oropharyngeal and 14 with hypopharyngeal tumors were included. Grade 2 or worse (LENT-SOMA scale) xerostomia 1 year after treatment was seen in 74% of patients receiving conventional radiotherapy versus 38% of patients in the IMRT group (P = .003). No differences were seen in the rates of locoregional control or survival.

Follow-Up After Radiotherapy

For patients whose cancer has been treated with radiotherapy, the recommended follow-up includes an assessment of thyroid function (i.e., the thyroid stimulating hormone [TSH] level should be determined every 6–12 months). Increased TSH levels have been detected in 20% to 25% of patients who received neck irradiation.[124]

Brachytherapy

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

Cancer of the Oral Cavity

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

Regional node involvement at presentation is evident in approximately 30% of patients, but the risk varies according to subsite. For example, primaries of the alveolar ridge and hard palate infrequently involve the neck, whereas occult neck metastasis is common (50%–60%) in patients with anterior tongue cancers. In general, all patients undergo either ipsilateral or bilateral selective neck dissection, which is guided by tumor thickness. If definitive radiotherapy is chosen for treatment of T1–2, N0 disease, at least 44–64 Gy is given to the neck (see page 602).

Workup and Staging

Imaging studies to evaluate mandibular involvement and a careful dental evaluation (including Panorex, as indicated) are particularly important for staging (see Table 1, available online, in these guidelines, at www.NCCN.org [ST-1]) and planning therapy for oral cavity cancers, in addition to a complete H&N examination, biopsy, and other appropriate studies (see page 599). For patients who appear to have stage III/IV disease, PET-CT may alter management by upstaging patients.[125]

Treatment

Surgery and radiotherapy represent the standards of care for early-stage and locally advanced resectable lesions in the oral cavity. The specific treatment is dictated by the TN stage and, if N0 at diagnosis, by the risk of nodal involvement (see pages 599–601). Multidisciplinary team involvement is particularly important for this site because of the critical physiologic functions of mastication, deglutition, and articulation of speech, which may be affected. Most panelists prefer surgical therapy for resectable oral cavity tumors, even for more advanced tumors. The concept of organ preservation using chemotherapy in the initial management of these patients has received less attention in the management of oral cavity cancers, because the functional outcome after primary surgical management is often good, given advances in reconstruction using microvascular techniques. Primary radiotherapy may be offered to select patients who are medically inoperable or refuse surgery.

Postoperative chemotherapy/radiotherapy (preferred, category 1) or reexcision of positive margins (if technically feasible) is recommended for all patients who have resected oral cavity cancers with the adverse pathologic features of extracapsular nodal spread and/or a positive mucosal margin.[61–64] For other risk features, such as pT3 or pT4 primary, N2 or N3 nodal disease, nodal disease in levels IV or V, or perineural invasion or vascular tumor embolism, clinical judgment should be used when considering whether to add chemotherapy to radiotherapy or treat with radiotherapy alone.

Follow-Up/Surveillance

Recommendations for surveillance are provided in the algorithm.

Cancer of the Oropharynx

The oropharynx includes the base of the tongue, tonsils, soft palate, and posterior pharyngeal wall. The oropharynx is extremely rich in lymphatics. Depending on the subsite involved, 15% to 75% of

patients present with lymph node involvement. Efforts to improve the outcome of patients with locally advanced disease are ongoing. Participation in clinical trials is strongly recommended.

Workup and Staging

A multidisciplinary consultation is encouraged. Accurate staging (see Table 2, available online, at www.NCCN.org [ST-3]) depends on complete H&N examination coupled with appropriate imaging studies (see page 603).[12,126] Tumor HPV testing is suggested for cancers of the oropharynx given the established relationship between prior HPV infection and the development of a significant proportion of oropharyngeal cancers.

HPV Testing

Several studies have recently documented an increase in the incidence of HPV-related cancer, now estimated to constitute up to 60% to 70% of newly diagnosed cancers of the oropharynx in the United States and parts of the European Union.[11,127,128] A strong causal relationship has been established, particularly between HPV type 16 and the development of oropharyngeal cancer.[4] Prospective and retrospective analyses of clinical trials indicate that patients with HPV-positive cancers have improved response to treatment and improved survival and progression-free survival when compared with HPV-negative tumors.[129–134] How this information should be used in routine clinical decision-making and in the design of clinical trials is currently a matter of intense investigation among NCCN Member Institutions. There is growing consensus that HPV status should be used as a stratification factor or should be addressed in separate trials (HPV related vs. unrelated disease) for which patients with oropharyngeal cancer are eligible.

Except for in cancers of unknown primary (see NCCN Clinical Practice Guidelines in Oncology for Occult Primary, available online, in these guidelines, at www.NCCN.org [OCC-1–6 and OCC-A]), the panel believes that HPV status currently should not be a routine consideration in treatment selection. Additional studies are needed to better understand the effect of HPV status on response to different therapies, treatment outcome, and patterns of failure, and in relation to other prognostic or predictive factors, such as smoking history and stage. Several clinical trial groups are reporting retrospective analyses of response to therapy in HPV-related versus HPV-unrelated oropharynx cancers.[129–131,133] The panel strongly urges that patients with HPV-related cancers be enrolled in clinical trials evaluating biologic and treatment-related questions, when available.

HPV testing options in a clinical setting include HPV in situ hybridization [ISH]) and a surrogate marker, p16 immunohistochemistry (which is a more widely available test that has been shown in several studies to strongly correlate with HPV status and is similarly associated with improved prognosis).[131–133,135] Sufficient pathologic material for HPV testing can be obtained by fine-needle aspiration (FNA).[136] The panel notes that HPV testing may prompt questions about prognosis (i.e., a favorable vs. less favorable forecast) and sexual history that the clinician should be prepared to address. Thus, without a specific reason for testing, HPV information may add anxiety and stress for some patients. Alternatively, understanding the cause of the cancer can result in reduced anxiety for some patients.

Treatment

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

Early-stage (T1–2, N0–1) oropharyngeal cancers may be treated with primary surgery, including neck dissection, as indicated, or with definitive radiotherapy. The panel members felt that the third option of radiotherapy plus systemic therapy (category 2B for systemic therapy) was only appropriate for T2, N1 (see page 604). Adjuvant chemotherapy/radiotherapy is recommended (category 1) for adverse pathologic features of extracapsular nodal spread and/or positive mucosal margin.[61–63]

For locally advanced resectable disease (T3–4a, N0–1; or any T, N2–3), 3 treatment approaches are recommended, in addition to enrollment in a multimodality clinical trial that includes function evaluation. The 3 approaches are: 1) concurrent systemic therapy/radiotherapy cisplatin (category 1; salvage surgery is used for managing residual or recurrent disease)[91]; 2) surgery with appropriate adjuvant therapy (chemo/radiotherapy or radiotherapy); or 3) induction chemotherapy followed by radiotherapy or chemo/radiotherapy, for which there was major disagreement among panel members.

Concurrent systemic therapy/radiotherapy with cisplatin alone (category 1) is preferred for treat-

ment of locally or regionally advanced cancer (T3–4a, N0–1, or any T, N2–3) of the oropharynx. Panel members differed in their opinion as to whether induction chemotherapy should be considered a standard treatment option for T3–4a, N0–1 disease. This disagreement is reflected by a category 3 recommendation in the algorithms (see the following section on The Induction Chemotherapy Controversy).[91,137–146] Notably, for patients with any T, N2–3 disease, the category designation is 2B for induction chemotherapy because of the increased risk for distant metastases in patients with more advanced neck disease (see page 606).

The Induction Chemotherapy Controversy

Defining the optimal role of induction chemotherapy in the management of locally or regionally advanced H&N cancer has generated considerable discussion among the panel in recent years. The algorithm for the management of advanced oropharynx cancer illustrates well the lack of consensus among NCCN Member Institutions despite the extensive discussion. Thus, induction chemotherapy has a category 3 designation (major disagreement) for the management of T3–4a, N0–1 oropharyngeal disease. In addition, induction chemotherapy has a category 2B designation (non-uniform consensus, no major disagreement) for any T, N2–3 oropharyngeal disease. However, the lack of consensus is not unique to the oropharyngeal cancer algorithm; it is also apparent in other algorithms (see pages 608–613, 614 and 615, and 616–618) in which category 3 designations are common. Only for hypopharyngeal cancers less than T4a in extent (which, if managed surgically, would require total laryngectomy) is the use of induction chemotherapy—used here as part of a larynx preservation strategy—associated with a higher level of panel consensus (i.e., category 2A).

A brief review of the available data helps provide some perspective on the panel's deliberations. Most randomized trials of induction chemotherapy followed by radiotherapy and/or surgery compared with locoregional treatment alone published in the 1980s and 1990s did not show an improvement in overall survival with the incorporation of chemotherapy.[142] However, a change in the pattern of failure with less-distant metastases was noted in some studies[147]; also, a correlation seemed to be present between response to induction chemotherapy and subsequent durable response to radiation.[147,148] Thus, the concept developed that in selected patients, induction chemotherapy could facilitate organ preservation, avoid morbid surgery, and improve overall quality of life even though overall survival was not improved. Because total laryngectomy is among the procedures most feared by patients,[149] larynx preservation was the focus of initial studies.

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

Nonetheless, renewed interest has been shown in the role of induction chemotherapy for a few reasons. Given improvements in locoregional control now achieved with advances in surgery, radiotherapy, and concurrent chemotherapy/radiotherapy, the role of distant metastases as a source of treatment failure has increased and induction chemotherapy allows greater drug delivery for this purpose.[162] Concern has been growing regarding the long-term morbidity of concurrent chemoradiotherapy and related increasing interest in exploring alternative approaches that might have a different and hopefully more favorable side effect profile. Finally, a more effective triplet chemotherapy regimen has been identified compared to the standard cisplatin/5-FU used in induction tri-

als of the 1980s and 1990s, and the related meta-analyses. Results from 3 phase III trials, which compared induction cisplatin plus infusional 5-FU with or without the addition of a taxane (docetaxel or paclitaxel) followed by the same locoregional treatment, showed significantly improved outcomes (response rates, disease-free survival, or overall survival depending on the trial) for patients in the 3-drug induction group compared with those receiving 2 drugs (cisplatin plus 5-FU).[139,141,144,145] A randomized trial in the larynx preservation setting similarly showed superior larynx preservation outcomes when induction docetaxel/cisplatin/5-FU (TPF) and cisplatin/5-FU were compared.[163]

However, a clear advantage in overall survival from the addition of induction chemotherapy to concurrent chemoradiation has not been shown yet. A randomized phase II study in patients with stage III or IV squamous cell H&N cancer of induction TPF followed by concurrent cisplatin/5-FU with radiotherapy versus concurrent cisplatin/5-FU with radiotherapy alone did report a higher radiologic complete response rate with the incorporation of induction chemotherapy.[164] However, a randomized 3-arm study comparing concurrent cisplatin/radiotherapy versus induction chemotherapy with TPF or cisplatin/5-FU followed by concurrent cisplatin/radiotherapy reported a decrease in time to treatment failure with the incorporation of induction therapy, but no difference in survival. Furthermore, approximately 3 times as many patients were not included in the efficacy assessments on the induction arms, suggesting potential toxicity concerns.[165]

There also remains considerable uncertainty and disagreement among panel members concerning which radiation or chemoradiation plan should follow induction.[166] Panel members agree that high-dose cisplatin (100 mg/m^2 every 21 days × 3) may not be feasible for many patients in this setting,[165,167] raising concerns that any efficacy gains of induction may be offset by the use of better-tolerated but potentially less-effective concurrent programs or poorer patient compliance with the radiation-based part of treatment. No one concurrent chemotherapy regimen is preferred. Panel members agreed that many different alternatives are reasonable (including concurrent low-dose weekly cisplatin, weekly taxanes, cetuximab, or combinations thereof), but are inadequately studied, to be specifically recommended.[168]

After induction chemotherapy, the use of cetuximab is supported by data from the TREMPLIN study, in which patients with advanced laryngeal or hypopharyngeal cancer who had a major response to induction TPF were randomized to high-dose cisplatin for 3 cycles versus weekly cetuximab concurrent with radiotherapy. Patients on the cetuximab arm tolerated therapy better, had better compliance with drug delivery, and had similar 3-month laryngeal preservation rates to those observed in patients on the cisplatin arm.[167] Some panel members specifically considered exclusive use of low-dose weekly carboplatin in this setting to be inadequate.[169] Some evidence suggests that chemotherapy with weekly carboplatin might be equivalent to cisplatin; however, data are from the nasopharyngeal setting.[170] Other sequential induction-concurrent regimens, using less-aggressive induction or less-intensive concurrent chemotherapy, seem to have higher compliance rates.[141,171] However, a definitive study has not compared these newer strategies with concurrent chemoradiotherapy alone.

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

Radiation Therapy Fractionation

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

Follow-Up/Surveillance

Recommendations for surveillance are provided in the algorithm.

Cancer of the Hypopharynx

The hypopharynx extends from the superior border of the hyoid bone to the lower border of the

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

Workup and Staging

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

At diagnosis, approximately 60% of patients with cancer of the hypopharynx have locally advanced disease with spread to regional nodes. Furthermore, autopsy series have shown a high rate of distant metastases (60%) involving virtually every organ.[172] Thus, the prognosis for patients with cancer of the hypopharynx can be poor despite aggressive combined modality treatment.

Treatment

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

Patients with more advanced disease (defined as T1, N+; T2–3, any N) requiring total laryngectomy and partial or total pharyngectomy may be managed with 3 approaches (see page 610) in addition to enrollment in multimodality clinical trials: 1) induction chemotherapy followed by definitive radiotherapy if a complete response was achieved at the primary site[147] or followed by other options depending on the response (see page 611); 2) surgery with neck dissection and postoperative radiation or chemoradiation as dictated by pathologic risk features; or 3) concurrent chemotherapy/radiotherapy, cisplatin preferred. Given the functional loss resulting from this surgery and the poor prognosis, participation in clinical trials is emphasized.

The recommendation of the induction chemotherapy/definitive radiotherapy option is based on the results of an EORTC randomized trial.[147] This trial enrolled 194 eligible patients with stage II, III, or IV resectable squamous cell carcinoma of the pyriform sinus (n = 152) and aryepiglottic fold (n = 42), excluding patients with T1 or N2c disease. Patients were randomly assigned either to laryngopharyngectomy and postoperative radiotherapy, or to chemotherapy with cisplatin and 5-FU for a maximum of 3 cycles, followed by definitive radiotherapy. A complete response to induction chemotherapy was required to proceed with definitive radiotherapy. The published results showed equivalent survival, with median survival duration and 3-year survival rate of 25 months and 43%, respectively, for the surgery group versus 44 months and 57%, respectively, for the induction chemotherapy group.[147] A functioning larynx was preserved in 42% of patients who did not undergo surgery. Local or regional failure rates did not differ between patients treated with surgery and those treated with chemotherapy, although the chemotherapy recipients showed a significant reduction in distant metastases as a site of first failure (P = .041). Adherence to the requirements for complete response to chemotherapy and for inclusion of only patients with the specified TN stage is emphasized.

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

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

Options for patients with T4a, any N disease (see page 612) include surgery plus neck dissection (preferred) followed by adjuvant chemotherapy/radiotherapy or radiotherapy; multimodality clinical trials; or category 3 recommendations.

Follow-Up/Surveillance

Recommendations for surveillance are provided in the algorithm.

Cancer of the Nasopharynx

Carcinoma of the nasopharynx is uncommon in the United States. Among H&N cancers, it has among the highest propensity to metastasize to distant sites. Nasopharyngeal cancer also poses a significant risk for isolated local recurrences after definitive radiation (without chemotherapy) for locally advanced disease.[174–177] Regional recurrences are uncommon in this disease, occurring in only 10% to 19% of patients.[177,178]

These NCCN Guidelines for the evaluation and management of carcinoma of the nasopharynx attempt to address risk for both local and distant disease. Stage is accepted as prognostically important. The prognostic significance of histology is still controversial. Radiotherapy was the standard treatment for all stages of this disease until the mid-1990s when trial data showed improved survival for locally advanced tumors treated with concurrent radiotherapy and cisplatin.[179]

Workup and Staging

The workup of nasopharyngeal cancer includes a complete H&N examination and other studies (see page 614), which are important for determining the full extent of tumor to assign appropriate stage and to design radiation ports that will encompass all disease with appropriate doses. Multidisciplinary consultation is encouraged. The 2010 AJCC staging classification (7th edition) is used as the basis for treatment recommendations (see Table 2, available online, in these guidelines, at www.NCCN.org [ST-3]).[12]

Treatment

Patients with T1, N0, M0 nasopharyngeal tumors may be treated with definitive radiotherapy alone (see page 615). For early-stage cancer in this setting, radiation doses of 66 to 70 Gy given with standard fractions are necessary for control of gross tumor (see page 615). The local control rate for these tumors ranges from 80% to 90%, whereas T3–4 tumors have a control rate of 30% to 65% with radiotherapy alone.[180,181]

The combination of radiotherapy and concurrent platinum-based chemotherapy followed by adjuvant cisplatin/5-FU has been shown to increase the local control rate from 54% to 78%. The Intergroup trial 0099, which randomly assigned patients to chemotherapy plus external-beam radiotherapy versus external radiation alone, closed early when an interim analysis disclosed a significant survival and progression-free survival advantage favoring the combined chemotherapy and radiation group.[179] The addition of chemotherapy also decreased local, regional, and distant recurrence rates.

A similar randomized study conducted in Singapore, which was modeled after the Intergroup treatment regimen, continued to show the benefit of the addition of chemotherapy to radiotherapy. Adjuvant chemotherapy after combined chemotherapy and radiation was also given in this trial.[182] In addition, the administration of the cisplatin dose was spread out over several days, and this regimen seemed to reduce toxicity while still providing a beneficial antitumor effect.

Another phase III randomized trial showed that concurrent chemo/radiotherapy (using weekly cisplatin) increased survival compared with radiotherapy alone.[183] The 5-year overall survival was 70% for the chemo/radiotherapy group versus 59% for the radiotherapy group. A randomized trial compared chemo/radiotherapy using cisplatin versus carboplatin and found that the 3-year overall survival rates were similar (78% vs. 79%).[170] However, these NCCN Guidelines recommend cisplatin for chemo/radiotherapy in patients who do not have a contraindication to the drug, because more randomized data support the use of cisplatin in this setting.

These NCCN Guidelines recommend concurrent chemotherapy (cisplatin) plus radiotherapy (category 1) followed by adjuvant cisplatin/5-FU for T1, N1–3; and for T2–T4, any N lesions (see page 615). Although an unusual occurrence, patients with residual disease in the neck and a complete response at the primary should undergo a neck dissection. Initial therapy for patients who present with metastatic disease should consist of a platinum-based combination chemotherapy regimen (see page 615).

The management of patients with recurrent or persistent nasopharyngeal cancer is described on page 617. When chemotherapy is indicated, commonly used active agents alone or in combination include gemcitabine, paclitaxel, docetaxel, cisplatin, or carboplatin.[184–188] Cetuximab plus carboplatin has been studied for patients with recurrent or metastatic naso-

pharyngeal cancer for whom platinum-based therapy has failed[185]; however, this regimen is not currently recommended in these NCCN Guidelines.

Follow-Up/Surveillance

Recommendations for surveillance are provided in the algorithm.

Very Advanced H&N Cancers

Very advanced H&N cancers include newly diagnosed locally advanced T4b or unresectable nodal disease, metastatic disease, or recurrent disease. The treatment goal for patients with newly diagnosed but unresectable disease is cure (see Head and Neck Surgery, page 630). For the recurrent disease group, the goal is cure (if surgery or radiation remains feasible) or palliation (if the patient has received previous radiotherapy and the disease is unresectable). The goal for patients with metastatic disease is palliation or prolongation of life.

Treatment

Participation in clinical trials is preferred for all patients with very advanced H&N cancers.

Newly Diagnosed Advanced Disease: For patients with a performance status (PS) of 0 or 1, the standard treatment of newly diagnosed, very advanced disease is concurrent cisplatin chemotherapy and radiotherapy (category 1).[150] The panel had a major disagreement regarding whether induction chemotherapy (TPF) followed by radiotherapy or chemoradiation should be used for patients with a PS of 0 or 1, which is reflected in the category 3 recommendation (see The Induction Chemotherapy Controversy, page 637).[141,145] Other options for patients with PS 2 or 3 are described in the algorithm (see page 616).

Many randomized trials[64,88,89,150–156] and meta-analyses of clinical trials[142,157–160] show significantly improved overall survival, disease-free survival, and local control when a concomitant or alternating chemotherapy and radiation regimen is compared with radiotherapy alone for advanced disease. All combined chemoradiotherapy regimens are associated with various degrees of enhanced mucosal toxicities, which require close patient monitoring, ideally provided by a team experienced in treating patients with H&N cancer. Limited data are available comparing the efficacy of different chemoradiotherapy regimens. Single-agent cisplatin plus radiotherapy is effective and easy to administer, and typically uses conventional fractionation at 2.0 Gy/fraction to 70 Gy or more in 7 weeks, with single-agent cisplatin given every 3 weeks at 100 mg/m^2 (see page 618).[150]

Bonner et al.[189] randomly assigned 424 patients with locally advanced and measurable stage III/IV squamous cell carcinomas of the H&N to receive definitive radiotherapy with or without cetuximab. Locoregional control and median overall survival (49 vs. 29.3 months; P = .03) were significantly improved in patients treated with radiotherapy and cetuximab compared with radiotherapy alone. Radiotherapy and cetuximab may provide a therapeutic option for patients not considered medically fit for standard chemoradiotherapy regimens.

Other preferred chemoradiation options were also identified by the panel (see page 626).[190,191] Limited data are available comparing combination chemoradiation with a single-agent used concurrently with radiotherapy.

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

Metastatic Disease: Palliative adjunctive measures include radiotherapy to areas of symptomatic disease, analgesics, and other measures to control other manifestations of disease spread (e.g., hypercalcemia). Single agents and combination systemic chemotherapy regimens are both used (see page 626). Response rates to single agents range from 15% to 35%. The most active single agents include cisplatin, carboplatin, paclitaxel, docetaxel, 5-FU, methotrexate, ifosfamide, bleomycin, gemcitabine (for nasopharyngeal cancer), and cetuximab (for non-nasopharyngeal cancer).[186,192–194] Active combination regimens include 1) cisplatin or carboplatin, plus 5-FU[195,196] with cetuximab (for non-nasopharyngeal cancer)[197]; 2) cisplatin or carboplatin, plus a taxane[195,198]; 3) cisplatin with cetuximab (for non-nasopharyngeal cancer)[199]; or 4) cisplatin

with 5-FU.[195,196] These regimens, on average, result in a doubling of response rates compared with single agents.

Randomized trials assessing a cisplatin-based combination regimen (e.g., cisplatin plus 5-FU) versus single-agent therapy with cisplatin, 5-FU, or methotrexate have shown significantly higher response rates for the combination regimen. No difference in overall survival has been seen.[195,196,200–202] Historically, 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.[196] A randomized phase III trial comparing cisplatin plus 5-FU with cisplatin plus paclitaxel in patients with metastatic or recurrent H&N cancer found no significant differences in survival.[195]

The epidermal growth factor receptor (EGFR) is a trans-membrane glycoprotein; activation of EGFR triggers a cascade of downstream intracellular signaling events important for regulation of epithelial cell growth. Overexpression of EGFR and/or common ligands has been observed in greater than 90% of H&N squamous cell carcinomas. This finding has led to the development of EGFR inhibitors, such as the monoclonal antibody cetuximab and small molecule tyrosine kinase inhibitors (i.e., erlotinib and gefitinib).

Data from phase II studies indicate that in the cisplatin-refractory setting, the single-agent response rate of cetuximab is 12% to 14%. Burtness et al.[199] compared cisplatin plus cetuximab versus cisplatin plus placebo as first-line treatment of recurrent disease and reported a significant improvement in response rate with cetuximab (26% vs. 10%, respectively). Notably, a phase III randomized trial (EXTREME) of 442 patients with recurrent or metastatic squamous cell carcinoma found that cetuximab plus cisplatin/5-FU or carboplatin/5-FU improved median survival compared with the standard chemotherapy doublet (10.1 vs. 7.4 months; $P = .04$).[197] The response rate was also improved with cetuximab (20%–36%; $P < .001$). Available data for tyrosine kinase inhibitors (such as erlotinib and gefitinib) have not established them as treatment options for recurrent or metastatic H&N cancer outside of a clinical trial. In one randomized trial, treatment with 2 different dosing schedules of gefitinib offered no survival advantage over treatment with methotrexate.[203]

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

Recommended Reading List

Adelstein DJ, Li Y, Adams GL, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. J Clin Oncol 2003;21:92–98.

Adelstein DJ, Ridge JA, Gillison ML, et al. Head and neck squamous cell cancer and the human papillomavirus: summary of a National Cancer Institute State of the Science Meeting, November 9–10, 2008, Washington, D.C. Head Neck 2009;31:1393–1422.

Al-Sarraf M, LeBlanc M, Giri PG, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. J Clin Oncol 1998;16:1310–1317.

Bernier J, Cooper JS, Pajak TF, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). Head Neck 2005;27:843–850.

Bernier J, Domenge C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med 2004;350:1945–1952.

Bourhis J, Overgaard J, Audry H, et al. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. Lancet 2006;368:843–854.

Brizel DM, Albers ME, Fisher SR, et al. Hyperfractionated irradiation with or without concurrent chemotherapy for locally advanced head and neck cancer. N Engl J Med 1998;338:1798–1804.

Colevas AD. Chemotherapy options for patients with metastatic or recurrent squamous cell carcinoma of the head and neck. J Clin Oncol 2006;24:2644–2652.

Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med 2004;350:1937–1944.

DeVita VT Jr, Lawrence TS, Rosenberg SA, eds. Cancer: Principles & Practice of Oncology, 8th edition. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.

Fu KK, Pajak TF, Trotti A, et al. A Radiation Therapy Oncology Group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: first report of RTOG 9003. Int J Radiat Oncol Biol Phys 2000;48:7–16.

Furniss CS, McClean MD, Smith JF, et al. Human papillomavirus 16 and head and neck squamous cell carcinoma. Int J Cancer 2007;120:2386–2392.

Gillison ML, Koch WM, Capone RB, et al. Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. J Natl Cancer Inst 2000;92:709–720.

Kutler DI, Patel SG, Shah JP. The role of neck dissection following definitive chemoradiation. Oncology (Williston Park) 2004;18:993–998; discussion 999, 1003–1004, 1007.

Laurie SA, Licitra L. Systemic therapy in the palliative management of advanced salivary gland cancers. J Clin Oncol 2006;24:2673–2678.

Lefebvre JL, Chevalier D, Luboinski B, et al. Larynx preservation in pyriform sinus cancer: preliminary results of a European Organization for Research and Treatment of Cancer phase III trial. EORTC Head and Neck Cancer Cooperative Group. J Natl Cancer Inst 1996;88:890–899.

Piccirillo JF. Importance of comorbidity in head and neck cancer. Laryngoscope 2000;110:593–602.

Pignon JP, Bourhis J, Domenge C, et al. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. Lancet 2000;355:949–955.

Rosenthal DI, Trotti A. Strategies for managing radiation-induced mucositis in head and neck cancer. Semin Radiat Oncol 2009;19:29–34.

Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 2008;359:1116–1127.

References

1. DeVita V Jr, Lawrence T, Rosenberg S, eds. Cancer: Principles & Practice of Oncology, 8th edition. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.
2. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin 2010;60:277–300.
3. American Cancer Society. Cancer Facts & Figures 2010. Atlanta: American Cancer Society; 2010. Available at: http://www.cancer.org/downloads/STT/Cancer_Facts_and_Figures_2010.pdf. Accessed April 12, 2011.
4. Gillison ML, Koch WM, Capone RB, et al. Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. J Natl Cancer Inst 2000;92:709–720.
5. Kreimer AR, Clifford GM, Boyle P, Franceschi S. Human papillomavirus types in head and neck squamous cell carcinomas worldwide: a systematic review. Cancer Epidemiol Biomarkers Prev 2005;14:467–475.
6. Applebaum KM, Furniss CS, Zeka A, et al. Lack of association of alcohol and tobacco with HPV16-associated head and neck cancer. J Natl Cancer Inst 2007;99:1801–1810.
7. D'Souza G, Kreimer AR, Viscidi R, et al. Case-control study of human papillomavirus and oropharyngeal cancer. N Engl J Med 2007;356:1944–1956.
8. Schlecht NF, Burk RD, Adrien L, et al. Gene expression profiles in HPV-infected head and neck cancer. J Pathol 2007;213:283–293.
9. Sturgis EM, Cinciripini PM. Trends in head and neck cancer incidence in relation to smoking prevalence: an emerging epidemic of human papillomavirus-associated cancers? Cancer 2007;110:1429–1435.
10. Adelstein DJ, Ridge JA, Gillison ML, et al. Head and neck squamous cell cancer and the human papillomavirus: summary of a National Cancer Institute State of the Science Meeting, November 9–10, 2008, Washington, D.C. Head Neck 2009;31:1393–1422.
11. Chaturvedi AK, Engels EA, Anderson WF, Gillison ML. Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States. J Clin Oncol 2008;26:612–619.
12. Edge S, Byrd D, Compton C, et al. AJCC Cancer Staging Manual, 7th ed. New York, NY: Springer; 2010.
13. Greene F, Page D, Fleming I, et al. AJCC Cancer Staging Manual, 6th ed. New York, NY: Springer-Verlag; 2002.
14. Colasanto JM, Prasad P, Nash MA, et al. Nutritional support of patients undergoing radiation therapy for head and neck cancer. Oncology (Williston Park) 2005;19:371–379.
15. Schnoll RA, Zhang B, Rue M, et al. Brief physician-initiated quit-smoking strategies for clinical oncology settings: a trial coordinated by the Eastern Cooperative Oncology Group. J Clin Oncol 2003;21:355–365.
16. Gritz ER, Carr CR, Rapkin D, et al. Predictors of long-term smoking cessation in head and neck cancer patients. Cancer Epidemiol Biomarkers Prev 1993;2:261–270.
17. Feinstein AR. The pre-therapeutic classification of co-morbidity in chronic disease. J Chronic Dis 1970;23:455–468.
18. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–383.
19. Piccirillo JF. Importance of comorbidity in head and neck cancer. Laryngoscope 2000;110:593–602.
20. Piccirillo JF, Lacy PD, Basu A, Spitznagel EL. Development of a new head and neck cancer-specific comorbidity index. Arch Otolaryngol Head Neck Surg 2002;128:1172–1179.
21. Piccirillo JF. Impact of comorbidity and symptoms on the prognosis of patients with oral carcinoma. Arch Otolaryngol Head Neck Surg 2000;126:1086–1088.
22. Chen AY, Matson LK, Roberts D, Goepfert H. The significance of comorbidity in advanced laryngeal cancer. Head Neck 2001;23:566–572.
23. Singh B, Bhaya M, Stern J, et al. Validation of the Charlson comorbidity index in patients with head and neck cancer: a multi-institutional study. Laryngoscope 1997;107:1469–1475.
24. Hall SF, Rochon PA, Streiner DL, et al. Measuring comorbidity in patients with head and neck cancer. Laryngoscope 2002;112:1988–1996.
25. Hall SF, Groome PA, Rothwell D. The impact of comorbidity on the survival of patients with squamous cell carcinoma of the head and neck. Head Neck 2000;22:317–322.
26. Ribeiro KC, Kowalski LP, Latorre MR. Impact of comorbidity, symptoms, and patients' characteristics on the prognosis of oral carcinomas. Arch Otolaryngol Head Neck Surg 2000;126:1079–1085.
27. de Graeff A, de Leeuw JR, Ros WJ, et al. Pretreatment factors predicting quality of life after treatment for head and neck cancer. Head Neck 2000;22:398–407.
28. Funk GF, Karnell LH, Whitehead S, et al. Free tissue transfer versus pedicled flap cost in head and neck cancer. Otolaryngol Head Neck Surg 2002;127:205–212.
29. Farwell DG, Reilly DF, Weymuller EA, et al. Predictors of perioperative complications in head and neck patients. Arch Otolaryngol Head Neck Surg 2002;128:505–511.

30. Kaplan MH, Feinstein AR. The importance of classifying initial co-morbidity in evaluatin the outcome of diabetes mellitus. J Chronic Dis 1974;27:387–404.
31. Bang D, Piccirillo J, Littenberg B, et al. The Adult Comorbidity Evaluation-27 (ACE-27) test: a new comorbidity index for patients with cancer [abstract]. J Clin Oncol 2000;(Suppl 1):Abstract 1701.
32. Piccirillo J, Costas I, Claybour P, et al. The measurement of comorbidity by cancer registries. J Registry Manag 2003;30:8–14.
33. Patrick D, Erickson P. Health Status and Health Policy: Quality of Life in Health Care Evaluation and Resource Allocation. New York, NY: Oxford University Press; 1993.
34. Yueh B. Measuring and Reporting Quality of Life in Head and Neck Cancer. McLean, Virginia; 2002.
35. Rogers SN, Gwanne S, Lowe D, et al. The addition of mood and anxiety domains to the University of Washington quality of life scale. Head Neck 2002;24:521–529.
36. Bjordal K, Hammerlid E, Ahlner-Elmqvist M, et al. Quality of life in head and neck cancer patients: validation of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-H&N35. J Clin Oncol 1999;17:1008–1019.
37. Cella D. Manual for the Functional Assessment of Cancer Therapy (FACT) Measurement System (version 4). Chicago: Rush Medical Center; 1997.
38. List MA, D'Antonio LL, Cella DF, et al. The Performance Status Scale for head and neck cancer patients and the Functional Assessment of Cancer Therapy-Head and Neck Scale. A study of utility and validity. Cancer 1996;77:2294–2301.
39. Harrison L, Sessions R, Hong W. Head and Neck Cancer: A Multidisciplinary Approach, 3rd edition. Philadelphia, PA: Lippincott Williams & Wilkins; 2009.
40. Robbins KT, Shaha AR, Medina JE, et al. Consensus statement on the classification and terminology of neck dissection. Arch Otolaryngol Head Neck Surg 2008;134:536–538.
41. Byers RM. Neck dissection: concepts, controversies, and technique. Semin Surg Oncol 1991;7:9–13.
42. Stringer SP. Current concepts in surgical management of neck metastases from head and neck cancer. Oncology (Williston Park) 1995;9:547–554.
43. Robbins KT, Clayman G, Levine PA, et al. Neck dissection classification update: revisions proposed by the American Head and Neck Society and the American Academy of Otolaryngology-Head and Neck Surgery. Arch Otolaryngol Head Neck Surg 2002;128:751–758.
44. Candela FC, Kothari K, Shah JP. Patterns of cervical node metastases from squamous carcinoma of the oropharynx and hypopharynx. Head Neck 1990;12:197–203.
45. Candela FC, Shah J, Jaques DP, Shah JP. Patterns of cervical node metastases from squamous carcinoma of the larynx. Arch Otolaryngol Head Neck Surg 1990;116:432–435.
46. Shah JP, Candela FC, Poddar AK. The patterns of cervical lymph node metastases from squamous carcinoma of the oral cavity. Cancer 1990;66:109–113.
47. Ferlito A, Rinaldo A, Silver CE, et al. Elective and therapeutic selective neck dissection. Oral Oncol 2006;42:14–25.
48. Schmitz S, Machiels JP, Weynand B, et al. Results of selective neck dissection in the primary management of head and neck squamous cell carcinoma. Eur Arch Otorhinolaryngol 2009;266:437–443.
49. Patel RS, Clark J, Wyten R, et al. Squamous cell carcinoma from an unknown head and neck primary site: a "selective treatment" approach. Arch Otolaryngol Head Neck Surg 2007;133:1282–1287.
50. Sivanandan R, Kaplan MJ, Lee KJ, et al. Long-term results of 100 consecutive comprehensive neck dissections: implications for selective neck dissections. Arch Otolaryngol Head Neck Surg 2004;130:1369–1373.
51. Liauw SL, Mancuso AA, Amdur RJ, et al. Postradiotherapy neck dissection for lymph node-positive head and neck cancer: the use of computed tomography to manage the neck. J Clin Oncol 2006;24:1421–1427.
52. Porceddu SV, Jarmolowski E, Hicks RJ, et al. Utility of positron emission tomography for the detection of disease in residual neck nodes after (chemo)radiotherapy in head and neck cancer. Head Neck 2005;27:175–181.
53. Yao M, Smith RB, Hoffman HT, et al. Clinical significance of postradiotherapy [18F]-fluorodeoxyglucose positron emission tomography imaging in management of head-and-neck cancer-a long-term outcome report. Int J Radiat Oncol Biol Phys 2009;74:9–14.
54. Lango MN, Myers JN, Garden AS. Controversies in surgical management of the node-positive neck after chemoradiation. Semin Radiat Oncol 2009;19:24–28.
55. Isles MG, McConkey C, Mehanna HM. A systematic review and meta-analysis of the role of positron emission tomography in the follow up of head and neck squamous cell carcinoma following radiotherapy or chemoradiotherapy. Clin Otolaryngol 2008;33:210–222.
56. Corry J, Peters L, Fisher R, et al. N2-N3 neck nodal control without planned neck dissection for clinical/radiologic complete responders-results of Trans Tasman Radiation Oncology Group Study 98.02. Head Neck 2008;30:737–742.
57. Lau H, Phan T, Mackinnon J, Matthews TW. Absence of planned neck dissection for the N2-N3 neck after chemoradiation for locally advanced squamous cell carcinoma of the head and neck. Arch Otolaryngol Head Neck Surg 2008;134:257–261.
58. Ong SC, Schoder H, Lee NY, et al. Clinical utility of 18F-FDG PET/CT in assessing the neck after concurrent chemoradiotherapy for locoregional advanced head and neck cancer. J Nucl Med 2008;49:532–540.
59. Nayak JV, Walvekar RR, Andrade RS, et al. Deferring planned neck dissection following chemoradiation for stage IV head and neck cancer: the utility of PET-CT. Laryngoscope 2007;117:2129–2134.
60. Abgral R, Querellou S, Potard G, et al. Does 18F-FDG PET/CT improve the detection of posttreatment recurrence of head and neck squamous cell carcinoma in patients negative for disease on clinical follow-up? J Nucl Med 2009;50:24–29.
61. Bernier J, Domenge C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med 2004;350:1945–1952.
62. Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med 2004;350:1937–1944.
63. Bernier J, Cooper JS, Pajak TF, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). Head Neck 2005;27:843–850.
64. Bachaud JM, Cohen-Jonathan E, Alzieu C, et al. Combined postoperative radiotherapy and weekly cisplatin infusion for

locally advanced head and neck carcinoma: final report of a randomized trial. Int J Radiat Oncol Biol Phys 1996;36:999–104.

65. Shah JP, Cendon RA, Farr HW, Strong EW. Carcinoma of the oral cavity. factors affecting treatment failure at the primary site and neck. Am J Surg 1976;132:504–507.
66. Looser KG, Shah JP, Strong EW. The significance of "positive" margins in surgically resected epidermoid carcinomas. Head Neck Surg 1978;1:107–111.
67. Johnson JT, Barnes EL, Myers EN, et al. The extracapsular spread of tumors in cervical node metastasis. Arch Otolaryngol 1981;107:725–729.
68. Feldman M, Fletcher GH. Analysis of the parameters relating to failures above the clavicles in patients treated by postoperative irradiation for squamous cell carcinomas of the oral cavity or oropharynx. Int J Radiat Oncol Biol Phys 1982;8:27–30.
69. Mirimanoff RO, Wang CC, Doppke KP. Combined surgery and postoperative radiation therapy for advanced laryngeal and hypopharyngeal carcinomas. Int J Radiat Oncol Biol Phys 1985;11:499–504.
70. Peters LJ, Goepfert H, Ang KK, et al. Evaluation of the dose for postoperative radiation therapy of head and neck cancer: first report of a prospective randomized trial. Int J Radiat Oncol Biol Phys 1993;26:3–11.
71. Thames HD Jr, Withers HR, Peters LJ, Fletcher GH. Changes in early and late radiation responses with altered dose fractionation: implications for dose-survival relationships. Int J Radiat Oncol Biol Phys 1982;8:219–226.
72. Withers H, Thames H, Peters L. Differences in the fractionation response of acutely and late-responding tissues. In: Kaercher K, Kogelnik H, Reinartz G, eds. Progress in Radio-Oncology II. Vol. 11. New York, NY: Raven Press; 1982:287–296.
73. Withers HR, Taylor JM, Maciejewski B. The hazard of accelerated tumor clonogen repopulation during radiotherapy. Acta Oncol 1988;27:131–146.
74. Harwood AR, Beale FA, Cummings BJ, et al. T4NOMO glottic cancer: an analysis of dose-time volume factors. Int J Radiat Oncol Biol Phys 1981;7:1507–1512.
75. Amornmarn R, Prempree T, Viravathana T, et al. A therapeutic approach to early vocal cord carcinoma. Acta Radiol Oncol 1985;24:321–325.
76. Schwaibold F, Scariato A, Nunno M, et al. The effect of fraction size on control of early glottic cancer. Int J Radiat Oncol Biol Phys 1988;14:451–454.
77. Kim RY, Marks ME, Salter MM. Early-stage glottic cancer: importance of dose fractionation in radiation therapy. Radiology 1992;182:273–275.
78. Parson J. Time-dose-volume relationships in radiation therapy. In: Million R, Cassisi N, eds. Management of Head and Neck Cancer: A Multidisciplinary Approach, 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1994:203–243.
79. Horiot JC, Le Fur R, N'Guyen T, et al. Hyperfractionation versus conventional fractionation in oropharyngeal carcinoma: final analysis of a randomized trial of the EORTC cooperative group of radiotherapy. Radiother Oncol 1992;25:231–241.
80. Horiot JC. [Controlled clinical trials of hyperfractionated and accelerated radiotherapy in otorhinolaryngologic cancers]. Bull Acad Natl Med 1998;182:1247–1260; discussion 1261 [in French].
81. Horiot JC, Bontemps P, van den Bogaert W, et al. Accelerated fractionation (AF) compared to conventional fractionation (CF) improves loco-regional control in the radiotherapy of advanced head and neck cancers: results of the EORTC 22851 randomized trial. Radiother Oncol 1997;44:111–121.
82. Fu KK, Pajak TF, Trotti A, et al. A Radiation Therapy Oncology Group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: first report of RTOG 9003. Int J Radiat Oncol Biol Phys 2000;48:7–16.
83. Trotti A, Fu K, Pajak T, et al. Long term outcomes of RTOG 90-03: a comparison of hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinoma [abstract]. Int J Radiat Oncol Biol Phys 2005;63:S70–71.
84. Bourhis J, Overgaard J, Audry H, et al. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. Lancet 2006;368:843–854.
85. Budach V, Stuschke M, Budach W, et al. Hyperfractionated accelerated chemoradiation with concurrent fluorouracil-mitomycin is more effective than dose-escalated hyperfractionated accelerated radiation therapy alone in locally advanced head and neck cancer: final results of the radiotherapy cooperative clinical trials group of the German Cancer Society 95-06 Prospective Randomized Trial. J Clin Oncol 2005;23:1125–1135.
86. Budach W, Hehr T, Budach V, et al. A meta-analysis of hyperfractionated and accelerated radiotherapy and combined chemotherapy and radiotherapy regimens in unresected locally advanced squamous cell carcinoma of the head and neck. BMC Cancer 2006;6:28.
87. Bensadoun RJ, Benezery K, Dassonville O, et al. French multicenter phase III randomized study testing concurrent twice-a-day radiotherapy and cisplatin/5-fluorouracil chemotherapy (BiRCF) in unresectable pharyngeal carcinoma: results at 2 years (FNCLCC-GORTEC). Int J Radiat Oncol Biol Phys 2006;64:983–994.
88. Brizel DM, Albers ME, Fisher SR, et al. Hyperfractionated irradiation with or without concurrent chemotherapy for locally advanced head and neck cancer. N Engl J Med 1998;338:1798–1804.
89. Jeremic B, Shibamoto Y, Milicic B, et al. Hyperfractionated radiation therapy with or without concurrent low-dose daily cisplatin in locally advanced squamous cell carcinoma of the head and neck: a prospective randomized trial. J Clin Oncol 2000;18:1458–1464.
90. Ang K, Zhang Q, Wheeler RH, et al. A phase III trial (RTOG 0129) of two radiation-cisplatin regimens for head and neck carcinomas (HNC): impact of radiation and cisplatin intensity on outcome [abstract]. J Clin Oncol 2010;28(Suppl 15):Abstract 5507.
91. Denis F, Garaud P, Bardet E, et al. Final results of the 94-01 French Head and Neck Oncology and Radiotherapy Group randomized trial comparing radiotherapy alone with concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. J Clin Oncol 2004;22:69–76.
92. Denis F, Garaud P, Bardet E, et al. Late toxicity results of the GORTEC 94-01 randomized trial comparing radiotherapy with concomitant radiochemotherapy for advanced-stage oropharynx carcinoma: comparison of LENT/SOMA, RTOG/EORTC, and NCI-CTC scoring systems. Int J Radiat Oncol Biol Phys 2003;55:93–98.

93. Bourhis J, Calais G, Lapeyre M, et al. Concomitant radiochemotherapy or accelerated radiotherapy: analysis of two randomized trials of the French Head and Neck Cancer Group (GORTEC). Semin Oncol 2004;31:822–826.

94. Machtay M, Moughan J, Trotti A, et al. Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: an RTOG analysis. J Clin Oncol 2008;26:3582–3589.

95. Hartford AC, Palisca MG, Eichler TJ, et al. American Society for Therapeutic Radiology and Oncology (ASTRO) and American College of Radiology (ACR) practice guidelines for intensity-modulated radiation therapy (IMRT). Int J Radiat Oncol Biol Phys 2009;73:9–14.

96. Holmes T, Das R, Low D, et al. American Society of Radiation Oncology recommendations for documenting intensity-modulated radiation therapy treatments. Int J Radiat Oncol Biol Phys 2009;74:1311–1318.

97. Wu Q, Manning M, Schmidt-Ullrich R, Mohan R. The potential for sparing of parotids and escalation of biologically effective dose with intensity-modulated radiation treatments of head and neck cancers: a treatment design study. Int J Radiat Oncol Biol Phys 2000;46:195–205.

98. Chao KS, Majhail N, Huang CJ, et al. Intensity-modulated radiation therapy reduces late salivary toxicity without compromising tumor control in patients with oropharyngeal carcinoma: a comparison with conventional techniques. Radiother Oncol 2001;61:275–280.

99. Dogan N, King S, Emami B, et al. Assessment of different IMRT boost delivery methods on target coverage and normal-tissue sparing. Int J Radiat Oncol Biol Phys 2003;57:1480–1491.

100. Li Y, Taylor JM, Ten Haken RK, Eisbruch A. The impact of dose on parotid salivary recovery in head and neck cancer patients treated with radiation therapy. Int J Radiat Oncol Biol Phys 2007;67:660–669.

101. Pow EH, Kwong DL, McMillan AS, et al. Xerostomia and quality of life after intensity-modulated radiotherapy vs. conventional radiotherapy for early-stage nasopharyngeal carcinoma: initial report on a randomized controlled clinical trial. Int J Radiat Oncol Biol Phys 2006;66:981–991.

102. Kam MK, Leung SF, Zee B, et al. Prospective randomized study of intensity-modulated radiotherapy on salivary gland function in early-stage nasopharyngeal carcinoma patients. J Clin Oncol 2007;25:4873–4879.

103. Pfister D, Cassileth B, Deng G, et al. Acupuncture for pain and dysfunction after neck dissection: results of a randomized controlled trial. J Clin Oncol 2010;28:2565–2570.

104. Scarantino C, LeVeque F, Swann RS, et al. Effect of pilocarpine during radiation therapy: results of RTOG 97-09, a phase III randomized study in head and neck cancer patients. J Support Oncol 2006;4:252–258.

105. Petrone D, Condemi JJ, Fife R, et al. A double-blind, randomized, placebo-controlled study of cevimeline in Sjogren's syndrome patients with xerostomia and keratoconjunctivitis sicca. Arthritis Rheum 2002;46:748–754.

106. Galvin JM, De Neve W. Intensity modulating and other radiation therapy devices for dose painting. J Clin Oncol 2007;25:924–930.

107. Lauve A, Morris M, Schmidt-Ullrich R, et al. Simultaneous integrated boost intensity-modulated radiotherapy for locally advanced head-and-neck squamous cell carcinomas: II—clinical results. Int J Radiat Oncol Biol Phys 2004;60:374–387.

108. Schoenfeld GO, Amdur RJ, Morris CG, et al. Patterns of failure and toxicity after intensity-modulated radiotherapy for head and neck cancer. Int J Radiat Oncol Biol Phys 2008;71:377–385.

109. Lee NY, de Arruda FF, Puri DR, et al. A comparison of intensity-modulated radiation therapy and concomitant boost radiotherapy in the setting of concurrent chemotherapy for locally advanced oropharyngeal carcinoma. Int J Radiat Oncol Biol Phys 2006;66:966–974.

110. de Arruda FF, Puri DR, Zhung J, et al. Intensity-modulated radiation therapy for the treatment of oropharyngeal carcinoma: the Memorial Sloan-Kettering Cancer Center experience. Int J Radiat Oncol Biol Phys 2006;64:363–373.

111. Garden AS, Morrison WH, Wong PF, et al. Disease-control rates following intensity-modulated radiation therapy for small primary oropharyngeal carcinoma. Int J Radiat Oncol Biol Phys 2007;67:438–444.

112. Eisbruch A, Levendag PC, Feng FY, et al. Can IMRT or brachytherapy reduce dysphagia associated with chemoradiotherapy of head and neck cancer? The Michigan and Rotterdam experiences. Int J Radiat Oncol Biol Phys 2007;69:S40–42.

113. Wolden SL, Chen WC, Pfister DG, et al. Intensity-modulated radiation therapy (IMRT) for nasopharynx cancer: update of the Memorial Sloan-Kettering experience. Int J Radiat Oncol Biol Phys 2006;64:57–62.

114. Madani I, Bonte K, Vakaet L, et al. Intensity-modulated radiotherapy for sinonasal tumors: Ghent University Hospital update. Int J Radiat Oncol Biol Phys 2009;73:424–432.

115. Eisbruch A. Reducing xerostomia by IMRT: what may, and may not, be achieved. J Clin Oncol 2007;25:4863–4864.

116. Hodge CW, Bentzen SM, Wong G, et al. Are we influencing outcome in oropharynx cancer with intensity-modulated radiotherapy? An inter-era comparison. Int J Radiat Oncol Biol Phys 2007;69:1032–1041.

117. Veldeman L, Madani I, Hulstaert F, et al. Evidence behind use of intensity-modulated radiotherapy: a systematic review of comparative clinical studies. Lancet Oncol 2008;9:367–375.

118. Eisbruch A, Marsh LH, Dawson LA, et al. Recurrences near base of skull after IMRT for head-and-neck cancer: implications for target delineation in high neck and for parotid gland sparing. Int J Radiat Oncol Biol Phys 2004;59:28–42.

119. Rosenthal DI, Trotti A. Strategies for managing radiation-induced mucositis in head and neck cancer. Semin Radiat Oncol 2009;19:29–34.

120. Gomez DR, Zhung JE, Gomez J, et al. Intensity-modulated radiotherapy in postoperative treatment of oral cavity cancers. Int J Radiat Oncol Biol Phys 2009;73:1096–1103.

121. Lee NY, O'Meara W, Chan K, et al. Concurrent chemotherapy and intensity-modulated radiotherapy for locoregionally advanced laryngeal and hypopharyngeal cancers. Int J Radiat Oncol Biol Phys 2007;69:459–468.

122. Nutting CM, Morden JP, Harrington KJ, et al. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. Lancet Oncol 201112:127–136.

123. Nutting C, A'Hern R, Rogers MS, et al. First results of a phase III multicenter randomized controlled trial of intensity modulated (IMRT) versus conventional radiotherapy (RT) in head and neck cancer (PARSPORT: ISRCTN48243537; CRUK/03/005) [abstract]. J Clin Oncol 2009;27(Suppl 18):Abstract LBA6006.

124. Posner MR, Ervin TJ, Miller D, et al. Incidence of hypothyroidism following multimodality treatment for advanced squamous cell cancer of the head and neck. Laryngoscope 1984;94:451–454.

125. Fleming AJ Jr, Smith SP Jr, Paul CM, et al. Impact of [18F]-2-fluorodeoxyglucose-positron emission tomography/computed tomography on previously untreated head and neck cancer patients. Laryngoscope 2007;117:1173–1179.

126. Branstetter BF, Blodgett TM, Zimmer LA, et al. Head and neck malignancy: is PET/CT more accurate than PET or CT alone? Radiology 2005;235:580–586.

127. Nasman A, Attner P, Hammarstedt L, et al. Incidence of human papillomavirus (HPV) positive tonsillar carcinoma in Stockholm, Sweden: an epidemic of viral-induced carcinoma? Int J Cancer 2009;125:362–366.

128. Hammarstedt L, Lindquist D, Dahlstrand H, et al. Human papillomavirus as a risk factor for the increase in incidence of tonsillar cancer. Int J Cancer 2006;119:2620–2623.

129. Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 2010;363:24–35.

130. Fakhry C, Westra WH, Li S, et al. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. J Natl Cancer Inst 2008;100:261–269.

131. Gillison ML, Harris J, Westra W, et al. Survival outcomes by tumor human papillomavirus (HPV) status in stage III-IV oropharyngeal cancer (OPC) in RTOG 0129 [abstract]. J Clin Oncol 2009;27(Suppl 15):Abstract 6003.

132. Rischin D, Young R, Fisher R, et al. Prognostic significance of HPV and p16 status in patients with oropharyngeal cancer treated on a large international phase III trial [abstract]. J Clin Oncol 2009;27(Suppl 15):Abstract 6004.

133. Lassen P, Eriksen JG, Hamilton-Dutoit S, et al. Effect of HPV-associated p16INK4A expression on response to radiotherapy and survival in squamous cell carcinoma of the head and neck. J Clin Oncol 2009;27:1992–1998.

134. Ragin CC, Taioli E. Survival of squamous cell carcinoma of the head and neck in relation to human papillomavirus infection: review and meta-analysis. Int J Cancer 2007;121:1813–1820.

135. Rischin D, Young RJ, Fisher R, et al. Prognostic significance of p16INK4A and human papillomavirus in patients with oropharyngeal cancer treated on TROG 02.02 phase III trial. J Clin Oncol 2010;28:4142–4148.

136. Begum S, Gillison ML, Nicol TL, Westra WH. Detection of human papillomavirus-16 in fine-needle aspirates to determine tumor origin in patients with metastatic squamous cell carcinoma of the head and neck. Clin Cancer Res 2007;13:1186–1191.

137. Vokes EE, Stenson K, Rosen FR, et al. Weekly carboplatin and paclitaxel followed by concomitant paclitaxel, fluorouracil, and hydroxyurea chemoradiotherapy: curative and organ-preserving therapy for advanced head and neck cancer. J Clin Oncol 2003;21:320–326.

138. Hitt R, Grau J, Lopez-Pousa A, et al. Phase II/III trial of induction chemotherapy (ICT) with cisplatin/5-fluorouracil (PF) vs. docetaxel (T) plus PF (TPF) followed by chemoradiotherapy (CRT) vs. CRT for unresectable locally advanced head and neck cancer (LAHNC) [abstract]. J Clin Oncol 2005;23(Suppl 16):Abstract 5578.

139. Hitt R, Lopez-Pousa A, Martinez-Trufero J, et al. Phase III study comparing cisplatin plus fluorouracil to paclitaxel, cisplatin, and fluorouracil induction chemotherapy followed by chemoradiotherapy in locally advanced head and neck cancer. J Clin Oncol 2005;23:8636–8645.

140. Hitt R, Grau J, Lopez-Pousa A, et al. Randomized phase II/III clinical trial of induction chemotherapy (ICT) with either cisplatin/5-fluorouracil (PF) or docetaxel/cisplatin/5-fluorouracil (TPF) followed by chemoradiotherapy (CRT) vs. crt alone for patients (pts) with unresectable locally advanced head and neck cancer (LAHNC) [abstract]. J Clin Oncol 2006;24(Suppl 18):Abstract 5515.

141. Posner MR, Hershock DM, Blajman CR, et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. N Engl J Med 2007;357:1705–1715.

142. Pignon JP, Bourhis J, Domenge C, Designe L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. Lancet 2000;355:949–955.

143. Paccagnella A, Orlando A, Marchiori C, et al. Phase III trial of initial chemotherapy in stage III or IV head and neck cancers: a study by the Gruppo di Studio sui Tumori della Testa e del Collo. J Natl Cancer Inst 1994;86:265–272.

144. Lorch JH, Goloubeva O, Haddad RI, et al. Induction chemotherapy with cisplatin and fluorouracil alone or in combination with docetaxel in locally advanced squamous-cell cancer of the head and neck: long-term results of the TAX 324 randomised phase 3 trial. Lancet Oncol 2011;12:152–159.

145. Vermorken JB, Remenar E, van Herpen C, et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. N Engl J Med 2007;357:1695–1704.

146. Pignon JP, le Maitre A, Maillard E, Bourhis J. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol 2009;92:4–14.

147. Lefebvre JL, Chevalier D, Luboinski B, et al. Larynx preservation in pyriform sinus cancer: preliminary results of a European Organization for Research and Treatment of Cancer phase III trial. EORTC Head and Neck Cancer Cooperative Group. J Natl Cancer Inst 1996;88:890–899.

148. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. The Department of Veterans Affairs Laryngeal Cancer Study Group. N Engl J Med 1991;324:1685–1690.

149. McNeil BJ, Weichselbaum R, Pauker SG. Speech and survival: tradeoffs between quality and quantity of life in laryngeal cancer. N Engl J Med 1981;305:982–987.

150. Adelstein DJ, Li Y, Adams GL, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. J Clin Oncol 2003;21:92–98.

151. Lo TC, Wiley AL Jr, Ansfield FJ, et al. Combined radiation therapy and 5-fluorouracil for advanced squamous cell carcinoma of the oral cavity and oropharynx: a randomized study. AJR Am J Roentgenol 1976;126:229–235.

152. Sanchiz F, Milla A, Torner J, et al. Single fraction per day versus two fractions per day versus radiochemotherapy in the treatment of head and neck cancer. Int J Radiat Oncol Biol Phys 1990;19:1347–1350.

153. Browman GP, Cripps C, Hodson DI, et al. Placebo-controlled randomized trial of infusional fluorouracil during standard

radiotherapy in locally advanced head and neck cancer. J Clin Oncol 1994;12:2648–2653.

154. Smid L, Lesnicar H, Zakotnik B, et al. Radiotherapy, combined with simultaneous chemotherapy with mitomycin C and bleomycin for inoperable head and neck cancer—preliminary report. Int J Radiat Oncol Biol Phys 1995;32:769–775.
155. Merlano M, Benasso M, Corvo R, et al. Five-year update of a randomized trial of alternating radiotherapy and chemotherapy compared with radiotherapy alone in treatment of unresectable squamous cell carcinoma of the head and neck. J Natl Cancer Inst 1996;88:583–589.
156. Wendt TG, Grabenbauer GG, Rodel CM, et al. Simultaneous radiochemotherapy versus radiotherapy alone in advanced head and neck cancer: a randomized multicenter study. J Clin Oncol 1998;16:1318–1324.
157. Munro AJ. An overview of randomised controlled trials of adjuvant chemotherapy in head and neck cancer. Br J Cancer 1995;71:83–91.
158. El-Sayed S, Nelson N. Adjuvant and adjunctive chemotherapy in the management of squamous cell carcinoma of the head and neck region. A meta-analysis of prospective and randomized trials. J Clin Oncol 1996;14:838–847.
159. Bourhis J, Amand C, Pignon JP. Update of MACH-NC (Meta-Analysis of Chemotherapy in Head & Neck Cancer) database focused on concomitant chemoradiotherapy [abstract]. J Clin Oncol 2004;22(Suppl 14):Abstract 5505.
160. Pignon JP, le Maitre A, Bourhis J. Meta-Analyses of Chemotherapy in Head and Neck Cancer (MACH-NC): an update. Int J Radiat Oncol Biol Phys 2007;69:S112–114.
161. Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Engl J Med 2003;349:2091–2098.
162. Argiris A, Haraf DJ, Kies MS, Vokes EE. Intensive concurrent chemoradiotherapy for head and neck cancer with 5-Fluorouracil- and hydroxyurea-based regimens: reversing a pattern of failure. Oncologist 2003;8:350–360.
163. Pointreau Y, Garaud P, Chapet S, et al. Randomized trial of induction chemotherapy with cisplatin and 5-fluorouracil with or without docetaxel for larynx preservation. J Natl Cancer Inst 2009;101:498–506.
164. Paccagnella A, Ghi MG, Loreggian L, et al. Concomitant chemoradiotherapy versus induction docetaxel, cisplatin and 5 fluorouracil (TPF) followed by concomitant chemoradiotherapy in locally advanced head and neck cancer: a phase II randomized study. Ann Oncol 2010;21:1515–1522.
165. Hitt R, Grau JJ, Lopez-Pousa A, et al. Final results of a randomized phase III trial comparing induction chemotherapy with cisplatin/5-FU or docetaxel/cisplatin/5-FU follow by chemoradiotherapy (CRT) versus CRT alone as first-line treatment of unresectable locally advanced head and neck cancer (LAHNC) [abstract]. J Clin Oncol 2009;27(Suppl 15):Abstract 6009.
166. Salama JK, Haddad RI, Kies MS, et al. Clinical practice guidance for radiotherapy planning after induction chemotherapy in locoregionally advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys 2009;75:725–733.
167. Lefebvre J, Pointreau Y, Rolland F, et al. Sequential chemoradiotherapy (SCRT) for larynx preservation (LP): preliminary results of the randomized phase II TREMPLIN study [abstract]. J Clin Oncol 2009;27(Suppl 15):Abstract 6010.
168. Buiret G, Combe C, Favrel V, et al. A retrospective, multicenter study of the tolerance of induction chemotherapy with docetaxel, cisplatin, and 5-fluorouracil followed by radiotherapy with concomitant cetuximab in 46 cases of squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys 2010;77:430–437.
169. Nutting CM, Bhide SA, Harrington KJ. Treatment of head and neck cancer. N Engl J Med 2008;358:1076–1077; author reply 1077–1078.
170. Chitapanarux I, Lorvidhaya V, Kamnerdsupaphon P, et al. Chemoradiation comparing cisplatin versus carboplatin in locally advanced nasopharyngeal cancer: randomised, non-inferiority, open trial. Eur J Cancer 2007;43:1399–1406.
171. Kies MS, Holsinger FC, Lee JJ, et al. Induction chemotherapy and cetuximab for locally advanced squamous cell carcinoma of the head and neck: results from a phase II prospective trial. J Clin Oncol 2010;28:8–14.
172. Kotwall C, Sako K, Razack MS, et al. Metastatic patterns in squamous cell cancer of the head and neck. Am J Surg 1987;154:439–442.
173. Lefebvre JL, Rolland F, Tesselaar M, et al. Phase 3 randomized trial on larynx preservation comparing sequential vs alternating chemotherapy and radiotherapy. J Natl Cancer Inst 2009;101:142–152.
174. Cooper JS, del Rowe J, Newall J. Regional stage IV carcinoma of the nasopharynx treated by aggressive radiotherapy. Int J Radiat Oncol Biol Phys 1983;9:1737–1745.
175. Bailet JW, Mark RJ, Abemayor E, et al. Nasopharyngeal carcinoma: treatment results with primary radiation therapy. Laryngoscope 1992;102:965–972.
176. Johansen LV, Mestre M, Overgaard J. Carcinoma of the nasopharynx: analysis of treatment results in 167 consecutively admitted patients. Head Neck 1992;14:200–207.
177. Sanguineti G, Geara FB, Garden AS, et al. Carcinoma of the nasopharynx treated by radiotherapy alone: determinants of local and regional control. Int J Radiat Oncol Biol Phys 1997;37:985–996.
178. Wang C. Radiation Therapy for Head and Neck Neoplasms, 3rd ed. New York, NY: Wiley-Liss; 1997.
179. Al-Sarraf M, LeBlanc M, Giri PG, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. J Clin Oncol 1998;16:1310–1317.
180. Mesic JB, Fletcher GH, Goepfert H. Megavoltage irradiation of epithelial tumors of the nasopharynx. Int J Radiat Oncol Biol Phys 1981;7:447–453.
181. Hoppe RT, Goffinet DR, Bagshaw MA. Carcinoma of the nasopharynx. Eighteen years' experience with megavoltage radiation therapy. Cancer 1976;37:2605–2612.
182. Wee J, Tan EH, Tai BC, et al. Randomized trial of radiotherapy versus concurrent chemoradiotherapy followed by adjuvant chemotherapy in patients with American Joint Committee on Cancer/International Union against cancer stage III and IV nasopharyngeal cancer of the endemic variety. J Clin Oncol 2005;23:6730–6738.
183. Chan AT, Leung SF, Ngan RK, et al. Overall survival after concurrent cisplatin-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma. J Natl Cancer Inst 2005;97:536–539.
184. Leong SS, Wee J, Tay MH, et al. Paclitaxel, carboplatin, and gemcitabine in metastatic nasopharyngeal carcinoma: a phase II trial using a triplet combination. Cancer 2005;103:569–575.

185. Chan AT, Hsu MM, Goh BC, et al. Multicenter, phase II study of cetuximab in combination with carboplatin in patients with recurrent or metastatic nasopharyngeal carcinoma. J Clin Oncol 2005;23:3568–3576.

186. Zhang L, Zhang Y, Huang PY, et al. Phase II clinical study of gemcitabine in the treatment of patients with advanced nasopharyngeal carcinoma after the failure of platinum-based chemotherapy. Cancer Chemother Pharmacol 2008;61:33–38.

187. Ngan RK, Yiu HH, Lau WH, et al. Combination gemcitabine and cisplatin chemotherapy for metastatic or recurrent nasopharyngeal carcinoma: report of a phase II study. Ann Oncol 2002;13:1252–1258.

188. Ma BB, Tannock IF, Pond GR, et al. Chemotherapy with gemcitabine-containing regimens for locally recurrent or metastatic nasopharyngeal carcinoma. Cancer 2002;95:2516–2523.

189. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 2006;354:567–578.

190. Garden AS, Harris J, Vokes EE, et al. Preliminary results of Radiation Therapy Oncology Group 97-03: a randomized phase II trial of concurrent radiation and chemotherapy for advanced squamous cell carcinomas of the head and neck. J Clin Oncol 2004;22:2856–2864.

191. Garden AS, Harris J, Vokes EE, et al. Results of Radiation Therapy Oncology Group 97-03—a randomized phase II trial of concurrent radiation and chemotherapy for advanced squamous cell carcinomas of the head and neck: long-term results and late toxicities [abstract]. Int J Radiat Oncol Biol Phys 2007;69:S140.

192. Vermorken JB, Trigo J, Hitt R, et al. Open-label, uncontrolled, multicenter phase II study to evaluate the efficacy and toxicity of cetuximab as a single agent in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck who failed to respond to platinum-based therapy. J Clin Oncol 2007;25:2171–2177.

193. Colevas AD. Chemotherapy options for patients with metastatic or recurrent squamous cell carcinoma of the head and neck. J Clin Oncol 2006;24:2644–2652.

194. Forastiere AA, Shank D, Neuberg D, et al. Final report of a phase II evaluation of paclitaxel in patients with advanced squamous cell carcinoma of the head and neck: an Eastern Cooperative Oncology Group trial (PA390). Cancer 1998;82:2270–2274.

195. Gibson MK, Li Y, Murphy B, et al. Randomized phase III evaluation of cisplatin plus fluorouracil versus cisplatin plus paclitaxel in advanced head and neck cancer (E1395): an intergroup trial of the Eastern Cooperative Oncology Group. J Clin Oncol 2005;23:3562–3567.

196. Forastiere AA, Metch B, Schuller DE, et al. Randomized comparison of cisplatin plus fluorouracil and carboplatin plus fluorouracil versus methotrexate in advanced squamous-cell carcinoma of the head and neck: a Southwest Oncology Group study. J Clin Oncol 1992;10:1245–1251.

197. Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 2008;359:1116–1127.

198. Samlowski WE, Moon J, Kuebler JP, et al. Evaluation of the combination of docetaxel/carboplatin in patients with metastatic or recurrent squamous cell carcinoma of the head and neck (SCCHN): a Southwest Oncology Group phase II study. Cancer Invest 2007;25:182–188.

199. Burtness B, Goldwasser MA, Flood W, et al. Phase III randomized trial of cisplatin plus placebo compared with cisplatin plus cetuximab in metastatic/recurrent head and neck cancer: an Eastern Cooperative Oncology Group study. J Clin Oncol 2005;23:8646–8654.

200. Jacobs C, Lyman G, Velez-Garcia E, et al. A phase III randomized study comparing cisplatin and fluorouracil as single agents and in combination for advanced squamous cell carcinoma of the head and neck. J Clin Oncol 1992;10:257–263.

201. Browman GP, Cronin L. Standard chemotherapy in squamous cell head and neck cancer: what we have learned from randomized trials. Semin Oncol 1994;21:311–319.

202. Clavel M, Vermorken JB, Cognetti F, et al. Randomized comparison of cisplatin, methotrexate, bleomycin and vincristine (CABO) versus cisplatin and 5-fluorouracil (CF) versus cisplatin (C) in recurrent or metastatic squamous cell carcinoma of the head and neck. A phase III study of the EORTC Head and Neck Cancer Cooperative Group. Ann Oncol 1994;5:521–526.

203. Stewart JS, Cohen EE, Licitra L, et al. Phase III study of gefitinib compared with intravenous methotrexate for recurrent squamous cell carcinoma of the head and neck [corrected]. J Clin Oncol 2009;27:1864–1871.

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