

## NCCN

# Head and Neck Cancers, Version 2.2014

## Clinical Practice Guidelines in Oncology

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### Overview

This selection from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Head and Neck (H&N) Cancers focuses on glottic laryngeal cancer, which is the most common type of laryngeal cancer and has an excellent cure

### Abstract

This selection from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Head and Neck Cancers focuses on glottic laryngeal cancer, which is the most common type of laryngeal cancer and has an excellent cure rate. The lymphatic drainage of the glottis is sparse, and early stage primaries rarely spread to regional nodes. Because hoarseness is an early symptom, most glottic laryngeal cancer is early stage at diagnosis. Updates to these guidelines for 2014 include revisions to "Principles of Radiation Therapy" for each site and "Principles of Surgery," and the addition of a new section on "Principles of Dental Evaluation and Management." (*J Natl Compr Canc Netw* 2014;12:1454–1487)

### NCCN Categories of Evidence and Consensus

**Category 1:** Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

**Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

**Category 2B:** Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

**Category 3:** Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

**All recommendations are category 2A unless otherwise noted.**

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

### Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way. **The full NCCN Guidelines for Head and Neck Cancers are not printed in this issue of JNCCN but can be accessed online at [NCCN.org](http://NCCN.org).**

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### Disclosures for the NCCN Head and Neck Cancers Panel

At the beginning of each NCCN Guidelines panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Head and Neck Cancers Panel members can be found on page 1487. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at [NCCN.org](http://NCCN.org).)

These guidelines are also available on the Internet. For the latest update, visit [NCCN.org](http://NCCN.org).

## Journal of the National Comprehensive Cancer Network

rate. The complete version of the NCCN Guidelines for H&N Cancers addresses tumors arising in the upper aerodigestive tract, including the lip, oral cavity, pharynx, glottic and supraglottic larynx, and paranasal sinuses, and addresses occult primary cancer, salivary gland cancer, and mucosal melanoma.<sup>1,2</sup> The complete version of the NCCN Guidelines for H&N Cancers is available at NCCN.org.

Updates to these guidelines for 2014 include revisions to “Principles of Radiation Therapy” for each site and “Principles of Surgery” (to view the most recent and complete version of the NCCN Guidelines for H&N Cancers, visit NCCN.org). A new section on “Principles of Dental Evaluation and Management” was also added (see DENT-A,

page 1464). A brief overview of the epidemiology and management of H&N cancers is provided in the following section. A recent review discusses the progress that has been made during the past 10 years in understanding the epidemiology, pathogenesis, and management of H&N cancers.<sup>3</sup> 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 panel members while developing these NCCN Guidelines. A 5% rule (omitting clinical scenarios that comprise less than 5% of all cases) was used to eliminate uncommon clinical occurrences or conditions from these NCCN Guidelines.

Text cont. on page 1466.

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Evaluation and Management.  
(Please note: Underlining denotes the lead of the subcommittee)

Specialties: †Medical Oncology; ¶Surgery/Surgical Oncology;  
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WORKUP<sup>a</sup>

- H&P<sup>b,c</sup> including a complete head and neck exam; mirror and fiberoptic examination as clinically indicated
  - Biopsy
  - Chest imaging as clinically indicated
  - CT with contrast and thin cuts through larynx and/or MRI of primary and neck
  - Consider PET-CT for stage III-IV disease
  - EUA with endoscopy
  - Preanesthesia studies
  - Dental evaluation as clinically indicated<sup>d</sup>
  - Nutrition, speech, and swallowing evaluation/therapy, and audiogram as clinically indicated<sup>e</sup>
  - Consider videostrobe for select patients
  - Consider pulmonary function tests for conservation surgery candidates
- Multidisciplinary consultation as clinically indicated

## CLINICAL STAGING

## TREATMENT OF PRIMARY AND NECK

Carcinoma in situ

Amenable to larynx-preserving  
(conservation) surgery  
(T1-T2, N0 or select T3)

T3 requiring (amenable to)  
total laryngectomy  
(N0-1)

T3 requiring (amenable to)  
total laryngectomy  
(N2-3)

T4a disease

T4b, any N  
or  
Unresectable  
nodal disease  
or  
Unfit for surgery

See Treatment of Primary and Neck (GLOT-3)

See Treatment of Primary and Neck (GLOT-4)

See Treatment of Primary and Neck (GLOT-6)

See Treatment of Very Advanced Head and Neck Cancer (ADV-1)\*

\*Available online, in these guidelines, at NCCN.org.

<sup>a</sup>Complete workup is not indicated for Tis, T1.

<sup>b</sup>Smoking cessation counseling as clinically indicated. All current smokers should be advised to quit smoking, and former smokers should be advised to remain abstinent from smoking. For additional cessation support and resources, smokers can be referred to [www.smokefree.org](http://www.smokefree.org).

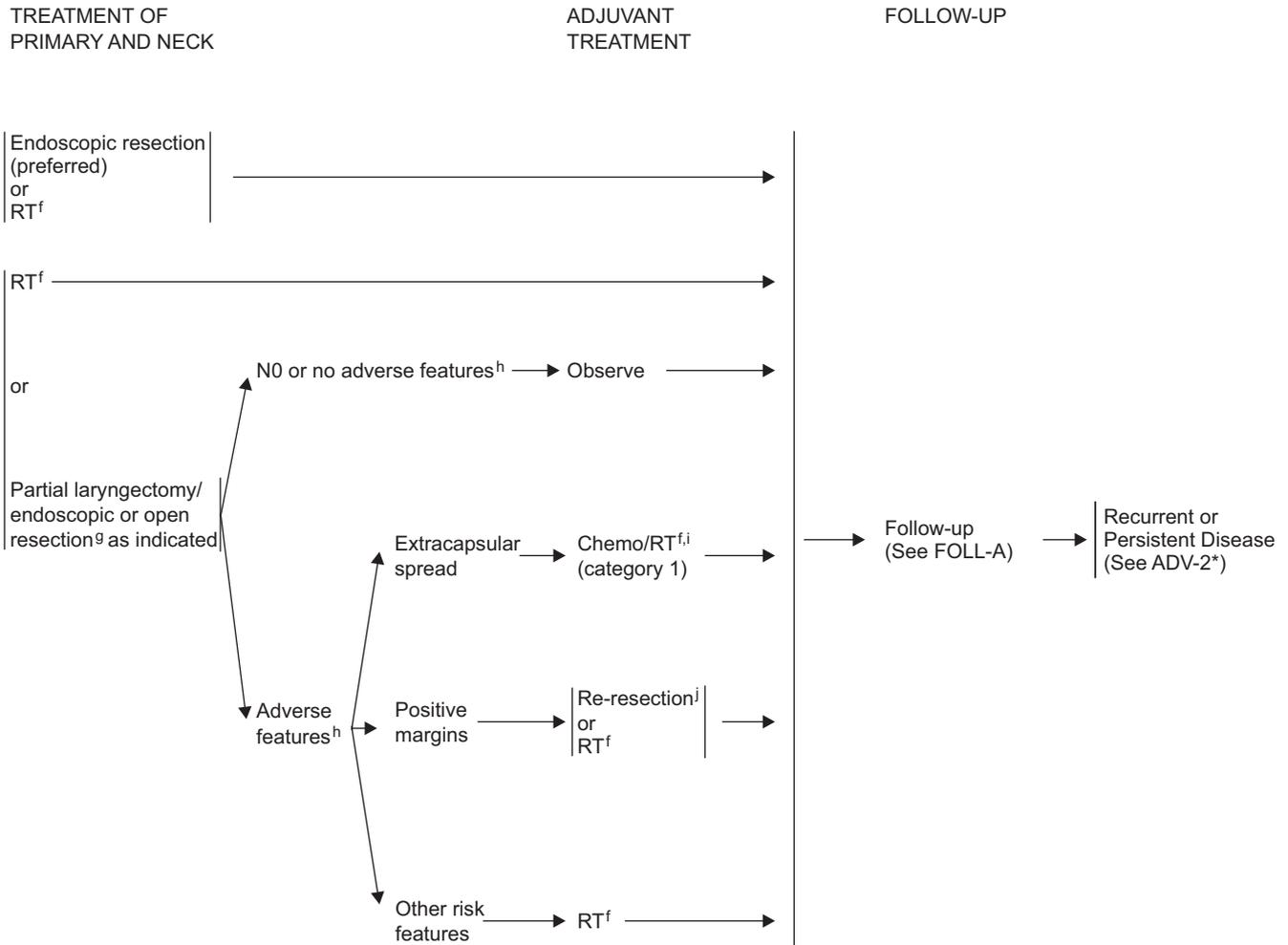
<sup>c</sup>Screen for depression (See NCCN Guidelines for Distress Management; to view the most recent version of these guidelines, visit NCCN.org).

<sup>d</sup>See Principles of Dental Evaluation and Management (DENT-A).

<sup>e</sup>See Principles of Nutrition: Management and Supportive Care (NUTR-A).\*

GLOT-1

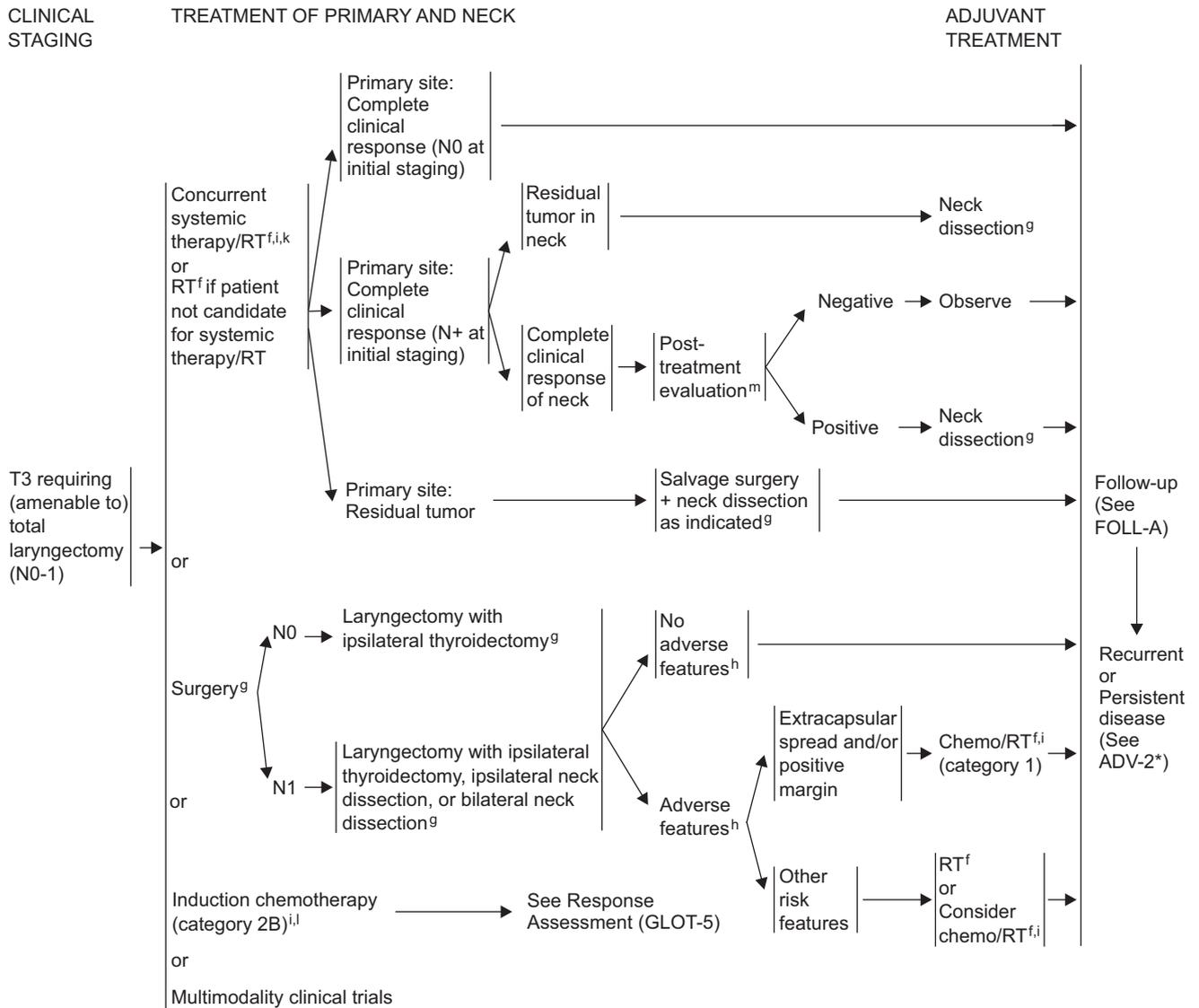
Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.



\*Available online, in these guidelines, at NCCN.org.

<sup>f</sup>See Principles of Radiation Therapy (GLOT-A).  
<sup>9</sup>See Principles of Surgery (SURG-A).  
<sup>h</sup>Adverse features: extracapsular nodal spread, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism (see Discussion).  
<sup>i</sup>See Principles of Systemic Therapy (CHEM-A).  
<sup>j</sup>Consider re-resection to achieve negative margins, if feasible.

GLOT-2

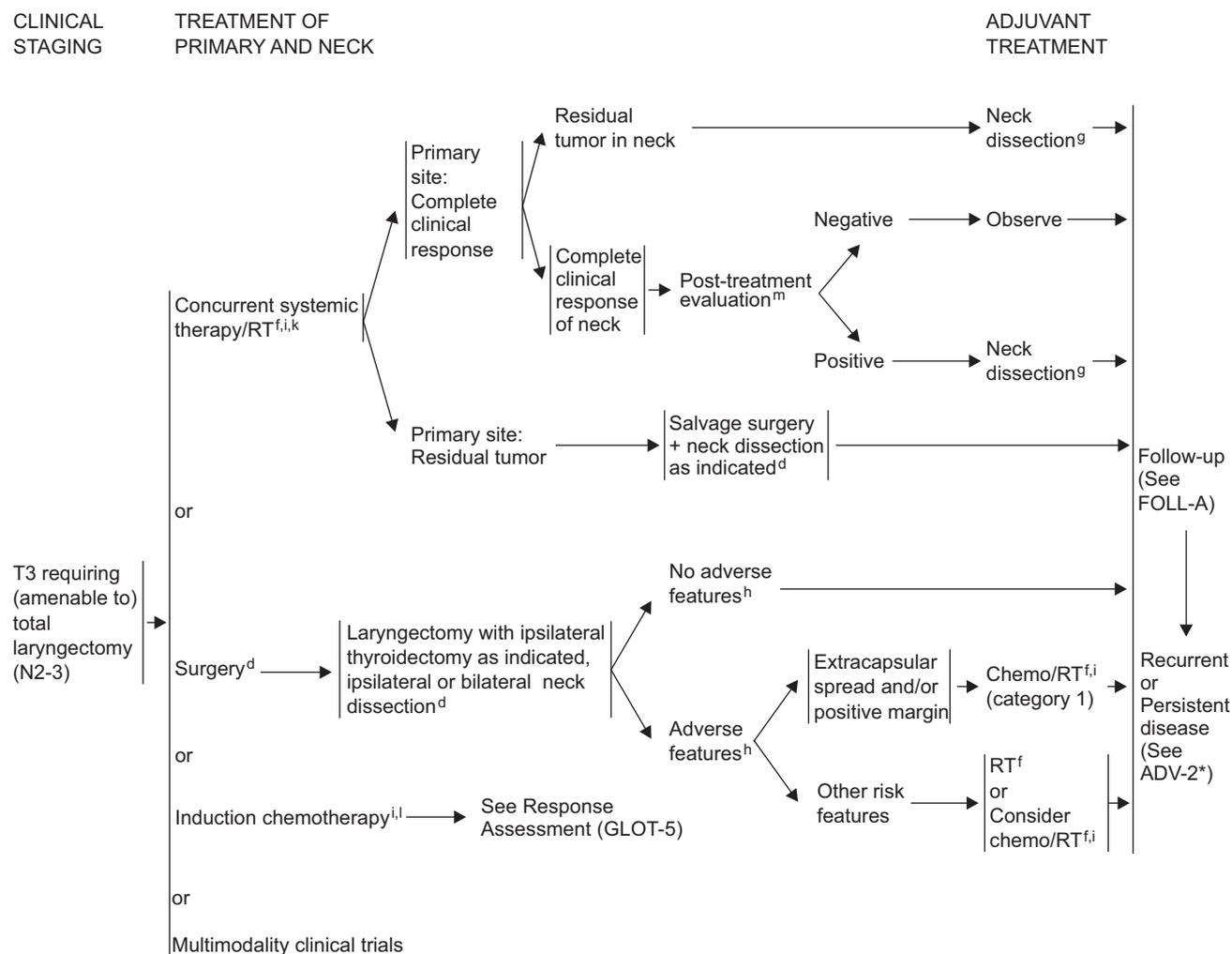


\*Available online, in these guidelines, at NCCN.org.

<sup>f</sup>See Principles of Radiation Therapy (GLOT-A).  
<sup>g</sup>See Principles of Surgery (SURG-A).\*  
<sup>h</sup>Adverse features: extracapsular nodal spread, positive margins, pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism (see Discussion).  
<sup>i</sup>See Principles of Systemic Therapy (CHEM-A).\*  
<sup>k</sup>When using concurrent chemotherapy/RT, the preferred agent is cisplatin (category 1).  
<sup>l</sup>See Discussion on induction chemotherapy  
<sup>m</sup>See Post Chemoradiation or RT Neck Evaluation (SURG-A 8 of 9).\*

GLOT-3

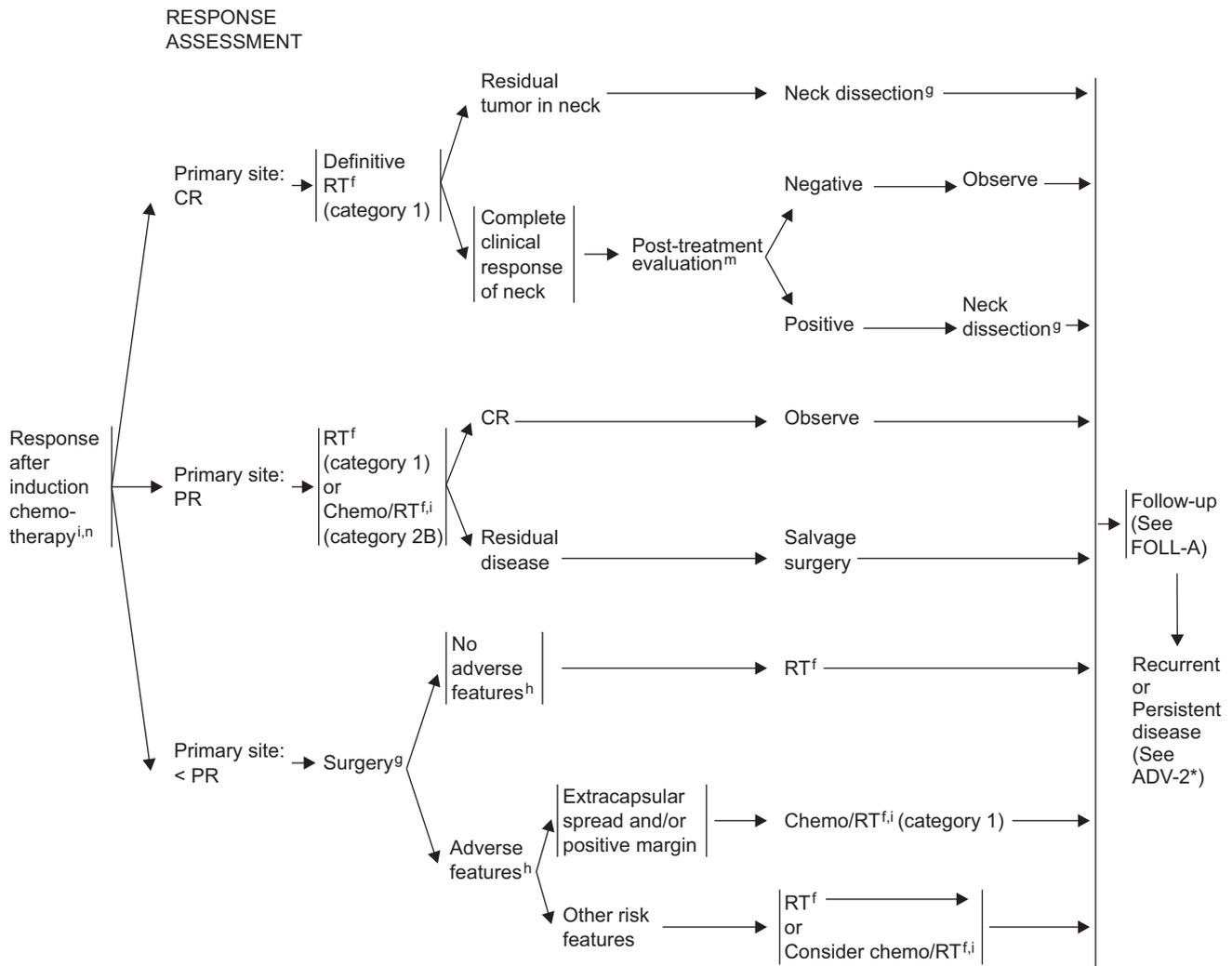
Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.



\*Available online, in these guidelines, at NCCN.org.

<sup>f</sup>See Principles of Radiation Therapy (GLOT-A).  
<sup>g</sup>See Principles of Surgery (SURG-A).\*  
<sup>h</sup>Adverse features: extracapsular nodal spread, positive margins, pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism (see Discussion).  
<sup>i</sup>See Principles of Systemic Therapy (CHEM-A).\*  
<sup>k</sup>When using concurrent chemotherapy/RT, the preferred agent is cisplatin (category 1).  
<sup>l</sup>See Discussion on induction chemotherapy.  
<sup>m</sup>See Post Chemoradiation or RT Neck Evaluation (SURG-A 8 of 9).\*

GLOT-4



\*Available online, in these guidelines, at NCCN.org.

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

<sup>g</sup>See Principles of Surgery (SURG-A).\*

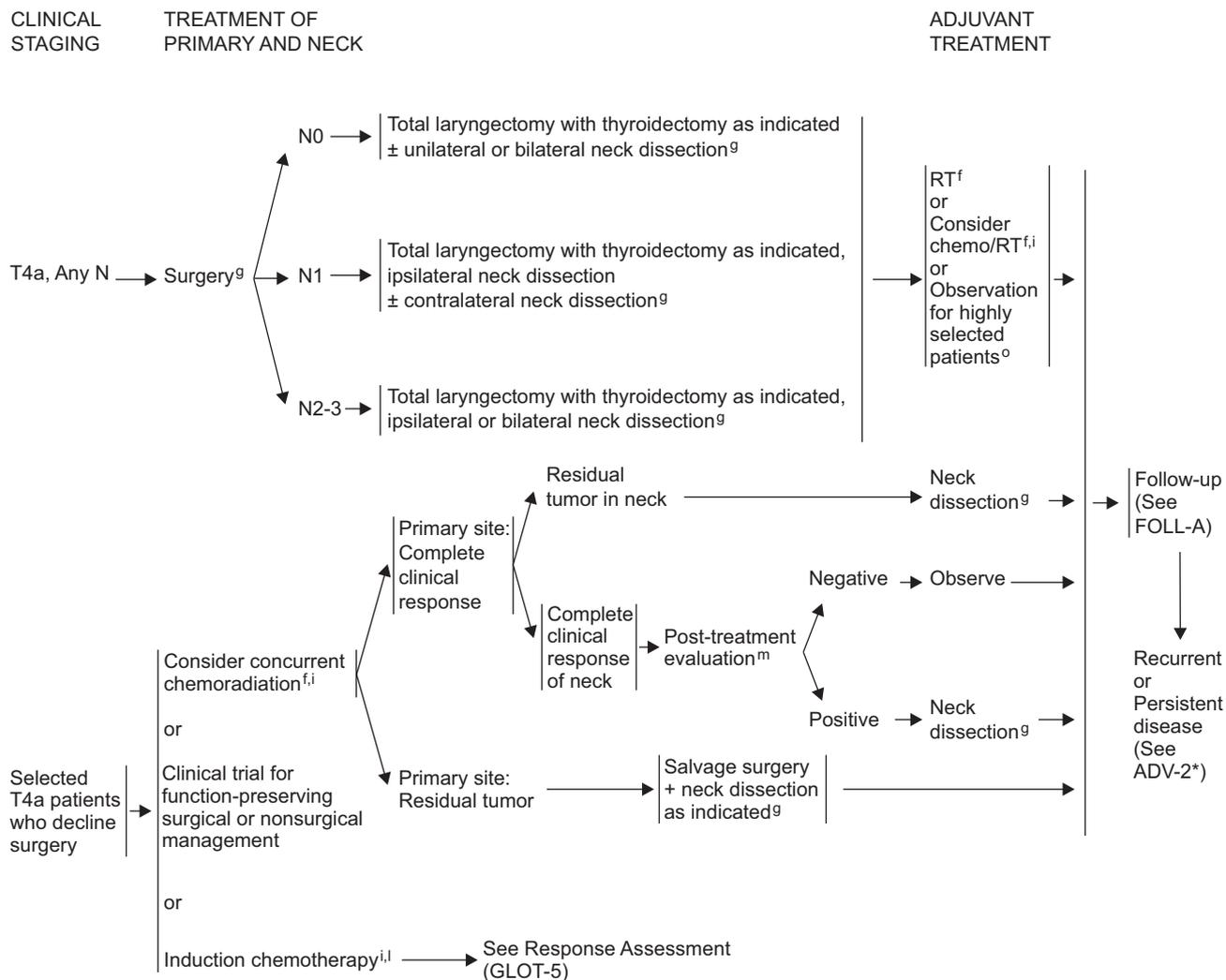
<sup>i</sup>See Principles of Systemic Therapy (CHEM-A).\*

<sup>m</sup>See Post Chemoradiation or RT Neck Evaluation (SURG-A 8 of 9).\*

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

<sup>n</sup>In randomized clinical trials, assessment of response has been done after 2 or 3 cycles.

GLOT-5



\*Available online, in these guidelines, at NCCN.org.

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

<sup>g</sup>See Principles of Surgery (SURG-A).\*

<sup>i</sup>See Principles of Systemic Therapy (CHEM-A).\*

<sup>m</sup>See Post Chemoradiation or RT Neck Evaluation (SURG-A 8 of 9).\*

<sup>l</sup>See Discussion on induction chemotherapy.

<sup>o</sup>Good risk features for favorable T4a patients who could be observed after surgery include:

- Indolent histopathology: papillary variant of squamous cell carcinoma, verrucous carcinoma.
- Widely negative margins, pN0 neck, especially central compartment (Level VI) without perineural invasion, or lymphovascular invasion.
- Low-volume disease with microscopic extralaryngeal extension beyond the laryngeal skeleton and widely negative margins.
- pN0, Broders' grade I-II, subglottic extension <1 cm.

GLOT-6

PRINCIPLES OF RADIATION THERAPY<sup>1</sup>

## DEFINITIVE:

## RT Alone

- Tis, N0: 60.75 Gy (2.25 Gy/fraction) to 66 Gy (2.0 Gy/fraction)
- T1, N0: 63 Gy (2.25 Gy/fraction) to 66 Gy (2.0 Gy/fraction)
- T2, N0: 65.25 (2.25 Gy/fraction) to 70 Gy (2.0 Gy/fraction)
- ≥ T2, N1:
  - ▶ PTV
    - ◊ High risk: Primary tumor and involved lymph nodes (this includes possible local subclinical infiltration at the primary site and at the high-risk level lymph node(s))
      - ※ Fractionation:
        - 66 Gy (2.2 Gy/fraction) to 70 Gy (2.0 Gy/fraction); daily Monday-Friday in 6-7 weeks<sup>2</sup>
        - 66-70 Gy (2.0 Gy/fraction; 6 fractions/week accelerated)
        - Concomitant boost accelerated RT: 72 Gy/6 weeks
        - (1.8 Gy/fraction, large field; 1.5 Gy boost as second daily fraction during last 12 treatment days)
        - Hyperfractionation: 79.2-81.6 Gy/7 weeks (1.2 Gy/fraction, twice daily)
    - ◊ Low to intermediate risk: Sites of suspected subclinical spread
      - ※ 44-50 Gy (2.0 Gy/fraction) to 54-63 Gy (1.6-1.8 Gy/fraction)<sup>3</sup>

CONCURRENT CHEMORADIATION<sup>4,5</sup>

- Planning target volume (PTV)
  - ▶ High risk: typically 70 Gy (2.0 Gy/fraction)
  - ▶ Low to intermediate risk: 44-50 Gy (2.0 Gy/fraction) to 54-63 Gy (1.6-1.8 Gy/fraction)<sup>3</sup>

## POSTOPERATIVE:

## RT

- Preferred interval between resection and postoperative RT is ≤6 weeks.
- PTV
  - ▶ High risk: adverse features such as positive margins (See footnote "h" on GLOT-3).
    - ◊ 60-66 Gy (2.0 Gy/fraction); daily Monday-Friday in 6.0-6.5 weeks
  - ▶ Low to intermediate risk: sites of suspected subclinical spread
    - ◊ 44-50 Gy (2.0 Gy/fraction) to 54-63 Gy (1.6-1.8 Gy/fraction)<sup>3</sup>

## POSTOPERATIVE CHEMORADIATION

- Concurrent single-agent cisplatin at 100 mg/m<sup>2</sup> every 3 weeks is recommended.<sup>6-9</sup>
- Either intensity-modulated RT (IMRT) or 3-D conformal RT is recommended.

<sup>1</sup> See Radiation Techniques (RAD-A)\* and Discussion.

<sup>2</sup> For doses >70 Gy, some clinicians feel that the fractionation should be slightly modified (eg, <2.0 Gy/fraction for at least some of the treatment) to minimize toxicity. An additional 2-3 doses can be added depending on clinical circumstances.

<sup>3</sup> Suggest 44-50 Gy in 3D conformal RT and sequentially planned IMRT or 54-63 Gy with IMRT dose painting technique (dependent upon dose per fraction).

<sup>4</sup> See Principles of Systemic Therapy (CHEM-A)\*.

<sup>5</sup> Based on published data, concurrent chemoradiation most commonly uses conventional fractionation at 2.0 Gy per fraction to a typical dose of 70 Gy in 7 weeks with single-agent cisplatin given every 3 weeks at 100 mg/m<sup>2</sup>; 2-3 cycles of chemotherapy are used depending on the radiation fractionation scheme (RTOG 0129) (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). When carboplatin and 5-FU are used, then the recommended regimen is standard fractionation plus 3 cycles of chemotherapy. (Bourhis J, Sire C, Graff P, et al. Concomitant chemoradiotherapy versus acceleration of radiotherapy with or without concomitant chemotherapy in locally advanced head and neck carcinoma (GORTEC 99-02): an open-label phase 3 randomised trial. *Lancet Oncol* 2012;13:145-153). Other fraction sizes (eg, 1.8 Gy, conventional), multiagent chemotherapy, other dosing schedules of cisplatin, or 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.

<sup>6</sup> Bernier J, Dommene 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.

<sup>7</sup> 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.

<sup>8</sup> 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.

<sup>9</sup> Cooper JS, Zhang Q, Pajak TF et al. Long-term follow-up of the RTOG 9501/intergroup phase III trial: postoperative concurrent radiation therapy and chemotherapy in high-risk squamous cell carcinoma of the head and neck. *Int J Radiat Oncol Biol Phys* 2012;84:1198-1205.

\*Available online, in these guidelines, at NCCN.org.

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## Head and Neck Cancers, Version 2.2014

**FOLLOW-UP RECOMMENDATIONS<sup>1</sup>****(based on risk of relapse, second primaries, treatment sequelae, and toxicities)**

- H&P exam (including a complete head and neck exam; mirror and fiberoptic examination as clinically indicated):<sup>2</sup>
  - ▶ Year 1, every 1-3 mo
  - ▶ Year 2, every 2-6 mo
  - ▶ Years 3-5, every 4-8 mo
  - ▶ >5 years, every 12 mo
- Post-treatment baseline imaging of primary (and neck, if treated) recommended within 6 mo of treatment<sup>3</sup> (category 2B)
  - ▶ Further reimaging as indicated based on signs/symptoms; not routinely recommended for patients without worrisome signs/symptoms.
- Chest imaging as clinically indicated for patients with smoking history (See NCCN Guidelines for Lung Cancer Screening; to view the most recent version of these guidelines, visit NCCN.org)
- Thyroid-stimulating hormone (TSH) every 6-12 mo if neck irradiated
- Speech/hearing and swallowing evaluation<sup>4</sup> and rehabilitation as clinically indicated
- Smoking cessation<sup>5</sup> and alcohol counseling as clinically indicated
- Dental evaluation<sup>6</sup>
  - ▶ Recommended for oral cavity and sites exposed to significant intraoral radiation treatment
- Consider EBV DNA monitoring for nasopharyngeal cancer

<sup>1</sup>Most recurrences are reported by the patient.<sup>2</sup>For mucosal melanoma, a physical exam should include endoscopic inspection for paranasal sinus disease.<sup>3</sup>For cancer of the oropharynx, hypopharynx, glottic larynx, supraglottic larynx, and nasopharynx: imaging is recommended for T3-4 or N2-3 disease only.<sup>4</sup>See Principles of Nutrition (NUTR-A), available online, in these guidelines, at NCCN.org.<sup>5</sup>All current smokers should be advised to quit smoking, and former smokers should be advised to remain abstinent from smoking. For additional cessation support and resources, smokers can be referred to [www.smokefree.org](http://www.smokefree.org).<sup>6</sup>See Principles of Dental Evaluation and Management (DENT-A).

FOLL-A

### PRINCIPLES OF DENTAL EVALUATION AND MANAGEMENT

Radiation therapy to the head and neck causes xerostomia and salivary gland dysfunction which dramatically increases the risk of dental caries and its sequelae, including dentoalveolar infection and osteoradionecrosis. Radiation therapy also affects the dental hard tissues increasing their susceptibility to demineralization<sup>1</sup> within the presence of xerostomia, microbial changes following RT and changes to a more cariogenic diet. IMRT and salivary gland sparing techniques are associated with dose-dependent recovery of salivary function over time,<sup>2-9</sup> and with reduced risk for dental caries long term for some patients.<sup>7,10</sup> Radiation-related caries and other dental hard tissue changes can appear within the first 3 months following RT.<sup>11,12</sup>

#### Goals of Pre-RT Dental/Oral evaluation:

1. Patient education, both oral and written, regarding oral and dental complications of RT and need for compliance with preventive protocols.<sup>13-16</sup>
  - Effect on salivary glands
    - ▶ Dry mouth strategies
      - ◊ Increased hydration
      - ◊ Salivary substitutes (eg, calcium phosphate-containing solutions,<sup>17</sup> gels containing lysozyme, lactoferrin, and peroxidase<sup>18-19</sup>)
      - ◊ Alcohol-free mouthwash
      - ◊ Salivary stimulation
        - ※ Gustatory stimulants (eg, xylitol-containing chewing gum, sorbitol/malic acid-containing lozenges, or xylitol-containing lozenges)
        - ※ Cholinergic agonists: pilocarpine, cevimeline<sup>20-23</sup>
    - ▶ Dental caries prevention
      - ◊ Diet counseling
      - ◊ High-potency topical fluoride – continue long term after therapy<sup>13,15,24-27</sup>
        - ※ Daily 1.1% NaF gel or SnF<sub>2</sub> gel, brush on or in custom dental trays or
        - ※ Daily 1.1% NaF dentifrice or
        - ※ Fluoride varnish application, 3 times per year<sup>14</sup>
        - ※ Calcium phosphate artificial saliva rinse<sup>17</sup>
      - ◊ Regular frequent dental evaluations to detect dental disease
    - Effect on bone in irradiated field
      - ▶ Need for pre-RT dental evaluation and determine need for dental extractions<sup>7,10,12,24,28-34</sup>
        - ◊ If yes, should be completed at least 2 weeks before start of RT
        - ◊ Long-term prognosis of teeth and patient motivation should be considered
        - ◊ Need to contact oncology team if any future extractions or surgery in irradiated field
    - Effect on masticatory muscles: potential for trismus<sup>11,12,35-38</sup>
      - ▶ Maintain range of motion
        - ◊ Tongue blades and gentle stretching
        - ◊ Custom mouth opening devices for rehabilitation of trismus and jaw motion
  - 2. Examination and assessment of patient with treatment plan<sup>11,26,34,39</sup>
    - Complete oral and head and neck examination, including radiographs of all teeth
    - Risk assessment for caries and periodontal disease
      - ▶ Existing periodontal and dental conditions
      - ▶ Radiographic evidence of periapical pathology
      - ▶ Oral hygiene
      - ▶ Past dental history
      - ▶ Patient motivation and compliance
    - Treatment plan
      - ▶ Eliminate potential sources of infection.
      - ▶ Extractions at least 2 weeks before start of RT
      - ▶ Treat active dental caries, periodontal disease
      - ▶ Silicone guards to minimize radiation backscatter, if patients have metal restorations
      - ▶ Prescribe potent topical fluoride for daily use. Duration of use to be determined by periodic caries risk assessment over time
      - ▶ Return visit for reevaluation and reinforcement of preventive protocol, during last week of RT
      - ▶ Evaluate for oral candidiasis and treat appropriately with antifungal agents

#### Goals of Dental Management Posttreatment:

1. Manage xerostomia
2. Prevent and minimize trismus
3. Prevent and treat dental caries
4. Prevent postradiation osteonecrosis
5. Prevent and manage oral candidiasis

#### Goals of Dental Management During Cancer Therapy:

1. Manage xerostomia
2. Prevent trismus of masticatory muscles.
3. Evaluate for oral candidiasis and treat as clinically indicated.

Dental recall visit interval based on risk,<sup>7</sup> at least once every 6 months, or more frequently for those with xerostomia, or those with new caries lesions following radiotherapy.

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## Head and Neck Cancers, Version 2.2014

## PRINCIPLES OF DENTAL EVALUATION AND MANAGEMENT (References)

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Text cont. from page 1455.

### Incidence and Etiology

In 2014, an estimated 12,630 new cases and 3610 deaths from laryngeal cancers will occur in the United States.<sup>4</sup> Squamous cell carcinoma or a variant is the histologic type in more than 90% of H&N cancers. Alcohol and tobacco abuse are common causative factors in H&N cancers. Because the entire aerodigestive tract epithelium may be exposed to these carcinogens, patients with H&N cancers are at risk for developing second primary neoplasms of the H&N, lung, esophagus, and other sites that share these risk factors.

### Staging

Stage at diagnosis predicts survival rates and guides management in patients with laryngeal cancer. The 2010 AJCC staging classification (7th edition) was used as a basis for the NCCN recommendations for glottic laryngeal cancer.<sup>5,6</sup> The TNM staging system developed by the AJCC for the larynx (glottis and supraglottis) is available online (see Table 3 online, in these guidelines, at NCCN.org [ST-6]).<sup>6</sup> T stage is based on subsite involvement and is specific to each subsite for the glottic larynx and supraglottic larynx. Definitions for regional lymph node (N) involvement and spread to distant metastatic sites (M) are described in the AJCC staging table. In general, stage I or II disease defines a 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. Protocols for the specific sites from the College of American Pathologists may also be useful.

In the 7th edition of the AJCC staging manual, the words *resectable* (T4a) and *unresectable* (T4b) were replaced by the terms *moderately advanced* (T4a) and *very advanced* (T4b).<sup>5</sup> These changes were made, because many resectable advanced-stage malignancies of the H&N are being treated nonsurgically. A clear consensus in criteria for resectability can be difficult to obtain. Some tumors deemed unresectable are in fact anatomically resectable, but surgery is not pursued because of medical contraindications to surgery or because it is anticipated that surgery will not improve prognosis (see “Resectable Versus Unresectable Disease,” facing page). This change in terminology allows the revision 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 the larynx. A designation of stage IV disease does not necessarily mean the disease is incurable, particularly in the absence of distant metastases.

### Management Approaches

Treatment is complex for patients with H&N cancers. The specific site of disease, stage, and pathologic findings guide treatment (ie, the appropriate surgical procedure, radiation targets, dose and fractionation, and indications for chemotherapy). Single-modality treatment with surgery or radiation therapy (RT) is generally recommended for patients who present with early-stage glottic laryngeal cancer (stage I or II) (see GLOT-2, page 1457). The 2 modalities result in similar survival in these individuals. Combined modality therapy is generally recommended for 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 the glottic larynx is addressed in the algorithm (see “Very Advanced Head and Neck Cancers” online, in these guidelines, at NCCN.org). Participation in clinical trials is a preferred or recommended treatment option in many situations. In formulating these NCCN Guidelines, panel members have tried to make them evidence-based while providing a statement of consensus as to the acceptable range of treatment options.

### Multidisciplinary Team Involvement

The initial evaluation and development of a plan for treating the patient with H&N cancer requires a multidisciplinary team of health care providers with expertise in caring for these patients. Similarly, managing and preventing sequelae after radical surgery, RT, and chemotherapy (eg, pain, xerostomia, speech and swallowing problems, depression) requires professionals familiar with the disease.<sup>7,8</sup> Follow-up for these sequelae should include a comprehensive H&N examination. Adequate nutritional support can help prevent severe weight loss in patients receiving treatment for H&N cancers; therefore, patients should be encouraged to see a dietician (see “Principles of Nutrition: Management and Supportive Care” online, in these guidelines, at

NCCN.org).<sup>9</sup> A new section on “Principles of Dental Evaluation and Management” was added in the 2014 update (see DENT-A, page 1464).

Patients should also be encouraged to stop smoking (and remain smoke-free) and to modify alcohol consumption if excessive, because these habits may decrease the efficacy of treatment and adversely affect other health outcomes.<sup>10,11</sup> Programs using behavioral counseling combined with medications that promote smoking cessation (approved by the FDA) can be very useful (1-800-QUIT-NOW is the national access number to state-based quit line services; www.smokefree.gov).

Patients are at risk for depression from H&N cancer and its sequela, and therefore screening for depression is advised (see the NCCN Guidelines for Distress Management; to view the most recent version of these guidelines, visit NCCN.org).<sup>12–15</sup> Specific components of patient support and follow-up are listed in the algorithm (see “Team Approach” online, in these guidelines, at NCCN.org [TEAM-1]). Panel members also recommend referring to the NCCN Guidelines for Supportive Care as needed (available at NCCN.org).

### Comorbidity and Quality of Life

Comorbidity refers to the presence of concomitant disease (in addition to H&N cancers) that may affect diagnosis, treatment, and prognosis.<sup>16–18</sup> Documentation of comorbidity is important to facilitate optimal treatment selection. Comorbidity is known to be a strong independent predictor for mortality in patients with H&N cancers,<sup>18–25</sup> and comorbidity also influences costs and utilization of care, and quality of life.<sup>26–28</sup> Traditional indices of comorbidity include the Charlson index<sup>17</sup> and the Kaplan-Feinstein Index and its modifications.<sup>18,29</sup> The Adult Comorbidity Evaluation-27 (ACE-27) is specific for H&N cancers and has excellent emerging reliability and validity.<sup>30,31</sup>

Health-related quality-of-life issues are paramount in H&N cancers. These tumors affect basic physiologic functions, the senses, and uniquely human characteristics, such as 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 in-

dividuals place on their health status and function.<sup>32</sup> An NIH-sponsored conference<sup>33</sup> recommended the use of patient-completed scales to measure quality of life. For H&N cancer-specific issues, the 3 validated and accepted measures are (1) the University of Washington Quality of Life scale (UW-QOL)<sup>34</sup>; (2) the EORTC Quality of Life Questionnaire (EORTC QLQ-H&N35)<sup>35</sup>; and (3) the Functional Assessment of Cancer Therapy-Head and Neck (FACT-H&N).<sup>36</sup> The Performance Status Scale is a clinician-rated performance scale that is widely used for patients with H&N cancers.<sup>37</sup>

## H&N Surgery

### Principles of Surgery

All patients should be evaluated by an H&N surgical oncologist before treatment. It is critical that multidisciplinary evaluation and treatment 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 the algorithm (see “Principles of Surgery” online, in these guidelines, at NCCN.org).<sup>38,39</sup> Resectable disease, neck dissection, postoperative management, and salvage surgery for high-risk disease are discussed in the following sections. Minimally invasive surgery may be useful for decreasing morbidity.<sup>40,41</sup> Use of robotic surgery is increasing in the United States. For H&N cancer surgery, transoral resection using robotic, endoscopic, or direct access surgery may offer advantages over conventional methods<sup>42,43</sup> (see the revised “Principles of Surgery” section online, in these guidelines, at NCCN.org).

### 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 where only a few patients with locally advanced H&N cancers are treated. The NCCN Member Institutions have teams experienced in the treatment of H&N cancers and maintain the multidisciplinary infrastructure needed for reconstruction

and rehabilitation. A patient's cancer is deemed unresectable if H&N surgeons at NCCN Member Institutions do not think they can remove all gross tumor on anatomic grounds or if they are certain that local control will not be achieved after surgery (even with the addition of RT to the treatment approach). Typically, these unresectable tumors densely involve the cervical vertebrae, brachial plexus, deep muscles of the neck, or carotid artery (see "Principles of Surgery" online, in these guidelines, at NCCN.org). Tumor involvement of certain sites is associated with poor prognosis (ie, direct extension of neck disease to involve the external skin; direct extension to mediastinal structures, prevertebral fascia, or cervical vertebrae).

Unresectable tumors—those 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). A subgroup of patients will refuse surgical management, but their tumors should also 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. 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 RT alone or RT combined with chemotherapy may represent equivalent or preferable approaches to surgery 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 patients with disease that truly cannot be removed.

### Neck Dissection

Historically, cervical lymph node (ie, 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 NCCN Panel prefers to classify cervical lymphadenectomy using contemporary nomenclature; thus, cervical lymph node dissections are classified as either *comprehensive* or *selective*.<sup>44</sup> 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. Comprehensive neck dissection is often recommended for N3 disease (see GLOT-4, page 1459 and "Neck Management in Principles of Surgery" online, in these guidelines, at NCCN.org).

Selective neck dissections have been developed based on the common pathways for spread of H&N cancers to regional nodes (see Figure 2 [MS-39] online, in these guidelines, at NCCN.org).<sup>45,46</sup> Selective neck dissection is often recommended for N0 disease (see GLOT-3, page 1458, and "Neck Management in Principles of Surgery" online, in these guidelines, at NCCN.org). To remove the nodes most commonly involved with metastases from the larynx, a selective neck dissection is recommended that includes the nodes in levels II to IV, and level VI when appropriate.<sup>44</sup> Elective level VI dissections are often considered appropriate for infraglottic laryngeal cancers. 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).<sup>47-49</sup>

The chief role of selective neck dissections in these NCCN Guidelines is to determine which patients are candidates for possible adjuvant chemotherapy/RT or adjuvant RT, although selective neck dissections may be used as treatment when neck tumor burden is low.<sup>50</sup> 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.<sup>51-53</sup> In these NCCN 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 the site of the tumor.<sup>38</sup> For example, bilateral neck dissection is often recommended for tumors at or near the midline and/or for tumor sites with bilateral drainage.

Careful and regular follow-up examinations by a trained H&N surgical oncologist are recommended for patients undergoing nonsurgical primary treatment so that any local or regional recurrence can be detected early, and salvage surgery (and neck dissection as indicated) can be performed. After either RT or chemoradiation, posttreatment evaluation with imaging (ie, CT and/or MRI with contrast, PET/CT) guides the use of neck dissection (see “Post Chemoradiation or RT Neck Evaluation in the Principles of Surgery” online, in these guidelines, at NCCN.org).<sup>54-57</sup> If PET/CT is used for follow-up, the first scan should be performed at a minimum of 12 weeks after treatment to reduce the false-positive rate.<sup>55,58</sup>

A *complete clinical response* (ie, clinically negative) may be defined as no visible or palpable neck disease and no radiographic findings (ie, the absence of either focally abnormal lymph nodes or large nodes [ $>1.5$  cm])<sup>54,59</sup>; a complete pathologic response requires pathologic confirmation. If a complete clinical response has been achieved in patients who were N0 at initial staging, all of the panel members recommend observing the patient.<sup>54,59,60</sup> In patients who have a clinically negative neck, a negative PET/CT is 90% reliable and further imaging is optional.<sup>61-63</sup> Panel members also concur that any patient with residual disease or suspected progression in the neck after RT or chemoradiation should undergo a neck dissection.<sup>54</sup> For patients with more equivocal PET/CT scan results in the neck, a recent study suggests that a repeat PET/CT scan 4 to 6 weeks later may help identify those who can be safely observed without surgery to the neck.<sup>64</sup>

### Postoperative Management of High-Risk Disease

Many factors influence survival and locoregional tumor control in patients with H&N cancers. The role of chemotherapy/RT in the postoperative management of the patient with adverse prognostic risk factors has been clarified by 2 separate multicenter randomized trials for patients with high-risk cancers of the oral cavity, oropharynx, larynx, or hypopharynx<sup>65,66</sup>; long-term follow-up was recently reported for one of the trials.<sup>67</sup> A combined analysis of data from the 2 trials has been performed.<sup>68</sup>

The US Intergroup trial (RTOG 9501) randomly assigned patients with 2 or more involved

nodes, positive margins, or extracapsular nodal spread of tumor to receive standard postoperative RT or the same RT plus cisplatin (100 mg/m<sup>2</sup> every 3 weeks for 3 doses).<sup>66</sup> Long-term results from RTOG 9501 were recently published.<sup>67</sup> The European trial (EORTC 22931) was designed using the same chemotherapy treatment and similar RT dosing but also included as high-risk factors the presence of perineural or perivascular disease and nodal involvement at levels 4 and 5 from an oral cavity or oropharyngeal cancer.<sup>65</sup> 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 been shown to improve survival in this setting in a randomized trial.<sup>69</sup>

To better define risk, a combined analysis of prognostic factors and outcome 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 RT. For those with multiple involved regional nodes without extracapsular spread, no survival advantage was seen.<sup>67,68</sup> The combined analysis was considered exploratory by the authors, because it was not part of the initial protocol design.<sup>68</sup> These publications form the basis for the NCCN recommendations.

In NCCN Member Institutions, patients with extracapsular nodal spread and/or positive surgical margins receive adjuvant chemoradiotherapy after surgery.<sup>69-75</sup> The presence of other adverse risk factors—multiple positive nodes (without extracapsular nodal spread), vascular/perineural invasion, and pT4 primary—are established indications for postoperative RT. 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 RT compared with RT alone, the NCCN Panel added “consider chemoradiation” for these features.<sup>65</sup>

### Salvage Surgery

Patients with advanced carcinoma (any T,N2-3) who undergo nonsurgical primary treatment, such as concurrent chemotherapy/RT, need very close

follow-up both to evaluate for local recurrence and to assess for ipsilateral or contralateral neck recurrence (see FOLL-A, page 1463). For patients who do not have a complete clinical response to chemotherapy/RT, salvage surgery plus neck dissection is recommended as indicated. However, all panel members 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.

Panel members 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.

## H&N Radiotherapy

RT for H&N cancers has grown increasingly complex. The availability and technical precision of intensity-modulated RT (IMRT) has markedly increased, perhaps beyond the current ability to estimate the 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 “Principles of Radiation Therapy” for each site in the NCCN Guidelines are not all-inclusive (available online, in these guidelines, at NCCN.org). 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. Guidelines from the American College of Radiology may be useful for technical details.

### Recent Updates

For the 2014 update, the “Principles of Radiation Therapy” were revised for each site, including glottic larynx (see GLOT-A, page 1462). The maximum dose limits for definitive standard fractionation for areas at high risk for recurrence (ie, primary tumor and high-risk level lymph nodes) were decreased for many sites. For example, the maximum dose limits were decreased to 70 Gy (2 Gy/fraction) for glottic

larynx. For sites of suspected subclinical spread (at low to intermediate risk of recurrence), the doses for IMRT or 3-dimensional conformal RT were clarified for many sites, including glottic larynx.

A new section on “Palliative RT” was added in 2013 and revised for 2014 (see “Radiation Techniques” online, in these guidelines, at NCCN.org). For 2013, the RT sections for each site were revised to include contemporary nomenclature (eg, planning target volume) and the fractionation was revised for clarity. Instead of using the phrase *primary and gross adenopathy*, the high-risk sites are now specified as *primary tumor and involved lymph nodes*. Instead of using the phrase *uninvolved nodal stations*, the intermediate-risk and low-risk sites are now specified as *sites of suspected subclinical spread*. Minimum and maximum dose limits are precisely defined for high-risk sites and intermediate- and low-risk sites.

### 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 GLOT-A, page 1462, and “Radiation Techniques” online, in these guidelines, at NCCN.org). When using conventional definitive fractionation, the primary tumor and involved lymph nodes (ie, high-risk sites) generally require a total of 66 Gy (2.2 Gy/fraction) to 70 Gy (2.0 Gy/fraction).<sup>76–78</sup> For doses greater than 70 Gy, some clinicians feel that the fractionation should be slightly modified (eg, <2.0 Gy/fraction for at least some of the treatment) to minimize toxicity; an additional 2 to 3 doses can be added depending on clinical circumstances. External-beam radiation doses exceeding 72 Gy using conventional fractionation (2.0 Gy/fraction) may lead to unacceptable rates of normal tissue injury.<sup>76,79–83</sup> When using hyperfractionation, high-risk sites generally require up to 81.6 Gy (1.2 Gy/fraction).<sup>76,77</sup>

Elective irradiation to low-risk and intermediate-risk sites requires 44 Gy (2.0 Gy/fraction) to 63 Gy (1.6–1.8 Gy/fraction), depending on the estimated level of tumor burden, and on whether 3-dimensional conformal RT or IMRT is used. For 3-dimensional conformal RT and sequentially planned IMRT, suggest 44 to 50 Gy (2.0 Gy/fraction).<sup>84,85</sup> For IMRT, suggest 54 to 63

Gy (1.6–1.8 Gy/fraction).<sup>85–87</sup> Postoperative irradiation is recommended based on stage, histology, and surgical-pathologic findings. Postoperative RT is recommended for selected risk factors, including advanced T stage, depth of invasion, multiple positive nodes (without extracapsular nodal spread), and perineural/lymphatic/vascular invasion. Higher doses of postoperative RT alone (60–66 Gy), or with chemotherapy, are recommended for the high-risk features of extracapsular disease and/or positive margins.<sup>67,68</sup> The preferred interval is 6 weeks or less between resection and commencement of postoperative RT.

### Fractionation in RT Alone

No single fractionation schedule has proven to be best for all tumors. Data strongly indicate that squamous cancers of the H&N can grow rapidly and may compensate for RT-induced cell loss through the mechanism of accelerated repopulation.<sup>88–90</sup> Especially in RT alone settings, schedules delivering at least 1000 cGy/wk are recommended.<sup>91–95</sup> Trials in early-stage glottic laryngeal cancer have shown higher recurrence rates with daily fraction sizes less than 200 cGy, with a cumulative weekly dose less than 1000 cGy.<sup>96,97</sup>

Randomized trials from Europe have reported improved locoregional control using altered fractionation. The 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. Patients in the accelerated fractionation arm had significantly better locoregional control at 5 years ( $P=.02$ ). Disease-specific survival showed a trend in favor of the accelerated fractionation arm ( $P=.06$ ). Acute and late toxicity were increased with acceleration, however, raising questions about the net advantages of accelerated fractionation.<sup>98</sup> The RTOG reported the results of a 4-armed, phase III, randomized clinical trial (RTOG 90-03) comparing hyperfractionation and 2 variants of accelerated fractionation versus standard fractionation.<sup>76,77,99</sup> 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 with

accelerated fractionation. No significant difference was shown in the frequency of grade 3 or worse late effects reported at 6 to 24 months after treatment start among the various treatment groups. Long-term follow-up confirmed a statistically significant improvement in locoregional control and overall survival with hyperfractionation compared with standard fractionation.<sup>77</sup>

A meta-analysis of updated individual patient data from 15 randomized trials analyzed the effect of hyperfractionated or accelerated RT on the survival of patients with H&N cancers.<sup>100</sup> Standard fractionation constituted the control arm in all of the trials in this meta-analysis.<sup>78</sup> An absolute survival benefit for altered fractionation of 3.4% at 5 years (hazard ratio, 0.92; 95% CI, 0.86–0.97;  $P=.003$ ) was reported. This benefit, however, was limited to patients younger than 60 years.<sup>100</sup> Hyperfractionation was associated with a benefit of 8% after 5 years.<sup>101</sup> However, the recent GORTEC 99-02 trial reported that altered fractionation did not improve outcomes compared with conventional fractionation.<sup>102,103</sup> Consensus regarding altered fractionation schedules with concomitant boost or hyperfractionation for stage III or IV oral cavity, oropharynx, supraglottic larynx, and hypopharyngeal squamous cell cancers has not yet emerged among NCCN Member Institutions.<sup>100,104,105</sup>

### Fractionation in Concurrent Chemoradiation

Panel members do not agree about the optimal radiation dose fractionation scheme to use with concurrent chemotherapy. Most published studies have used conventional fractionation (at 2.0 Gy/fraction, to a typical dose of 70 Gy in 7 weeks) with single-agent high-dose cisplatin (given every 3 weeks at 100 mg/m<sup>2</sup>).<sup>106</sup> Other fraction sizes (eg, 1.8 Gy, conventional), cisplatin dosing schedules, 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.<sup>105,107–109</sup> RTOG 0129 assessed accelerated fractionation with 2 cycles of concurrent cisplatin versus standard fractionation with 3 cycles of concurrent cisplatin. No significant difference was seen in overall survival between the arms.<sup>106,110</sup>

Concurrent chemoradiation increases acute toxicity compared with radiation alone, although an

increase in late toxicity beyond that caused by RT alone is less clear.<sup>111–113</sup> Altered fractionation and/or multiagent chemotherapy may further increase the toxicity burden.<sup>114</sup> 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.

### IMRT and Palliative RT

The intensity of the radiation beam can be modulated to decrease doses to normal structures without compromising the doses to the cancer targets.<sup>115,116</sup> IMRT is an advanced form of conformal RT permitting more precise cancer targeting while reducing dose to normal tissues.<sup>85,117–121</sup> Xerostomia is a common long-term side effect of RT, which can be reduced with use of IMRT, drug therapy (eg, pilocarpine, cevimeline), salivary substitutes, and other novel approaches (eg, acupuncture).<sup>122–127</sup>

*IMRT dose painting* refers to the method of assigning different dose levels to different structures within the same treatment fraction (eg, 2.0 to gross tumor, 1.7 to microscopic tumor, <1.0 Gy to parotid gland) resulting in different total doses to different targets (eg, 70 Gy, 56 Gy, <26 Gy).<sup>128,129</sup> Although dose painting has been used to simplify radiation planning, hot spots associated with higher toxicity can occur.<sup>129,130</sup> 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-a-day schemas (see “Radiation Techniques” online, in these guidelines, at NCCN.org).<sup>120,131</sup>

IMRT is now widely used in H&N cancers and is the predominant technique used at NCCN Member Institutions.<sup>132,133</sup> It is useful in reducing long-term toxicity.<sup>86,123,124,134–141</sup> Overall survival is similar between patients treated with IMRT and those receiving conventional RT.<sup>135,142–144</sup> In-field recurrences, low-grade mucositis in areas away from the cancer targets, and posterior neck hair loss can occur with IMRT.<sup>145–148</sup> The application of IMRT to the larynx is evolving.<sup>149–156</sup>

A new section on palliative RT was recently added to the NCCN Guidelines (see “Radiation Techniques” online, in these guidelines, at NCCN.org). Although several palliative RT regimens are provided, no single regimen is preferred; specific

regimens vary widely among NCCN Member Institutions.<sup>157–159</sup> Any palliative RT regimen that might cause severe toxicities should be avoided. More hypofractionated regimens may be useful for patients with end-stage disease.<sup>160</sup>

### Follow-up After RT

For patients whose cancer has been treated with RT, the recommended follow-up (see FOLL-A, page 1463) includes an assessment of thyroid function (ie, 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; patients are at increased risk of hypothyroidism.<sup>161–163</sup>

### Principles of Nutrition and Supportive Care

A new section on “Principles of Nutrition” was recently added to these NCCN Guidelines (to view the most recent version, visit NCCN.org). This section outlines nutritional management and supportive care for patients with H&N cancers who are prone to weight loss, which can often be severe, as a result of treatment-related toxicity, disease, and health behaviors such as poor nutritional habits.<sup>7,164,165</sup> Patients with H&N cancers are also at risk for dehydration. Multidisciplinary evaluation is integral to minimizing or decreasing weight loss and should involve a registered dietitian and a speech-language/swallowing therapist.

Patients who have experienced significant weight loss (>10% body weight) clearly need nutritional evaluation and close monitoring of their weight to prevent further weight loss.<sup>166,167</sup> All patients should receive nutritional evaluation before and after treatment to assess the need for interventions (eg, enteral support via feeding tubes).<sup>168,169</sup> Patients are also at risk for problems with speech. Treatment and/or the progression of their disease may cause deterioration in their ability to speak and/or swallow.<sup>170–172</sup> Evaluation by a speech-language/swallowing therapist is valuable before and after treatment, because it can help mitigate potential problems.<sup>173–175</sup> Patients are also at risk for dental problems (see DENT-A, page

1464, and “Principles of Dental Evaluation and Management,” next section).<sup>7</sup>

NCCN Panel Members agree that reactive feeding tube placement is appropriate in selected patients with H&N cancers.<sup>165,169</sup> No consensus exists about whether prophylactic tube placement is appropriate, although this is commonly done if high-risk patients will be receiving intense multimodality therapy that is anticipated to cause severe problems (eg, concurrent chemoradiation).<sup>165,167,176</sup> These NCCN Guidelines provide recommendations for prophylactic tube placement, which should be strongly considered in high-risk patients (eg, those with severe pretreatment weight loss, ongoing dehydration or dysphagia, significant comorbidities, severe aspiration, anticipated swallowing issues; see “Principles of Nutrition: Management and Supportive Care” online, in these guidelines, at NCCN.org). These NCCN Guidelines do not recommend prophylactic tube placement in lower-risk patients (ie, those without significant pretreatment weight loss, significant aspiration, or severe dysphagia), although these patients need to carefully monitor their weight.

## Principles of Dental Evaluation and Management

For the 2014 update, a new section on “Principles of Dental Evaluation and Management” was added (see DENT-A, page 1464). Patients with H&N are at risk of oral and dental complications after RT because of treatment-induced xerostomia and salivary gland dysfunction, which are associated with increased dental caries.<sup>177–179</sup> RT to the dental hard tissues is also associated with bone demineralization and trismus of the masticatory muscles. Using IMRT and limiting the RT dose to the teeth have been shown to decrease xerostomia and damage to the teeth.<sup>177,178,180–187</sup> Dental/oral evaluation and management can help decrease dental caries and associated problems, such as dentoalveolar infection and osteoradionecrosis.<sup>179,180,187–200</sup>

The recommended dental/oral evaluations before, during, and after RT are described in detail in the algorithm and summarized in this section. A dental/oral treatment plan must be implemented before RT and should include the following:

(1) eliminating potential sources of infection; (2) performing any dental extractions at least 2 weeks before RT; (3) treating active dental caries and periodontal disease; (4) treating oral candidiasis; and (5) educating patients about preventive strategies.<sup>188</sup> Some of the strategies to decrease oral and dental complications are to (1) decrease dry mouth (eg, by using salivary substitutes and stimulation);<sup>201–205</sup> (2) decrease dental caries (eg, by using topical fluoride);<sup>189,206–210</sup> (3) decrease dentoalveolar infection (eg, with frequent evaluations to detect and treat disease promptly); (4) decrease osteoradionecrosis (eg, by extracting teeth before RT);<sup>192</sup> (5) decrease trismus of the masticatory muscles (eg, by using custom mouth opening devices to maintain range of motion);<sup>211–213</sup> and (6) evaluate during and after treatment to help minimize complications.<sup>201,202,208,214,215</sup>

During and after treatment, the goals of dental/oral management include managing xerostomia, preventing trismus; and detecting and treating oral candidiasis.<sup>188</sup> Additional goals after treatment include preventing and treating dental caries, preventing postradiation osteonecrosis, and preventing oral candidiasis.<sup>188</sup>

## Cancer of the Larynx

These NCCN Guidelines focus on cancer of the glottic larynx, which is the most common type of laryngeal cancer. The larynx is divided into 3 regions: supraglottis, glottis, and subglottis. The distribution of cancers is as follows: 30% to 35% in the supraglottic region, 60% to 65% in the glottic region, and 5% in the subglottic region. Supraglottic laryngeal cancer is described in the complete version of these NCCN Guidelines (see “Cancer of the Supraglottic Larynx,” available online at NCCN.org). Subglottic laryngeal cancer is not discussed in these NCCN Guidelines, because it is so uncommon. The incidence and pattern of metastatic spread to regional nodes vary with the primary region. The lymphatic drainage of the glottis is sparse, and early-stage primaries rarely spread to regional nodes. Because hoarseness is an early symptom, most glottic laryngeal cancer is early stage at diagnosis. Thus, cancer of the glottic larynx has an excellent cure rate of 80% to 90%. Nodal involvement adversely affects survival rates.

### Workup and Staging

Evaluation of the patient to determine tumor stage is shown in the algorithm (see GLOT-1, page 1456). Multidisciplinary consultation is critical because of the potential for loss of speech and, sometimes, for swallowing dysfunction (see “Principles of Nutrition: Management and Supportive Care” online, in these guidelines, at NCCN.org). The 2010 AJCC staging classification (7th edition) for laryngeal primary tumors is determined by the number of subsites involved, vocal cord mobility, and the presence of metastases (see Table 3 online, in these guidelines, at NCCN.org [ST-6]).<sup>5</sup>

### Treatment

In the NCCN Guidelines, the treatment of patients with laryngeal cancer is divided into 2 categories: tumors of the glottic larynx and tumors of the supraglottic larynx. For the 2104 update, extensive revisions were made to the radiation guidelines for laryngeal cancer (see GLOT-A, page 1462).

For patients with carcinoma in situ of the larynx, recommended treatment options include endoscopic removal (ie, stripping, laser), which is preferred, or RT.<sup>216,217</sup> For early-stage glottic cancer, surgery (partial laryngectomy) or RT have similar effectiveness (see GLOT-2, page 1457).<sup>218</sup> The choice of treatment modality depends on anticipated functional outcome, the patient's wishes, reliability of follow-up, and general medical condition. Adjuvant treatment depends on the presence (or absence) of adverse features. Based on the recent update of RTOG 95-01, the panel deleted the recommendation for “consider [adjuvant] chemotherapy/RT” for patients with T2,N0 glottic cancer with either other risk features or positive margins.<sup>67</sup> The long-term update of RTOG 95-01 reported that locoregional control and disease-free survival were not improved with the addition of adjuvant chemotherapy/RT compared with RT alone in patients with 2 or more involved lymph nodes. However, an unplanned subgroup analysis did show improvement in locoregional control and disease-free survival in patients with extracapsular spread and/or positive margins.

Resectable, advanced-stage glottic primaries are usually managed with a combined modality

approach (see GLOT-3, page 1458). If treated with primary surgery, total laryngectomy is usually indicated, although selected cases can be managed with conservation surgical techniques that preserve vocal function. Pulmonary function tests should be considered before surgery. If total laryngectomy is indicated but laryngeal preservation is desired, concurrent systemic therapy/RT is recommended.<sup>219,220</sup> When using systemic therapy/RT, high-dose cisplatin (category 1) is preferred (at 100 mg/m<sup>2</sup> on days 1, 22, and 43).<sup>219</sup>

Induction chemotherapy with management based on response is an option (either category 2A or 2B, depending on the setting) for all but T1–2,N0 glottic cancer. Based on the long-term update of RTOG 91-11, panel members added an option for the use of induction chemotherapy when patients require (are amenable to) total laryngectomy (see GLOT-3, page 1458, and “The Induction Chemotherapy Controversy” online, in these guidelines, at NCCN.org).<sup>219</sup> The panel revised the recommendations for the use of induction chemotherapy from category 3 to category 2A for T3,N2–3 when patients require total laryngectomy (see GLOT-4, page 1459, and “The Induction Chemotherapy Controversy” online, in these guidelines, at NCCN.org).<sup>219</sup> Definitive RT (without chemotherapy) is an option for patients with T3,N0–1 disease who are medically unfit or refuse chemotherapy (see GLOT-3, page 1458). Surgery is reserved for managing the neck as indicated, for patients whose disease persists after chemotherapy/RT or RT, or for patients who develop a subsequent locoregional recurrence (see “Postchemoradiation or RT Neck Evaluation in Principles of Surgery” online, in these guidelines, at NCCN.org).

The NCCN recommendations for managing locally advanced, resectable glottic cancers (in which total laryngectomy is indicated but laryngeal preservation is desired) with concurrent cisplatin and radiation are based on Intergroup trial R91-11.<sup>219,220</sup> Before 2002, either induction chemotherapy with cisplatin/5-FU followed by RT (based on the VA Laryngeal Cancer Study Group trial<sup>221</sup>) or definitive RT alone (without chemotherapy) were the standard-of-care options recommended in these NCCN Guidelines. However, concurrent RT and systemic therapy (eg, cisplatin

100 mg/m<sup>2</sup>, preferred [category 1]) is now the recommended option for achieving laryngeal preservation.<sup>219,220</sup> R91-11 was a successor trial to the VA trial and compared 3 nonsurgical regimens: (1) induction cisplatin/5-FU followed by RT (control arm and identical to that in the VA trial); (2) concurrent RT and high-dose cisplatin 100 mg/m<sup>2</sup> on days 1, 22, and 43; and (3) RT alone. RT was uniform in all 3 arms (70 Gy/7 weeks, 2 Gy/fraction), as was the option of surgery (including total laryngectomy) for treatment failures in all arms. Patients with stage III and IV (M0) disease were eligible, excluding T1 primaries and high-volume T4 primaries (tumor extending more than 1 cm into the base of the tongue or tumor penetrating through cartilage).

The key findings of the R91-11 trial were (1) a statistically significant higher 2-year laryngeal preservation (local control) rate of 88% for concurrent RT with cisplatin, compared with 74% for induction chemotherapy and 69% for RT alone; (2) no significant difference in laryngeal preservation between induction and RT-alone treatments; and (3) similar survival for all treatment groups. These R91-11 results changed the standard of care to concurrent RT and systemic therapy (cisplatin preferred [category 1]) for achieving laryngeal preservation for most T3, any N glottic cancers.<sup>220</sup> Recent long-term follow-up (10 years) of R91-11 indicates that laryngeal preservation continues to be better (ie, statistically different) with concurrent cisplatin/RT compared with either induction chemotherapy or RT alone.<sup>219</sup> Overall survival was not statistically different for all treatment groups; more non-cancer-related mortality was seen among patients treated with concurrent cisplatin/RT.

For patients with glottic T4a tumors, the standard approach is total laryngectomy with thyroidectomy and neck dissection as indicated (depending on node involvement) followed by adjuvant treatment (see GLOT-6, page 1461, and “Principles of Surgery” online, in these guidelines, at NCCN.org). For patients with glottic T4a laryngeal cancer, postoperative observation is an option for highly selected patients with good-risk features (eg, indolent histopathology). For selected patients with T4a tumors who decline surgery, the NCCN Panel recommends considering con-

current chemoradiation, clinical trials, or induction chemotherapy with additional management based on response.<sup>219,220</sup>

### Follow-up/Surveillance

Recommendations for surveillance are provided in the algorithm (see FOLL-A, page 1463). Follow-up examinations in many of these patients may need to be supplemented with serial endoscopy or high-resolution, advanced radiologic imaging techniques because of the scarring, edema, and fibrosis that occur in the laryngeal tissues and neck after high-dose radiation.

### Very Advanced H&N Cancers

Very advanced H&N cancers include (1) newly diagnosed locally advanced T4b (M0) tumors; (2) newly diagnosed unresectable nodal disease; (3) metastatic disease; (4) recurrent or persistent disease; or (5) patients unfit for surgery. The treatment goal is cure for patients with newly diagnosed but unresectable disease (see “Resectable Versus Unresectable Disease,” page 1467). For the recurrent disease group, the goal is cure (if surgery or radiation remains feasible) or palliation (if the patient has received previous RT and the disease is unresectable). For patients with metastatic disease, the goal is palliation or prolongation of life.

### Treatment

Participation in clinical trials is preferred for all patients with very advanced H&N cancers. For the 2014 update, extensive revisions were made to the radiation guidelines (see “Principles of Radiation Therapy” in “Very Advanced Head and Neck Cancer” [ADV-A] online, in these guidelines, at NCCN.org, and “H&N Radiotherapy,” page 1470).

### 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 systemic therapy and RT (with high-dose cisplatin as the preferred [category 1] systemic agent).<sup>222</sup> Other category 1 systemic therapy/RT options include carboplatin/5-FU or (2) cetuximab.<sup>102,223</sup> Other recommended systemic therapy/RT options are listed in the guidelines (see “Principles of Systemic Therapy” online, in these guidelines, at NCCN.org). The NCCN Panel had

a major disagreement regarding whether induction chemotherapy (eg, cisplatin/docetaxel/5-FU) followed by RT or chemoradiation should be used for patients with a PS of 0 or 1, which is reflected in the category 3 recommendation (see also “The Induction Chemotherapy Controversy” online, in these guidelines, at NCCN.org).<sup>224,225</sup> Other options for patients with PS of 2 to 3 are described in the algorithm (see “Very Advanced Head and Neck Cancer” [ADV-A] online, in these guidelines, at NCCN.org).

Many randomized trials<sup>69,108,109,222,226–231</sup> and meta-analyses of clinical trials<sup>232–235</sup> show significantly improved overall survival, disease-free survival, and local control when a concomitant or alternating chemotherapy and radiation regimen is compared with RT alone for advanced disease. All combined chemoradiotherapy regimens are associated with mucosal toxicities, which require close monitoring of patients, ideally by a team experienced in treating patients with H&N cancers. Limited data are available comparing the efficacy of different chemoradiotherapy regimens. High-dose cisplatin plus RT is effective and easy to administer and typically uses 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<sup>2</sup> (see “Very Advanced Head and Neck Cancer” [ADV-A] online, in these guidelines, at NCCN.org).<sup>222</sup>

Bonner et al<sup>236</sup> randomly assigned 424 patients with locally advanced and measurable stage III to IV squamous cell carcinomas of the H&N to receive definitive RT with or without cetuximab. Locoregional control and median overall survival (49.0 vs. 29.3 months;  $P=.03$ ) were significantly improved in patients treated with RT and cetuximab compared with RT alone. RT and cetuximab (category 1) may provide a therapeutic option for patients not considered medically fit for standard chemoradiotherapy regimens. Other chemoradiation options (eg, carboplatin/5-FU [category 1]) are also recommended by the NCCN Panel (see “Principles of Chemotherapy” online, in these guidelines, at NCCN.org).<sup>102,237,238</sup> Limited data are available comparing combination chemoradiation versus using a single agent concurrently with RT.

### Recurrent or Persistent Disease

Surgery is recommended for resectable recurrent or persistent locoregional disease; adjuvant therapy

depends on the risk factors (see “Very Advanced Head and Neck Cancer” [ADV-A] online, in these guidelines, at NCCN.org). If the recurrence is unresectable and the patient did not have prior RT, then RT with concurrent systemic therapy is recommended, depending on the PS (see “Very Advanced Head and Neck Cancer” [ADV-A] online, in these guidelines, at NCCN.org). For patients with recurrent disease not amenable to curative-intent radiation or surgery, the treatment approach is the same as that for patients with metastatic disease; enrollment in a clinical trial is preferred. The “Principles of Radiation Therapy” were extensively revised for patients with very advanced H&N cancers (available online, in these guidelines; see also “H&N Radiotherapy,” page 1470).

### Metastatic Disease

Palliative adjunctive measures include RT to areas of symptomatic disease, analgesics, and other measures to control other manifestations of disease spread (eg, hypercalcemia). Single agents and combination systemic chemotherapy regimens are both used (see “Principles of Chemotherapy” in the complete version of the NCCN Guidelines for H&N Cancers at NCCN.org).<sup>239</sup> Unless otherwise specified, regimens or single agents can be used for non-nasopharyngeal cancer (see “Principles of Systemic Therapy” online, in these guidelines, at NCCN.org). Response rates to single agents range from 15% to 35%.<sup>240–242</sup> Active and more commonly used single agents include cisplatin, carboplatin, paclitaxel, docetaxel, 5-FU, methotrexate, capecitabine, cetuximab (for non-nasopharyngeal cancer), and vinorelbine (for non-nasopharyngeal cancer).<sup>239,242–260</sup> For the 2014 update, the panel revised the recommendations to category 2B for both ifosfamide and bleomycin because these agents are less commonly used; previously these agents had a category 2A recommendation.

Active combination regimens include (1) cisplatin or carboplatin, plus 5-FU with cetuximab (for non-nasopharyngeal cancer only) (category 1);<sup>261</sup> (2) cisplatin or carboplatin, plus a taxane;<sup>262,263</sup> (3) cisplatin with cetuximab (for non-nasopharyngeal cancer only);<sup>244</sup> or (4) cisplatin with 5-FU.<sup>249,263</sup> These combination regimens, on average, result in a doubling of response rates

compared with single agents. Randomized trials assessing a cisplatin-based combination regimen (eg, cisplatin plus 5-FU) versus single-agent therapy with cisplatin, 5-FU, or methotrexate have shown significantly higher response rates, but no difference in overall survival, for the combination regimen.<sup>243,249,263–265</sup> Historically, the median survival with chemotherapy is approximately 6 months for patients with metastatic disease, and the 1-year survival rate is approximately 20%. Complete response is associated with longer survival and, although infrequent, has been reported more often with combination regimens.<sup>249</sup> A randomized phase III trial in patients with metastatic or recurrent H&N cancers found no significant difference in survival when comparing cisplatin plus 5-FU with cisplatin plus paclitaxel.<sup>263</sup> Activation of epidermal growth factor receptor (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 squamous cell carcinomas of the H&N. This finding has led to the development of EGFR inhibitors, such as the monoclonal antibody cetuximab and small molecule tyrosine kinase inhibitors (ie, erlotinib, 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<sup>244</sup> 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). 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 when compared with the standard chemotherapy doublet (10.1 vs 7.4 months;  $P=.04$ ).<sup>261</sup> The response rate was also improved with cetuximab (36% vs 20%;  $P<.001$ ). In one randomized trial, treatment with 2 different dosing schedules of gefitinib offered no survival advantage compared with treatment with methotrexate.<sup>248</sup> Available data for novel agents have not established them as treatment options for recurrent or metastatic H&N cancers outside of a clinical trial.<sup>266,267</sup>

For the 2014 update, the NCCN Panel added new combination regimens for recurrent, unresectable, or metastatic non-nasopharyngeal cancer: cisplatin/docetaxel/cetuximab<sup>268</sup> and cisplatin/paclitaxel/cetuximab.<sup>242,269</sup> For the cisplatin/docetaxel/cetuximab regimen, the median progression-free survival was 7.1 months and overall survival was 15.3 months, and the 1-year overall survival rate was 58.6%. This newer taxane-based regimen has impressive overall survival and is an option for patients with good PS. However, standard of care for recurrent, unresectable, or metastatic non-nasopharyngeal cancer are the category 1 regimens from the EXTREME trial of cetuximab plus cisplatin/5-FU or carboplatin/5-FU.<sup>261</sup> The standard treatment of patients with incurable, persistent, recurrent, or metastatic H&N cancers should be dictated largely by the patient's PS (see "Very Advanced Head and Neck Cancer" [ADV-A] online, in these guidelines, at NCCN.org). Patients should be fully informed about the goals of treatment, cost of combination chemotherapy, and potential for added toxicity.

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## Head and Neck Cancers, Version 2.2014

Individual Disclosures of the NCCN Head and Neck Cancers Panel					
Panel Member	Clinical Research Support/Data Safety Monitoring Board	Advisory Boards, Speakers Bureau, Expert Witness, or Consultant	Patent, Equity, or Royalty	Other	Date Completed
David M. Brizel, MD	None	Sobi Pharmaceuticals; Threshold Pharmaceuticals; and Pfizer Inc.	None	None	6/16/14
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Sharon Spencer, MD	None	None	None	None	6/13/14
Randal S. Weber, MD	None	None	None	None	6/5/14
Gregory T. Wolf, MD	None	IRX Therapeutics	None	None	5/2/14
Frank Worden, MD	Pfizer Inc.	Baxter International Inc.; Bristol-Myers Squibb Company; and Onyx Pharmaceuticals, Inc.	None	None	1/10/14
Sue S. Yom, MD, PhD	Genentech, Inc.	None	None	None	5/4/14

The NCCN guidelines staff have no conflicts to disclose.