National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Head and Neck Cancers

Version 1.2016

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Head and Neck Cancers

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NCCN Guidelines Panel Disclosures

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NCCN Guidelines Version 1.2016 Sub-Committees
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Head and Neck Cancers

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

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/physician.html.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise specified.

See NCCN Categories of Evidence and Consensus.

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NCCN Guidelines Version 1.2016 Updates
Head and Neck Cancers

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Head and Neck Table of Contents
Discussion

Updates in Version 1.2016 of the NCCN Guidelines for Head and Neck Cancers from Version 1.2015 include:

Global Changes

- Footnote regarding H&P for workup revised for all sites: "*H&P should include documentation and quantification (pack years smoked) of tobacco use history*. Smoking cessation counseling as clinically indicated..."
- Under "Workup," "PET/CT" clarified as "*FDG*-PET/CT."

TEAM-1

- Multidisciplinary Team:
  - New sentence added, "...optimal treatment and follow-up. *Outcomes are improved when patients with head and neck cancers are treated in high-volume centers*."
  - Specialty revised: "*Clinical* nutrition ~~support~~"
- Support Services: Revised, "Oral *nutrition* ~~supplements~~."

Cancer of the Lip

LIP-1

- Workup: Fourth bullet, second arrow-sub-bullet revised: "CT and/or MRI *with contrast* of primary and neck."
- "T3, T4a, N0; Any T, N1-3" pathway: "Poor surgical risk" changed to "*Unfit for surgery*."

LIP-2

- Treatment of Primary and Neck for T1-2, N0
  - A new treatment pathway was added for "*Consider resection of primary ± sentinel lymph node (SLN) biopsy (category 2B)*."
  - Fourth column: Language revised, "No adverse pathologic findings; *No positive nodes*."

Cancer of the Oral Cavity

OR-1

- Workup; Eighth bullet revised: "Dental/prosthodontic evaluation, including ~~jaw imaging~~ *Panorex or CT ± contrast* as clinically indicated."

Cancer of the Oropharynx

ORPH-1

- Footnote c regarding HPV testing revised: "~~Either immunohistochemistry for analysis of p16 expression or HPV in-situ hybridization for detection of HPV DNA in tumor cell nuclei is recommended~~. *P16 expression is highly correlated with HPV status and is widely available. HPV in situ hybridization or PCR-based assay is also available.* Although not used to guide treatment, HPV testing is valuable prognostically..."

ORPH-2

- Adjuvant Treatment for T1-2, N0-1: For patients with extracapsular spread ± *positive margins, "Systemic therapy/RT" changed from category 1 to category 2A.* Corresponding footnote j is new: *"The recommendations for patients at high risk with extracapsular spread + positive margins are based on randomized studies involving patients for whom the HPV status of their tumors was not specified."*

ORPH-3

- Adjuvant Treatment for T3-4a, N0-1: For patients with extracapsular spread *and/or positive margins, "Systemic therapy/RT" changed from category 1 to category 2A.* (Similar change also made for ORPH-4)

Continued

Cancer of the Oropharynx--continued

ORPH-A 1 of 2 Principles of Radiation Therapy

- **Reference 3 revised: "~~Lee NY, Zhang Q, Pfister DG, et al. Addition of bevacizumab to standard chemoradiation for locoregionally advanced nasopharyngeal carcinoma (RTOG 0615): a phase 2 multi-institutional trial. Lancet Oncol 2012;13:172-180~~. *Eisbruch A, Harris J, Garden AS, et al. Multi-institutional trial of accelerated hypofractionated intensity-modulated radiation therapy for early-stage oropharyngeal cancer (RTOG 00-22). Int J Radiat Oncol Biol Phys 2010;76:1333-1338.*" (Also for HYPO-A)**

Cancer of the Hypopharynx

HYPO-5

- **Treatment of Primary and Neck; T4a, any N: Revised "Surgery + neck dissection ~~(preferred)~~."**

Cancer of the Nasopharynx

NASO-1

- **Workup revised:**
  - **Fourth bullet: "MRI with ~~gadolinium~~ *contrast* including base of skull..."**
  - **Sixth bullet: "~~Imaging~~ *CT scan with contrast or FDG-PET/CT* of the upper mediastinum/chest as clinically indicated"**
  - **Eighth bullet: "Imaging for distant metastases (ie, chest, liver, bone) may include *FDG*-PET/CT and/or ~~other imaging modalities~~ *CT scan with contrast*..."**

NASO-2

- **Treatment of Primary and Neck**
  - **T1, N1-3; T2-T4, any N: "*Multimodality clinical trials (preferred)*" added as an option.**
  - **Any T, any N, M1: "*Clinical trials (preferred)*" added as an option.**

Cancer of the Glottic Larynx

GLOT-1

- **Workup; Fourth bullet revised: "CT with contrast and thin cuts through larynx and/or MRI *with contrast* of primary and neck."**
- **Footnote a revised: "Complete workup may not be indicated for Tis, T1, but history and physical examination *are required*. Direct laryngoscopy and biopsy under anesthesia are ~~required~~ *generally recommended*."**

GLOT-2

- **Treatment of Primary and Neck; Amenable to larynx-preserving (conservation) surgery (T1-T2 or select T3): Recommendation revised, "Partial laryngectomy/ endoscopic or open resection as indicated ~~or~~ *and* neck dissection as indicated."**

GLOT-4

- **Treatment of Primary and Neck; T3 requiring (amenable to) total laryngectomy (N2-3): Recommendation revised, "Laryngectomy with ~~ipsilateral~~ thyroidectomy as indicated, ipsilateral, *central, or* bilateral neck dissection."**

Continued

Cancer of the Supraglottic Larynx

SUPRA-2

- Pathology Stage
  - Pathway revised: "Positive node; Adverse features: positive margins ~~or other risk features~~."
  - New pathway added: "*Positive node; Other adverse risk features.*"
- Footnote g regarding adjuvant treatment revised: "*In highly select patients,* ~~consider~~ re-resection to achieve negative margins, if feasible."

SUPRA-3

- Treatment of Primary and Neck; Requiring (amenable to) total laryngectomy (T3, N0).: Revised, "Laryngectomy, ~~ipsilateral~~ thyroidectomy and with ipsilateral*, central,* or bilateral neck dissection."

SUPRA-5

- Footnote m regarding adjuvant treatment is new: "*In highly select patients, re-resection (if negative margins are feasible and can be achieved without total laryngectomy) where it would potentially change the subsequent indication for chemotherapy.*"

Ethmoid Sinus Tumors

ETHM-1

- Workup; Second bullet revised: "CT *with contrast* or MRI *with contrast of* skull base."

ETHM-A Principles of Radiation Therapy (Also for **MAXI-A**)

- Postoperative Chemoradiation: Recommendation revised, "Concurrent single-agent cisplatin ~~at 100 mg/m^2 every 3 weeks is recommended.~~"

Maxillary Sinus Tumors

MAXI-1

- Workup; Second bullet revised: "Complete head and neck CT with contrast and/or MRI *with contrast*."

MAXI-2

- Adjuvant Treatment; T1-2, N0 Adenoid cystic: After "Infrastructure," recommendation revised: "*Consider* observation *for margin negative, no perineural spread.*"

Very Advanced Head and Neck Cancer

ADV-3

- Recurrent or Persistent disease; Locoregional recurrence or second primary with prior RT; Treatment for "Resectable disease": Recommendation revised, "Surgery ± *postoperative* reirradiation ~~± systemic therapy,~~ *or systemic therapy/RT*, clinical trial preferred."
- Footnote g is new: "*Reirradiation should be limited to a highly select subset of patients (Janot F, de Raucourt D, Benhamou E, et al. Randomized trial of postoperative reirradiation combined with chemotherapy after salvage surgery compared with salvage surgery alone in head and neck carcinoma. J Clin Oncol 2008;26:5518-5523).*"

Occult Primary

OCC-1

- Workup for Squamous cell carcinoma, adenocarcinoma, and anaplastic/undifferentiated epithelial tumors: Second bullet revised, "CT with contrast or MRI with ~~gadolinium~~ *contrast* (skull base through thoracic inlet)."

OCC-3

- Definitive Treatment recomendations revised:
  - "Surgery (preferred for < N2 disease)" changed to "Surgery (preferred for *N1* disease)."
  - "RT for < N2 (category 2B)" changed to "RT for *N1* (category 2B)."

Salivary Gland Tumors

SALI-1

- Workup: Second bullet revised, "CT/MRI *with contrast,* if clinically indicated."

SALI-A Principles of Radiation Therapy

- Footnote 2 is new: *"Neutrons are still used in selected patients (Pfister DG, Spencer S, Brizel DM, et al. NCCN Head and Neck Cancers, Version 1.2015. J Natl Compr Canc Netw 2015;13:847-856)."*

Continued

Mucosal Melanoma

MM-1

- **Workup: Third bullet revised, "CT *with contrast* and/or MRI *with contrast* to determine anatomic extent of disease..."**

MM-A Principles of Radiation Therapy

- **Footnote 2: New reference added, "*Moreno MA, Roberts DB, Kupferman ME, et al. Mucosal melanoma of the nose and paranasal sinuses, a contemporary experience from the M. D. Anderson Cancer Center. Cancer 2010;116:2215-2213.*"**

FOLL-A Follow-up Recommendations

1 of 2

- **New bullet added: "*For response assessment immediately after chemoradiation or RT (see FOLL-A 2 of 2).*"**

2 of 2

- **The "Post Chemoradiation or RT Neck Evaluation" page was moved to the "Follow-up Recommendations" section. Previously it was part of the "Principles of Surgery" pages.**

SURG-A Principles of Surgery

1 of 8

- **Evaluation; First bullet revised: "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~~ *options, including those applicable* if initial *non-surgical* treatment is ~~non-surgical~~ *unsuccessful*."**

2 of 8

- **Primary Tumor Resection: Last bullet revised, "Transoral robotic *surgery (TORS)* or laser-assisted resections of primary cancers in the oral cavity, larynx..."**

5 of 8

- **Neck Management**
  - **First bullet revised, "...both sides of the neck are at risk for metastases, and bilateral neck dissections should be performed. ~~Elective neck dissection may not be recommended if postoperative radiation is planned.~~"**
  - **Second bullet revised: "Elective neck dissection should be based on risk of occult metastasis in the appropriate nodal basin. For oral cavity squamous cell carcinoma, *sentinel lymph node biopsy or the primary tumor* depth of invasion is currently the best predictor of occult metastatic disease and should be used to guide decision making...For a depth of 2–4 mm, clinical judgment (as to reliability of follow-up, clinical suspicion, and other factors) must be utilized to determine appropriateness of elective dissection. *Recent randomized trial evidence supports the effectiveness of elective neck dissection in patients with oral cavity cancers >3 mm in depth of invasion.* Elective..."**

Continued

SURG-A Principles of Surgery (continued)
6 of 8
- **Sentinel Lymph Node Biopsy: Second bullet revised, "...Also, cancers of certain locations such as upper gingiva and hard palate may not lend themselves well technically to this procedure. *Likewise, occult cervical metastases are uncommon in early lip cancer, but SLN has been shown to be feasible and effective in patients with lip cancers deemed to be at high risk of metastases generally based on tumor size or depth*.**

8 of 8
- **New references added**
  - ***D'Cruz AK, Vaish R, Kapre N, et al; Head and Neck Disease Management Group. Elective versus therapeutic neck dissection in node-negative oral cancer. N Engl J Med 2015;373:521-529.***
  - ***Sollamo MK, Limonen SK, Virolainen MS, Suominem SH. Sentinel lymph node biopsy in cN0 squamous cell carcinoma of the lip: a retrospective study. Head Neck; 2015 Oct 30 [epub ahead of print].***

RAD-A Radiation Techniques
1 of 3
- **New sentence added to introductory paragraph: "...Close cooperation and interdisciplinary management are critical to treatment planning and radiation targeting, especially in the postoperative setting or after induction chemotherapy. *FDG-PET/CT or MRI with contrast can be used for fusion in treatment planning*."**

2 of 3
- **New section added on "*Reirradiation With 3-D Conformal RT, SBRT, or IMRT.*"**

3 of 3
- **New references added to corresponded with new addition on page 2 of 3.**

CHEM-A Principles of Systemic Therapy
1 of 5
- **Squamous Cell Cancers: For postoperative chemoradiation revised, "Cisplatin (category 1 for high-risk *non-oropharyngeal cancers).*"**

2 of 5
- **Section title revised, "Recurrent, Unresectable, or Metastatic (~~incurable~~ *with no surgery or RT option*)."**
- **Under "Single agents" the following was added: "*Afatinib (category 2B) (non-nasopharyngeal, second line).*"**

NUTR-A (1 of 2) Principles of Nutrition
Assessment and Management; Nutrition: First arrow sub-bullet revised, "Close monitoring of nutritional status is recommended in patients who have: 1) significant weight loss ~~(>10% body weight)~~ *(5% weight loss over prior 1 month, or 10% weight loss over 6 months)*; and/or..."

MULTIDISCIPLINARY TEAM

The management of patients with head and neck cancers is complex. All patients need access to the full range of support services and specialists with expertise in the management of patients with head and neck cancer for optimal treatment and follow-up. Outcomes are improved when patients with head and neck cancers are treated in high-volume centers.

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

SUPPORT SERVICES

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

- General medical care
- Pain and symptom management
  (See NCCN Guidelines for Adult Cancer Pain)
- Nutritional support
  - Enteral feeding
  - Oral nutrition
- Dental care for RT effects
- Xerostomia management
- Smoking and alcohol cessation
- Speech and swallowing therapy
- Audiology
- Tracheotomy care
- Wound management
- Depression assessment and management
  (See NCCN Guidelines for Distress Management)
- Social work and case management
- Supportive care
  (See NCCN Guidelines for Palliative Care)

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

NCCN Guidelines Version 1.2016
Cancer of the Lip

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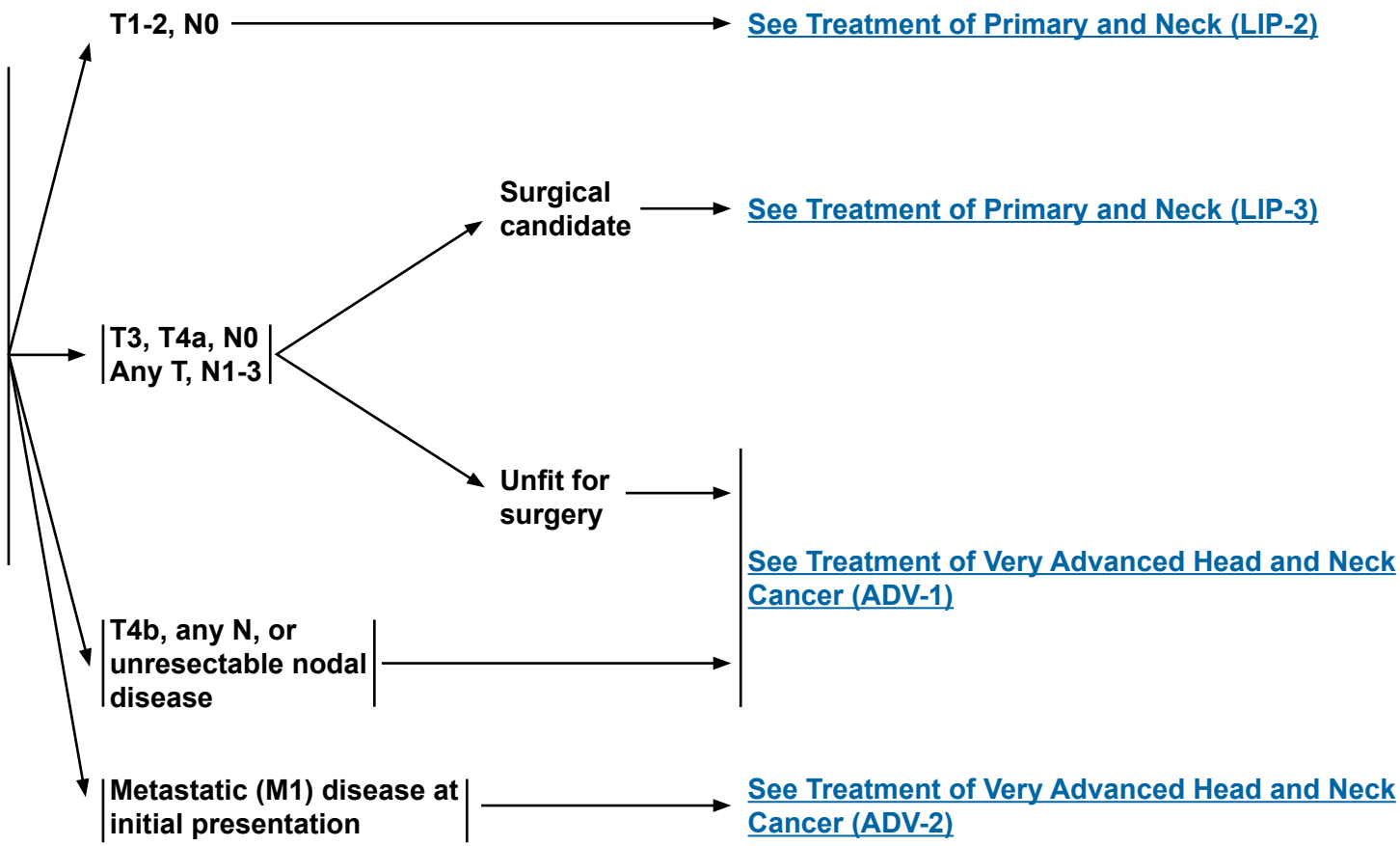
WORKUP

- History and physical (H&P)[a,b] including a complete head and neck exam; mirror and/or fiberoptic examination as clinically indicated
- Biopsy
- Chest imaging as clinically indicated
- As indicated for primary evaluation
  - Panorex
  - CT and/or MRI with contrast of primary and neck
- Preanesthesia studies as clinically indicated
- Dental evaluation[c]

Multidisciplinary consultation as indicated

CLINICAL STAGING



[a]H&P should include documentation and quantification (pack years smoked) of tobacco use history. 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 the NCCN Guidelines for Smoking Cessation and www.smokefree.gov.
[b]Screen for depression (See NCCN Guidelines for Distress Management).
[c]See Principles of Dental Evaluation and Management (DENT-A).

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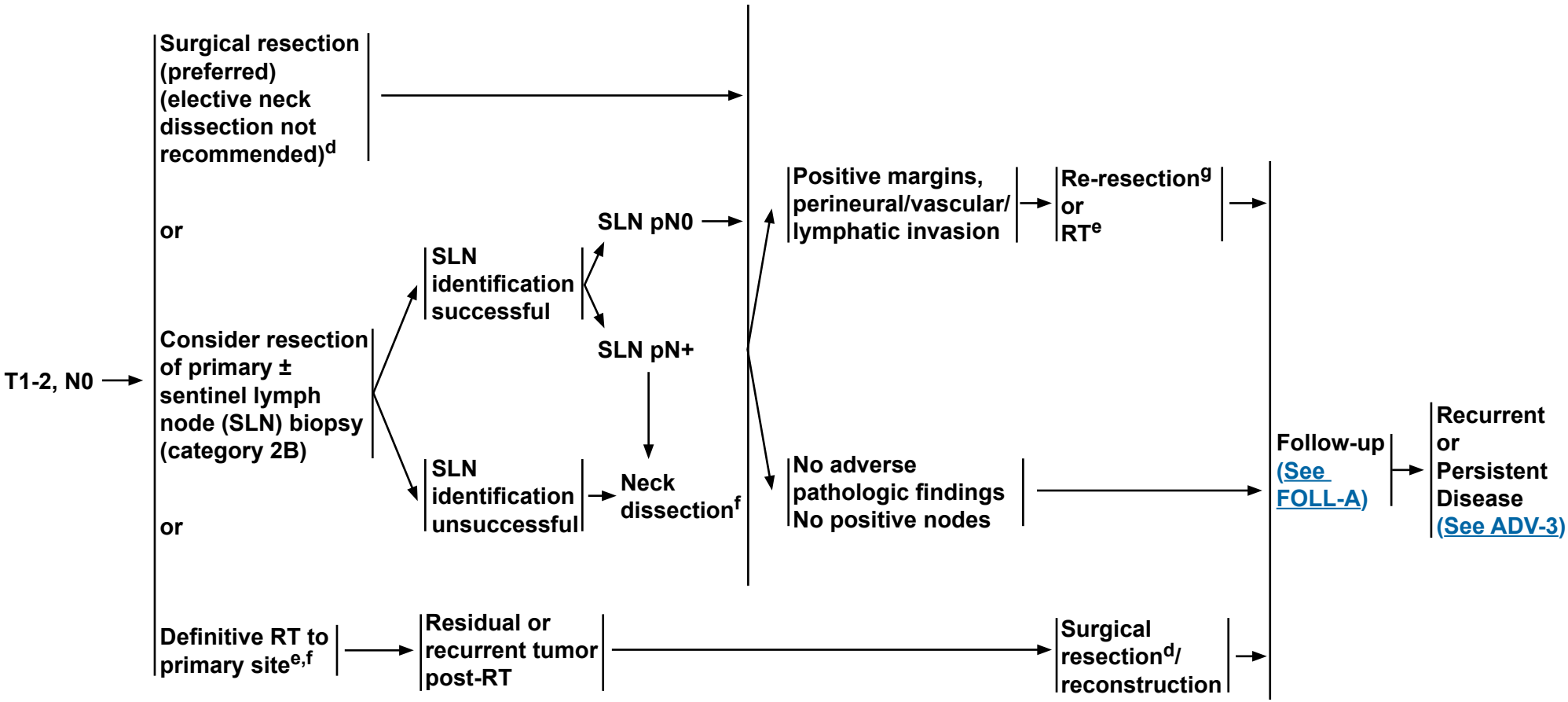

[d] See Principles of Surgery (SURG-A).
[e] See Principles of Radiation Therapy (LIP-A).
[f] No elective treatment to neck is preferred for the T1-2, N0.
[g] Consider re-resection to achieve negative margins, if feasible.

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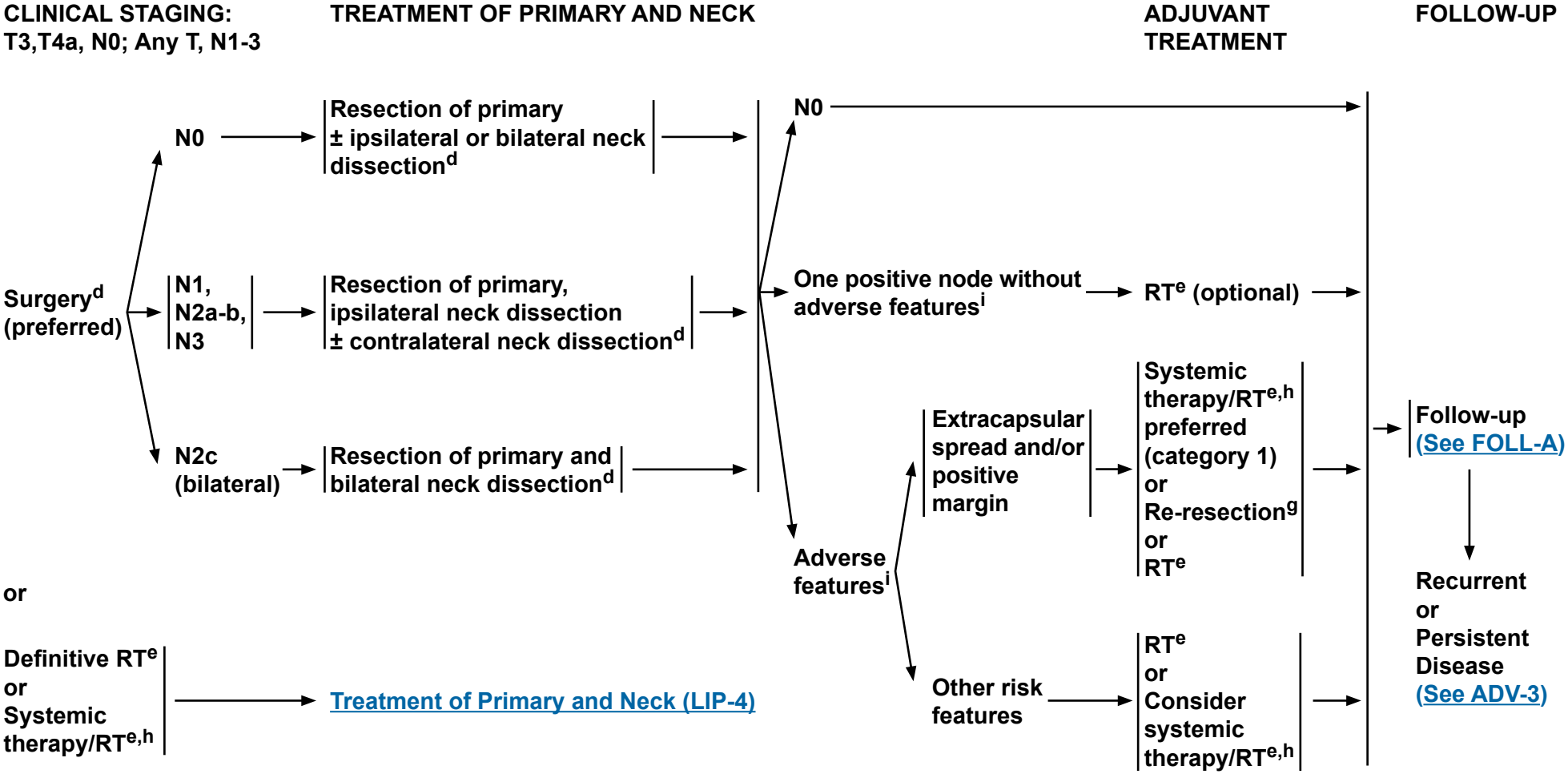

[d] See Principles of Surgery (SURG-A).
[e] See Principles of Radiation Therapy (LIP-A).
[g] Consider re-resection to achieve negative margins, if feasible.
[h] See Principles of Systemic Therapy (CHEM-A).
[i] Adverse features: extracapsular nodal spread, positive margins, multiple positive nodes, or perineural/lymphatic/vascular invasion.

Note: All recommendations are category 2A unless otherwise indicated.
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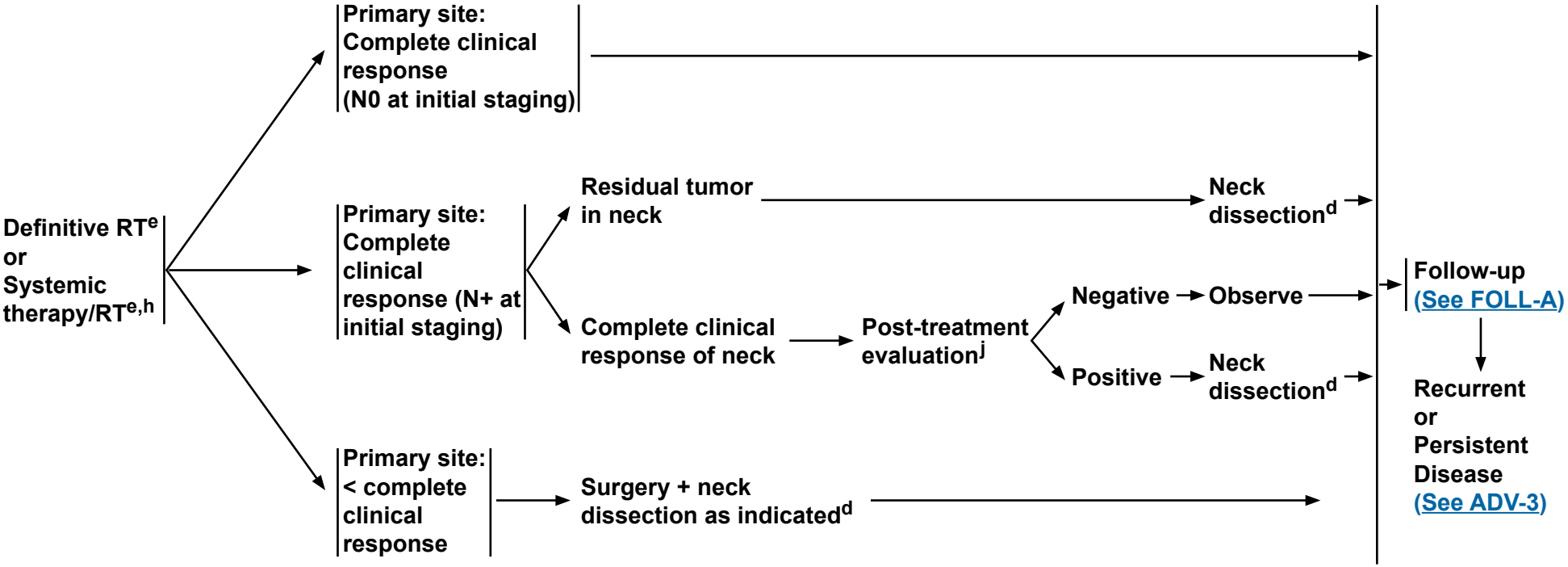
CLINICAL STAGING:
T3, T4a, N0; Any T, N1-3

TREATMENT OF PRIMARY AND NECK

ADJUVANT TREATMENT

FOLLOW-UP



[d] See Principles of Surgery (SURG-A).
[e] See Principles of Radiation Therapy (LIP-A).
[h] See Principles of Systemic Therapy (CHEM-A).
[j] See Post Chemoradiation or RT Neck Evaluation (FOLL-A 2 of 2).

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PRINCIPLES OF RADIATION THERAPY[1]

DEFINITIVE:

RT Alone

- Planning target volume (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))
    - ◊ 66 Gy (2.2 Gy/fraction) to 70 Gy (2.0 Gy/fraction); daily Monday–Friday in 6–7 weeks[2]
  - 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)[3]
- External beam RT (EBRT) ± brachytherapy[4,5]
- Brachytherapy
  - Interstitial brachytherapy is considered for selected cases.[4,5]
    - ◊ Low-dose rate (LDR) brachytherapy (0.4–0.5 Gy per hour):
      - – Consider LDR boost 20–35 Gy if combined with 50 Gy EBRT or 60–70 Gy over several days if using LDR as sole therapy
    - ◊ High-dose rate (HDR) brachytherapy:
      - – Consider HDR boost 21 Gy at 3 Gy/fraction if combined with 40–50 Gy EBRT or 45–60 Gy at 3–6 Gy/fraction if using HDR as sole therapy.

POSTOPERATIVE:

RT

- Preferred interval between resection and postoperative RT is ≤6 weeks.
- PTV
  - High risk: Adverse features such as positive margins (see footnote i on LIP-3)
    - ◊ 60–66 Gy (2.0 Gy/fraction) daily Monday–Friday in 6–6.5 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)[3]

Either intensity-modulated RT (IMRT) or 3-D conformal RT is recommended.

[1] See Radiation Techniques (RAD-A) and Discussion.

[2] 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.

[3] Suggest 44–50 Gy in 3D conformal RT and sequentially planned IMRT or 54–63 Gy with IMRT dose painting technique (dependent on dose per fraction).

[4] Brachytherapy should be performed at centers where there is expertise in this modality. (Nag S, Cano ER, Demanes DJ, et al. The American Brachytherapy Society recommendations for high-dose-rate brachytherapy for head-neck carcinomas. Int J Radiat Oncol Biol Phys 2001;50:1190-1198; and Mazeron JJ, Ardiet JM, Hale-Meder C, et al. GEC-ESTRO recommendations for brachytherapy for head and neck squamous cell carcinoma. Radiother Oncol 2009;91:150-156.)

[5] The interval between EBRT and brachytherapy should be as short as possible (1–2 weeks) depending on recovery from acute toxicity. The interval between HDR fractions should be at least 6 hours.

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

WORKUP

- **H&P[a,b] including a complete head and neck exam; mirror and fiberoptic examination as clinically indicated**
- **Biopsy**
- **Chest imaging as clinically indicated**
- **CT with contrast and/or MRI with contrast of primary and neck as indicated**
- **Consider FDG-PET/CT for stage III-IV disease[c]**
- **Examination under anesthesia (EUA) with endoscopy, if indicated**
- **Preanesthesia studies as clinically indicated**
- **Dental/prosthodontic evaluation,[d] including Panorex or CT ± contrast as clinically indicated**
- **Nutrition, speech, and swallowing evaluation/therapy as indicated[e]**
- **Multidisciplinary consultation as indicated**

CLINICAL STAGING

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

T3, N0 → **See Treatment of Primary and Neck (OR-3)**

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

T4a, any N → **See Treatment of Primary and Neck (OR-3)**

T4b, any N,
or
Unresectable nodal disease
or
Unfit for surgery → **See Treatment of Very Advanced Head and Neck Cancer (ADV-1)**

Metastatic (M1) disease at initial presentation → **See Treatment of Very Advanced Head and Neck Cancer (ADV-2)**

[a]H&P hould include documentation and quantification (pack years smoked) of tobacco use history. 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 the NCCN Guidelines for Smoking Cessation and www.smokefree.gov.
[b]Screen for depression (See NCCN Guidelines for Distress Management).
[c]See Discussion.
[d]See Principles of Dental Evaluation and Management (DENT-A).
[e]See Principles of Nutrition: Management and Supportive Care (NUTR-A).

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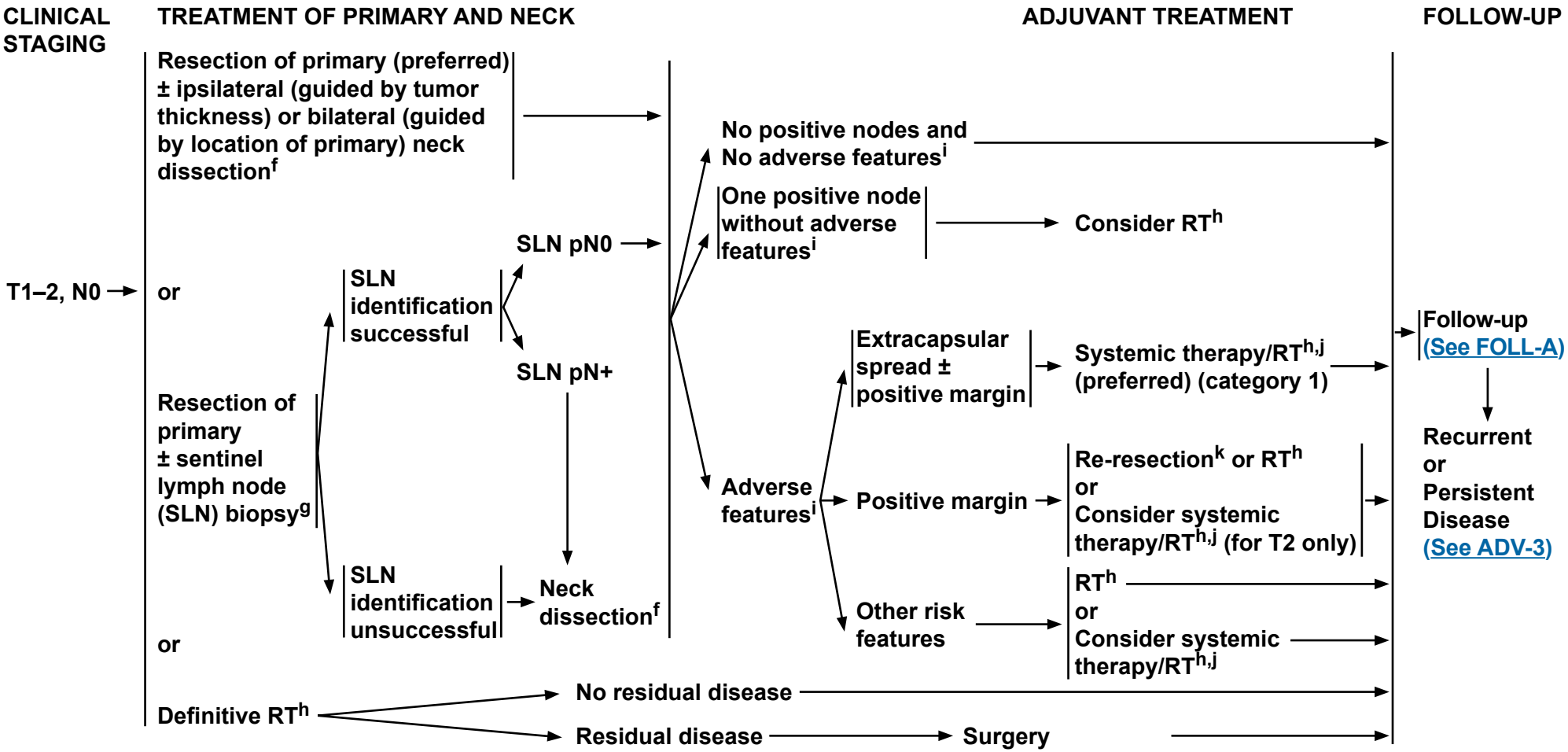
NCCN Guidelines Version 1.2016
Cancer of the Oral Cavity

NCCN Guidelines Index
Head and Neck Table of Contents
Discussion

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



[f]See Principles of Surgery (SURG-A).
[g]See Sentinel Lymph Node Biopsy in Principles of Surgery [SURG-A 6 of 9].
[h]Principles of Radiation Therapy (OR-A).

[i]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 (lymphovascular invasion) (See Discussion).
[j]See Principles of Systemic Therapy (CHEM-A).
[k]Consider re-resection to achieve negative margins, if feasible.

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Cancer of the Oral Cavity

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Head and Neck Table of Contents
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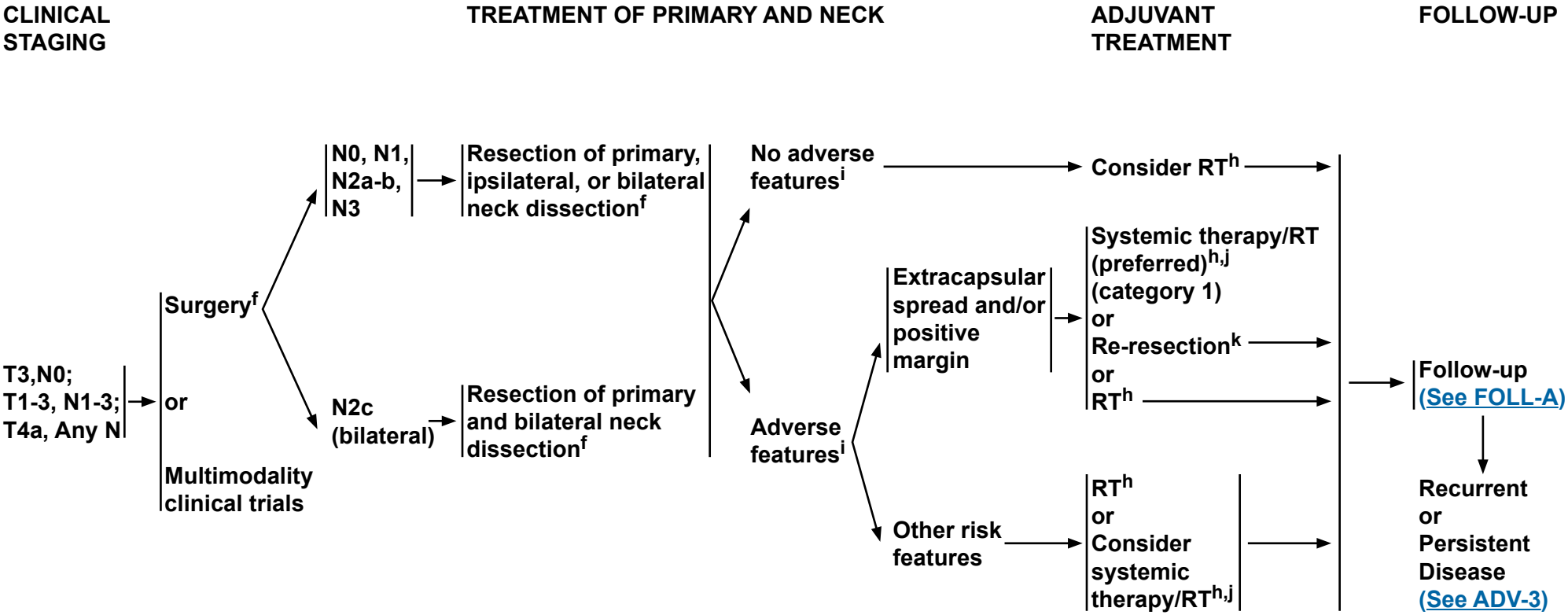
Buccal mucosa, floor of mouth, anterior tongue, alveolar ridge, retromolar trigone, hard palate



[f] See Principles of Surgery (SURG-A).
[h] See Principles of Radiation Therapy (OR-A).
[i] 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 (lymphovascular invasion) (See Discussion).
[j] See Principles of Systemic Therapy (CHEM-A).
[k] Consider re-resection to achieve negative margins, if feasible.

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PRINCIPLES OF RADIATION THERAPY[1]

DEFINITIVE:

RT Alone

- **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[2]**
      - – **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: 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)[3]**
- **Brachytherapy**
  - **Interstitial brachytherapy is considered for selected cases.[4,5]**
    - ◊ **LDR brachytherapy (0.4–0.5 Gy per hour):**
      - – **Consider LDR boost 20–35 Gy if combined with 50 Gy EBRT or 60–70 Gy over several days if using LDR as sole therapy.**
    - ◊ **HDR brachytherapy:**
      - – **Consider HDR boost 21 Gy at 3 Gy/fraction if combined with 40–50 Gy EBRT or 45–60 Gy at 3–6 Gy/fraction if using HDR as sole therapy.**

For unresectable disease, see ADV-1.

Either IMRT or 3-D conformal RT is recommended.

[1] See Radiation Techniques (RAD-A) and Discussion.

[2] 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.

[3] Suggest 44–50 Gy in 3D conformal RT and sequentially planned IMRT or 54–63 Gy with IMRT dose painting technique (dependent on dose per fraction).

[4] Brachytherapy should be performed at centers where there is expertise in this modality. (Nag S, Cano ER, Demanes DJ, et al. The American Brachytherapy Society recommendations for high-dose-rate brachytherapy for head-neck carcinomas. Int J Radiat Oncol Biol Phys 2001;50:1190-1198; and Mazeron JJ, Ardiet JM, Hale-Meder C, et al, GEC-ESTRO recommendations for brachytherapy for head and neck squamous cell carcinoma. Radiother Oncol 2009;91:150-156.)

[5] The interval between EBRT and brachytherapy should be as short as possible (1–2 weeks) depending on recovery from acute toxicity. The interval between HDR fractions should be at least 6 hours.

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PRINCIPLES OF RADIATION THERAPY[1]

POSTOPERATIVE:

RT

- **Preferred interval between resection and postoperative RT is ≤6 weeks.**
- **PTV**
  - **High risk: Adverse features such as positive margins (see footnote i on OR-3)**
    - **60–66 Gy (2.0 Gy/fraction); daily Monday–Friday in 6–6.5 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)[3]**

POSTOPERATIVE CHEMORADIATION:

- **Concurrent single-agent cisplatin at 100 mg/m² every 3 weeks is recommended.[6-9]**

Either IMRT or 3-D conformal RT is recommended.

[1] See Radiation Techniques (RAD-A) and Discussion.
[3] Suggest 44–50 Gy in 3D conformal RT and sequentially planned IMRT or 54–63 Gy with IMRT dose painting technique (dependent on dose per fraction).
[6] 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.
[7] 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.
[8] 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.
[9] 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.

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NCCN Guidelines Version 1.2016
Cancer of the Oropharynx

NCCN Guidelines Index
Head and Neck Table of Contents
Discussion

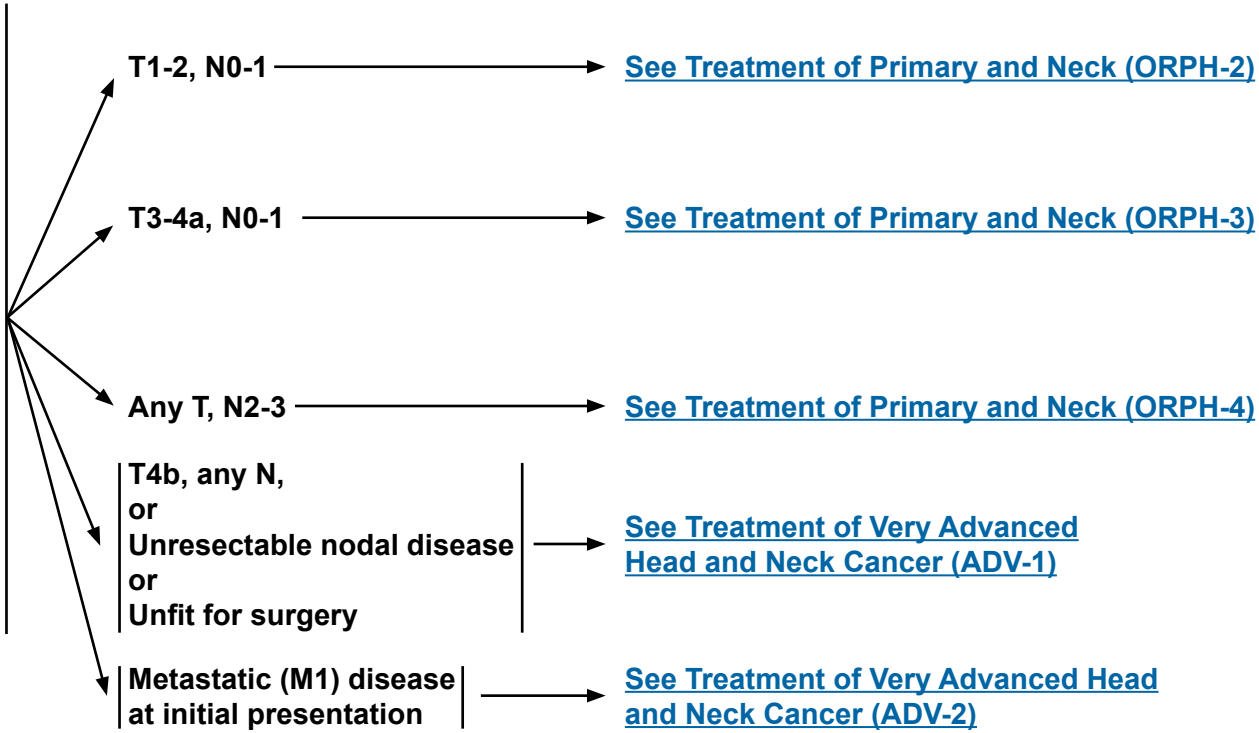
Base of tongue/tonsil/posterior pharyngeal wall/soft palate

WORKUP

- **H&P[a,b] including a complete head and neck exam; mirror and fiberoptic examination as clinically indicated**
- **Biopsy of primary site or FNA of the neck**
- **Tumor human papillomavirus (HPV) testing recommended[c]**
- **Chest imaging as clinically indicated**
- **CT with contrast and/or MRI with contrast of primary and neck**
- **Consider FDG-PET/CT for stage III-IV disease**
- **Dental evaluation,[d] including panorex as clinically indicated**
- **Nutrition, speech and swallowing evaluation/ therapy, and audiogram as clinically indicated[e]**
- **EUA with endoscopy as clinically indicated**
- **Pre-anesthesia studies**

Multidisciplinary consultation as clinically indicated

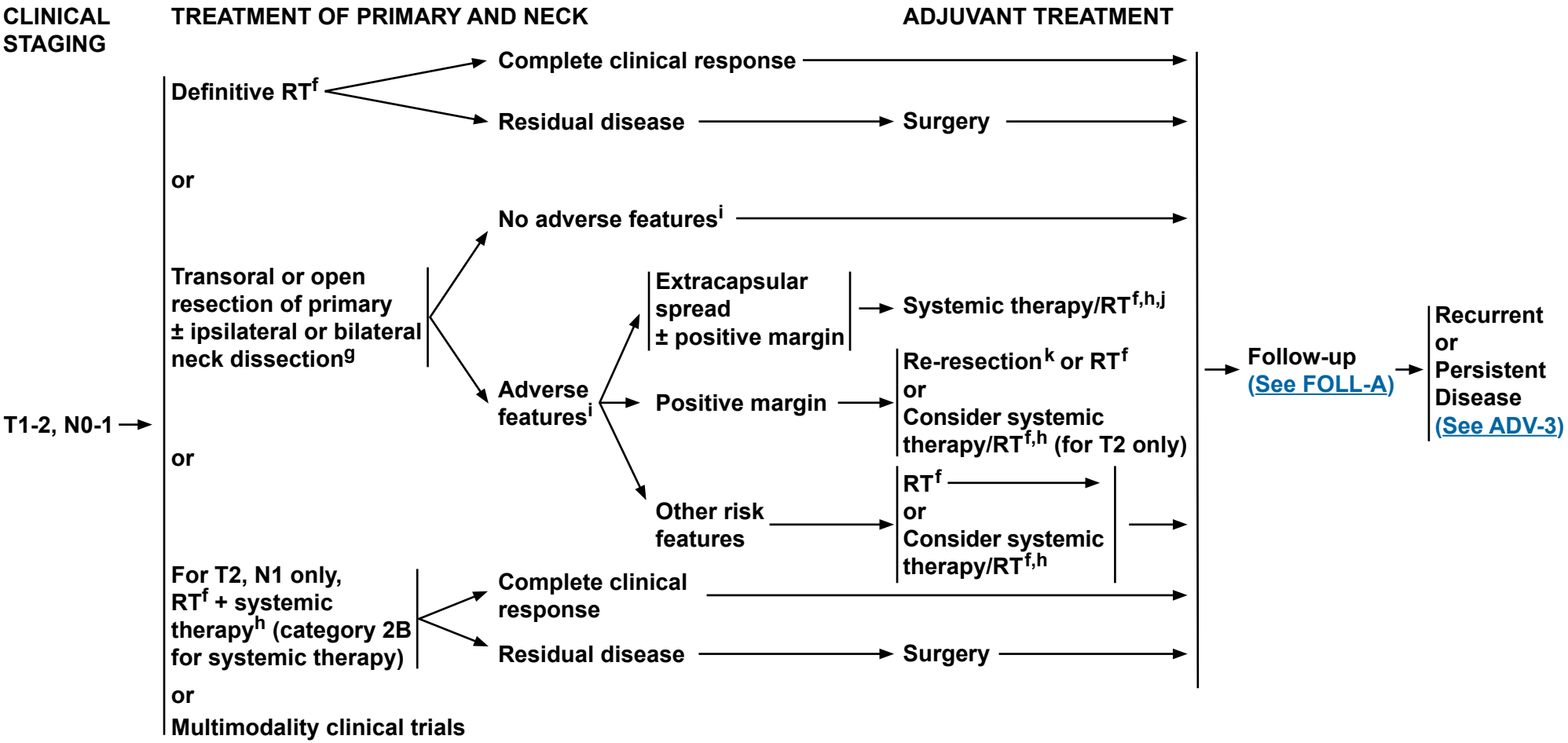
CLINICAL STAGING



[a]H&P should include documentation and quantification (pack years smoked) of tobacco use history. 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 the NCCN Guidelines for Smoking Cessation and www.smokefree.gov.
[b]Screen for depression (See NCCN Guidelines for Distress Management).
[c]P16 expression is highly correlated with HPV status and is widely available. HPV in situ hybridization or PCR-based assay is also available. 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.
[d]See Principles of Dental Evaluation and Management (DENT-A).
[e]See Principles of Nutrition: Management and Supportive Care (NUTR-A).

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

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



[f]See Principles of Radiation Therapy (ORPH-A).
[g]See Principles of Surgery (SURG-A).
[h]See Principles of Systemic Therapy (CHEM-A).
[i]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 (lymphovascular invasion) (See Discussion).
[j]The recommendations for patients at high risk with extracapsular spread + positive margins are based on randomized studies involving patients for whom the HPV status of their tumors was not specified.
[k]Consider re-resection to achieve negative margins, if feasible.

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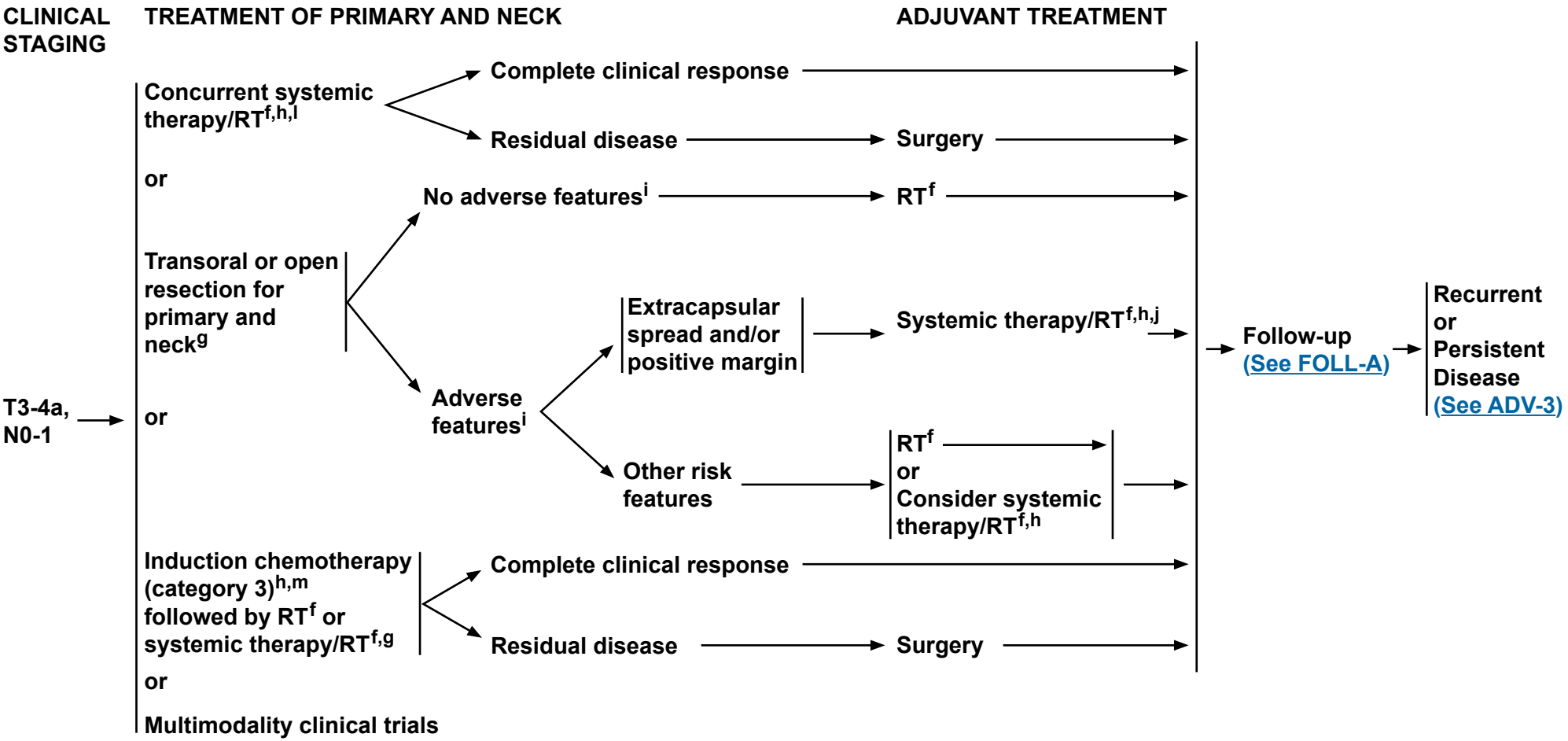
Base of tongue/tonsil/posterior pharyngeal wall/soft palate



[f]See Principles of Radiation Therapy (ORPH-A).
[g]See Principles of Surgery (SURG-A).
[h]See Principles of Systemic Therapy (CHEM-A).
[i]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 (lymphovascular invasion) (See Discussion).
[j]The recommendations for patients at high risk with extracapsular spread + positive margins are based on randomized studies involving patients for whom the HPV status of their tumors was not specified.
[l]When using concurrent systemic therapy/RT, the preferred agent is cisplatin (category 1). See Principles of Systemic Therapy (CHEM-A).
[m]See Discussion on induction chemotherapy.

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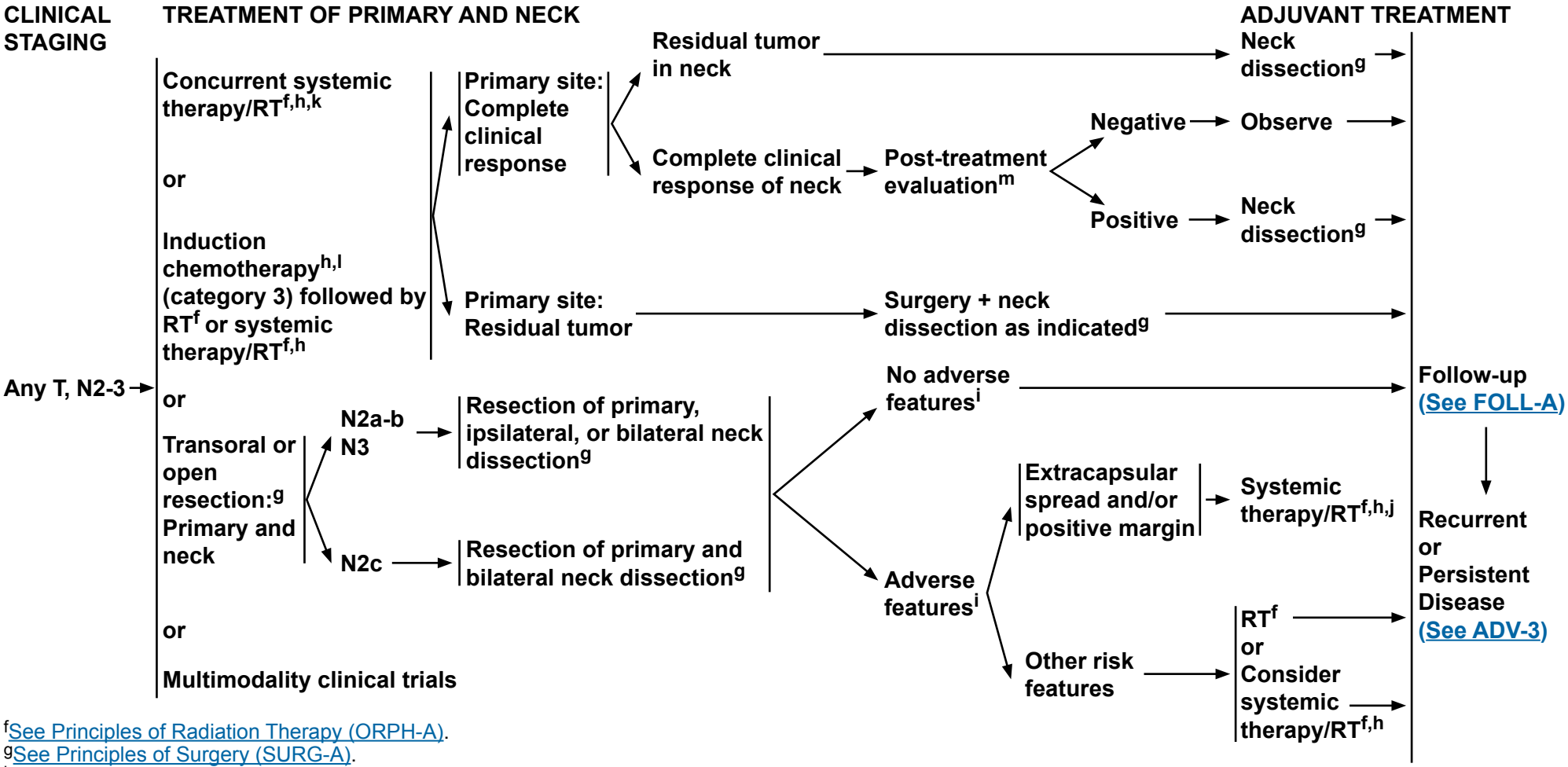
Base of tongue/tonsil/posterior pharyngeal wall/soft palate



[f] See Principles of Radiation Therapy (ORPH-A).
[g] See Principles of Surgery (SURG-A).
[h] See Principles of Systemic Therapy (CHEM-A).
[i] 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 (lymphovascular invasion) (See Discussion).
[j] The recommendations for patients at high risk with extracapsular spread + positive margins are based on randomized studies involving patients for whom the HPV status of their tumors was not specified.
[l] When using concurrent sytemic therapy/RT, the preferred agent is cisplatin (category 1). See Principles of Systemic Therapy (CHEM-A).
[m] See Discussion on induction chemotherapy.
[n] See Post Chemoradiation or RT Neck Evaluation (FOLL-A 2 of 2).

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PRINCIPLES OF RADIATION THERAPY[1]

DEFINITIVE:

RT Alone

- **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[2]**
      - **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: 81.6 Gy/7 weeks (1.2 Gy/fraction, twice daily)**
      - **69.96 Gy (2.12 Gy/fraction) daily Monday–Friday in 6–7 weeks[3]**
  - **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)[4]**

Either IMRT or 3-D conformal RT is recommended for cancers of the oropharynx in order to minimize dose to critical structures, especially the parotid glands.

CONCURRENT CHEMORADIATION:[5,6]

- **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)[4]**

[1] See Radiation Techniques (RAD-A) and Discussion.

[2] 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.

[3] Eisbruch A, Harris J, Garden AS, et al. Multi-institutional trial of accelerated hypofractionated intensity-modulated radiation therapy for early-stage oropharyngeal cancer (RTOG 00-22). Int J Radiat Oncol Biol Phys 2010;76:1333-1338.

[4] Suggest 44–50 Gy in 3D conformal RT and sequentially planned IMRT or 54–63 Gy with IMRT dose painting technique (dependent on dose per fraction).

[5] See Principles of Systemic Therapy (CHEM-A).

[6] 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^2 ; 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, 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.

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PRINCIPLES OF RADIATION THERAPY[1]

POSTOPERATIVE:

RT

- **Preferred interval between resection and postoperative RT is ≤6 weeks.**
- **PTV**
  - **High risk: Adverse features such as positive margins (See footnote i on ORPH-3).**
    - ◊ **60–66 Gy (2.0 Gy/fraction); daily Monday–Friday in 6–6.5 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)[4]**

POSTOPERATIVE CHEMORADIATION:

- **Concurrent single-agent cisplatin at 100 mg/m^2 every 3 weeks is recommended.[7-10]**

Either IMRT or 3-D conformal RT is recommended for cancers of the oropharynx in order to minimize dose to critical structures, especially the parotid glands.

[1] See Radiation Techniques (RAD-A) and Discussion.

[4] 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).
[7] 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.
[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, 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.
[10] 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.

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Cancer of the Hypopharynx

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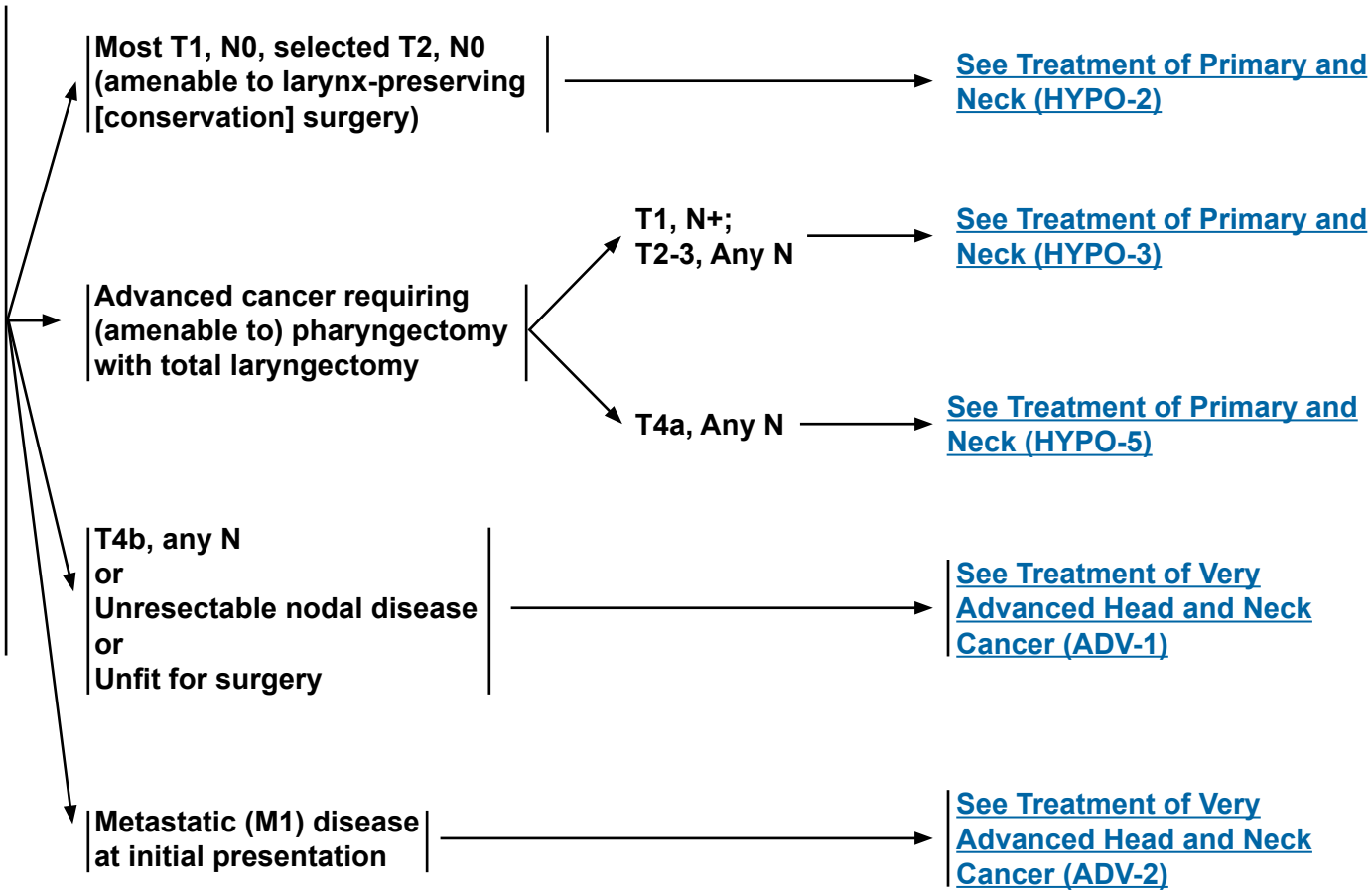
Head and Neck Table of Contents
Discussion

WORKUP

- **H&P[a,b] including a complete head and neck exam; mirror and fiberoptic examination as clinically indicated**
- **Biopsy of primary site or FNA of neck**
- **Chest imaging as clinically indicated**
- **CT with contrast and/or MRI with contrast of primary and neck**
- **Consider FDG-PET/CT[c] for stage III-IV disease**
- **EUA with endoscopy**
- **Preanesthesia studies as clinically indicated**
- **Nutrition, speech and swallowing evaluation/therapy, and audiogram as clinically indicated[d]**
- **Dental evaluation[e]**
- **Consider pulmonary function tests for conservation surgery candidates**

Multidisciplinary consultation as clinically indicated

CLINICAL STAGING



[a]H&P should include documentation and quantification (pack years smoked) of tobacco use history. 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 the NCCN Guidelines for Smoking Cessation and www.smokefree.gov.
[b]Screen for depression (See NCCN Guidelines for Distress Management).
[c]Anatomical imaging is also recommended.
[d]See Principles of Nutrition: Management and Supportive Care (NUTR-A).
[e]See Principles of Dental Evaluation and Management (DENT-A).

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Cancer of the Hypopharynx

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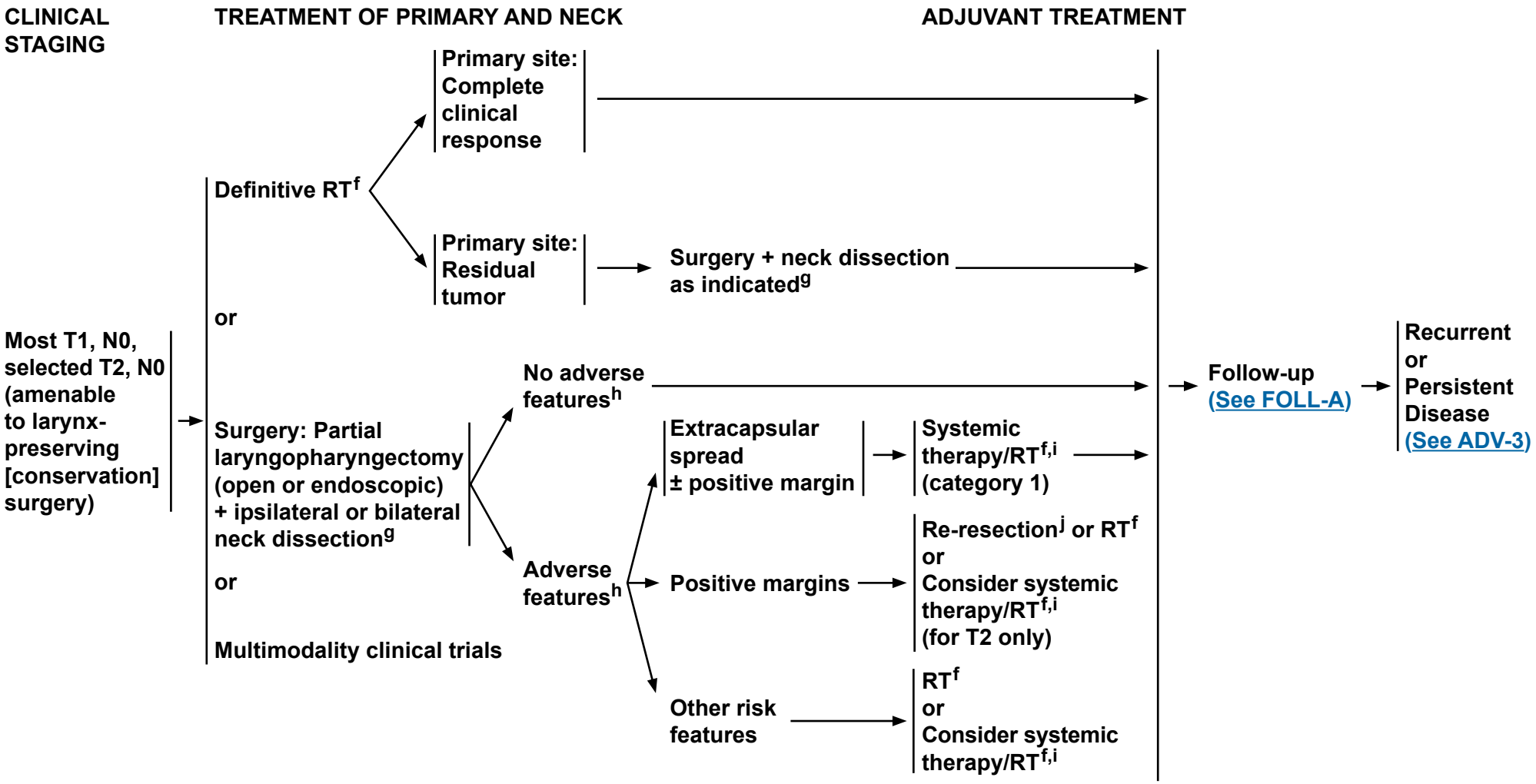

[f] See Principles of Radiation Therapy (HYPO-A).
[g] See Principles of Surgery (SURG-A).
[h] Adverse features: extracapsular nodal spread, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism (lymphovascular invasion) (See Discussion).
[i] See Principles of Systemic Therapy (CHEM-A).
[j] Consider re-resection to achieve negative margins, if feasible.

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Cancer of the Hypopharynx

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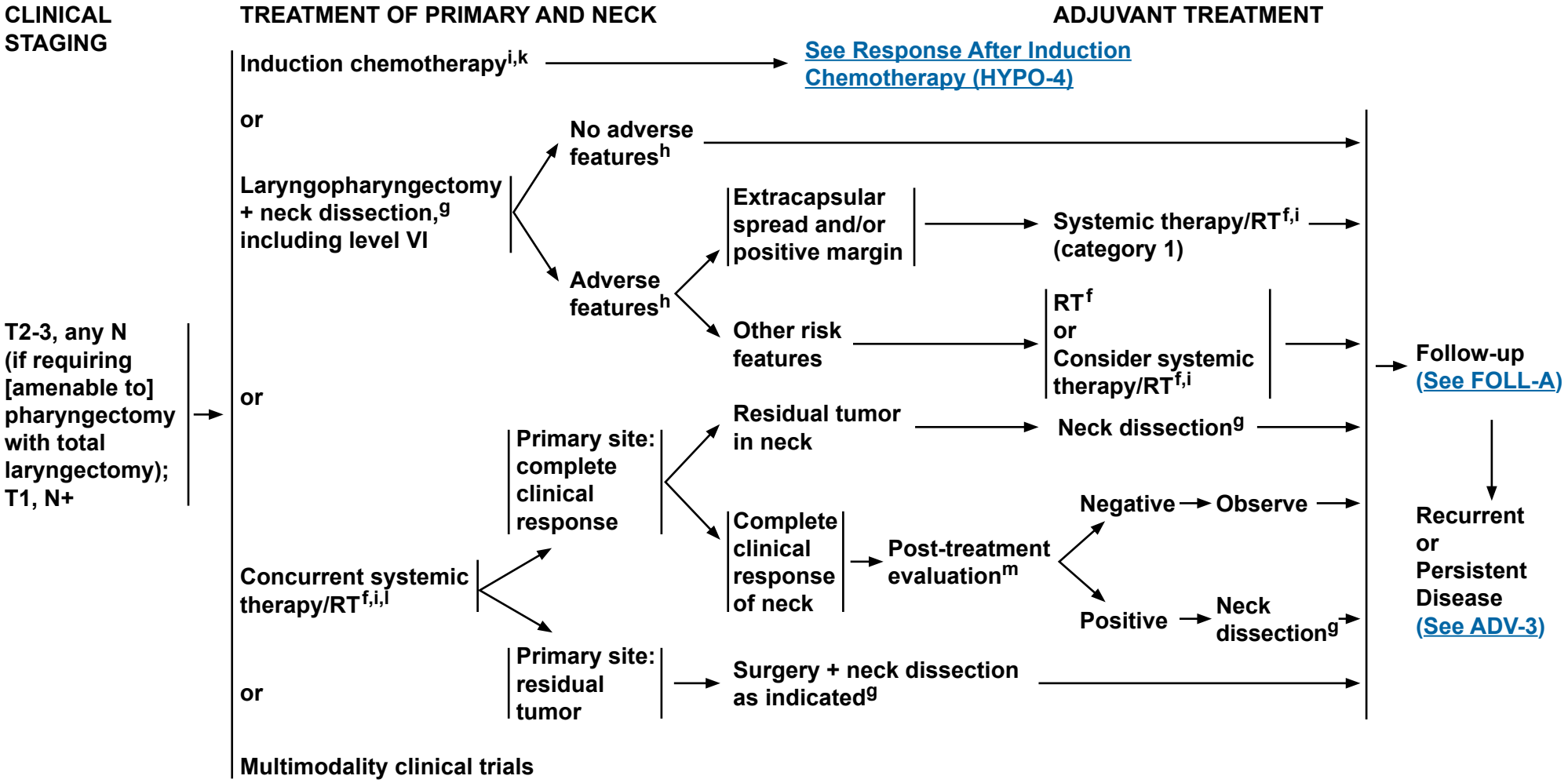

[f] See Principles of Radiation Therapy (HYPO-A).
[g] See Principles of Surgery (SURG-A).
[h] Adverse features: extracapsular nodal spread, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism (lymphovascular invasion) (See Discussion).
[i] See Principles of Systemic Therapy (CHEM-A).
[k] In randomized clinical trials, assessment of response has been done after 2 or 3 cycles.
[l] When using concurrent systemic therapy/RT, the preferred agent is cisplatin (category 1). See Principles of Systemic Therapy (CHEM-A).
[m] See Post Chemoradiation or RT Neck Evaluation (FOLL-A 2 of 2).

Note: All recommendations are category 2A unless otherwise indicated.
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NCCN Guidelines Version 1.2016
Cancer of the Hypopharynx

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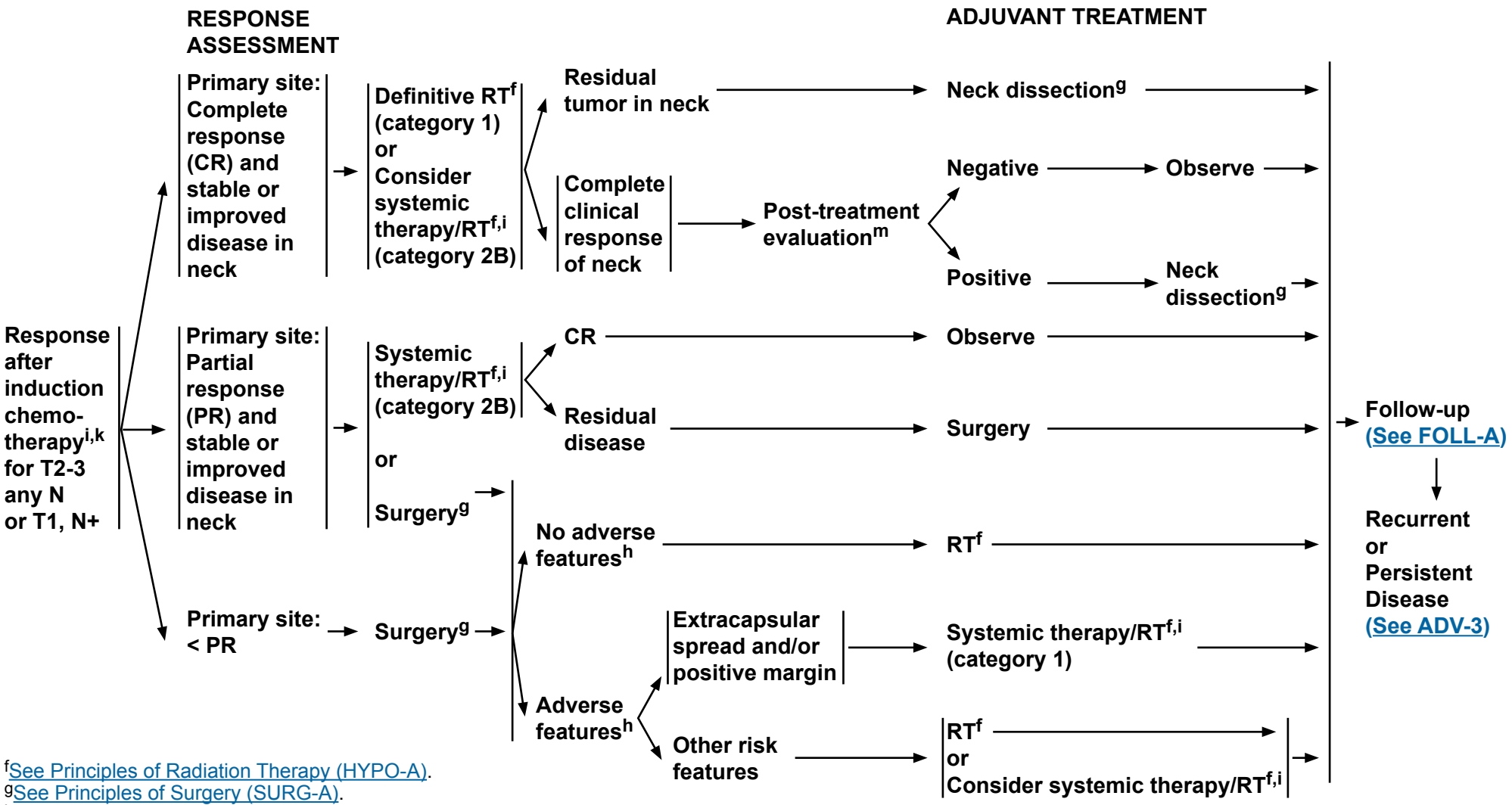
Discussion



[f] See Principles of Radiation Therapy (HYPO-A).
[g] See Principles of Surgery (SURG-A).
[h] Adverse features: extracapsular nodal spread, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism (lymphovascular invasion) (See Discussion).
[i] See Principles of Systemic Therapy (CHEM-A).
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Cancer of the Hypopharynx

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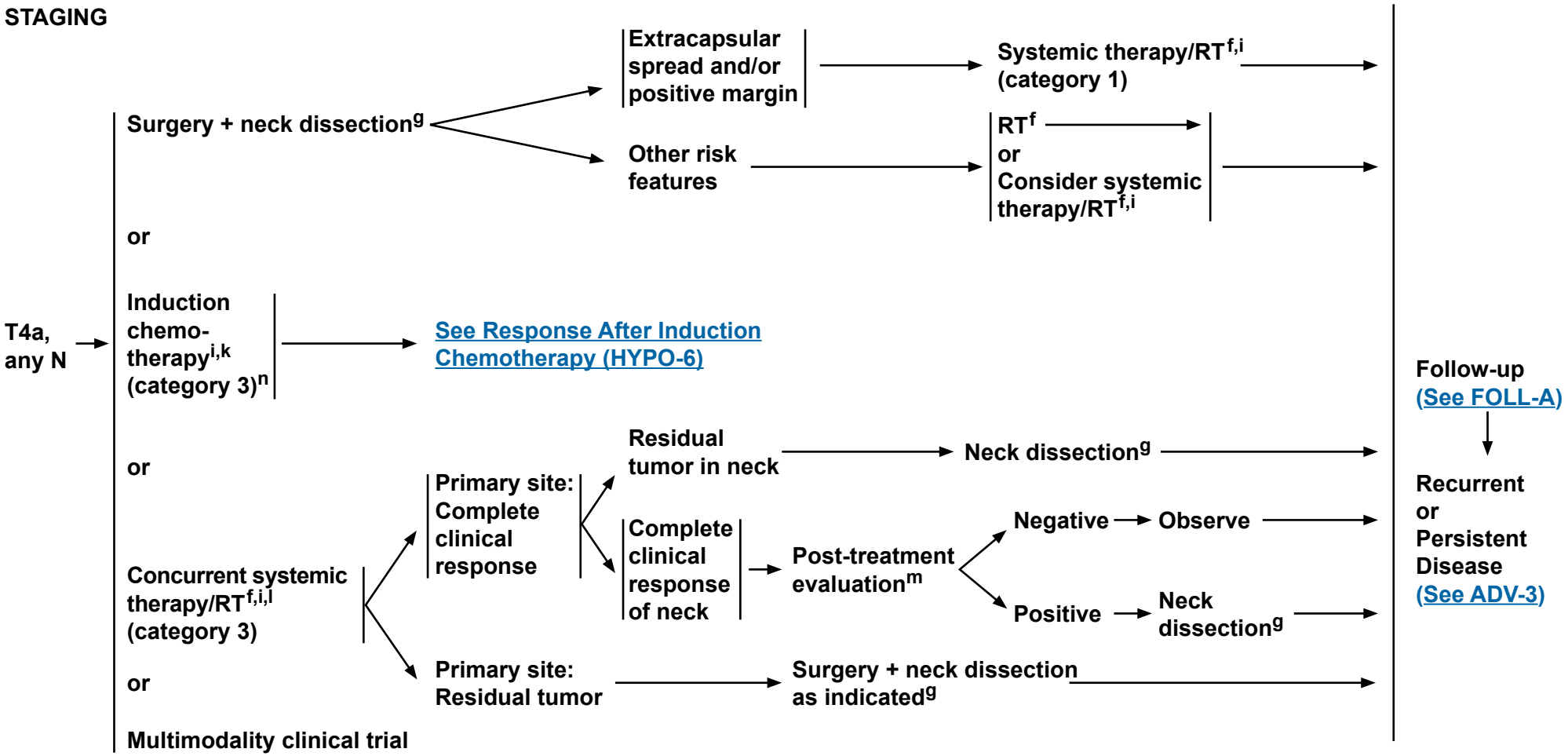

[f]See Principles of Radiation Therapy (HYPO-A).
[g]See Principles of Surgery (SURG-A).[i]See Principles of Systemic Therapy (CHEM-A).
[k]In randomized clinical trials, assessment of response has been done after 2 or 3 cycles.
[l]When using concurrent systemic therapy/RT, the preferred agent is cisplatin (category 1). See Principles of Systemic Therapy (CHEM-A).
[m]See Post Chemoradiation or RT Neck Evaluation (FOLL-A 2 of 2).
[n]See Discussion on induction chemotherapy.

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Cancer of the Hypopharynx

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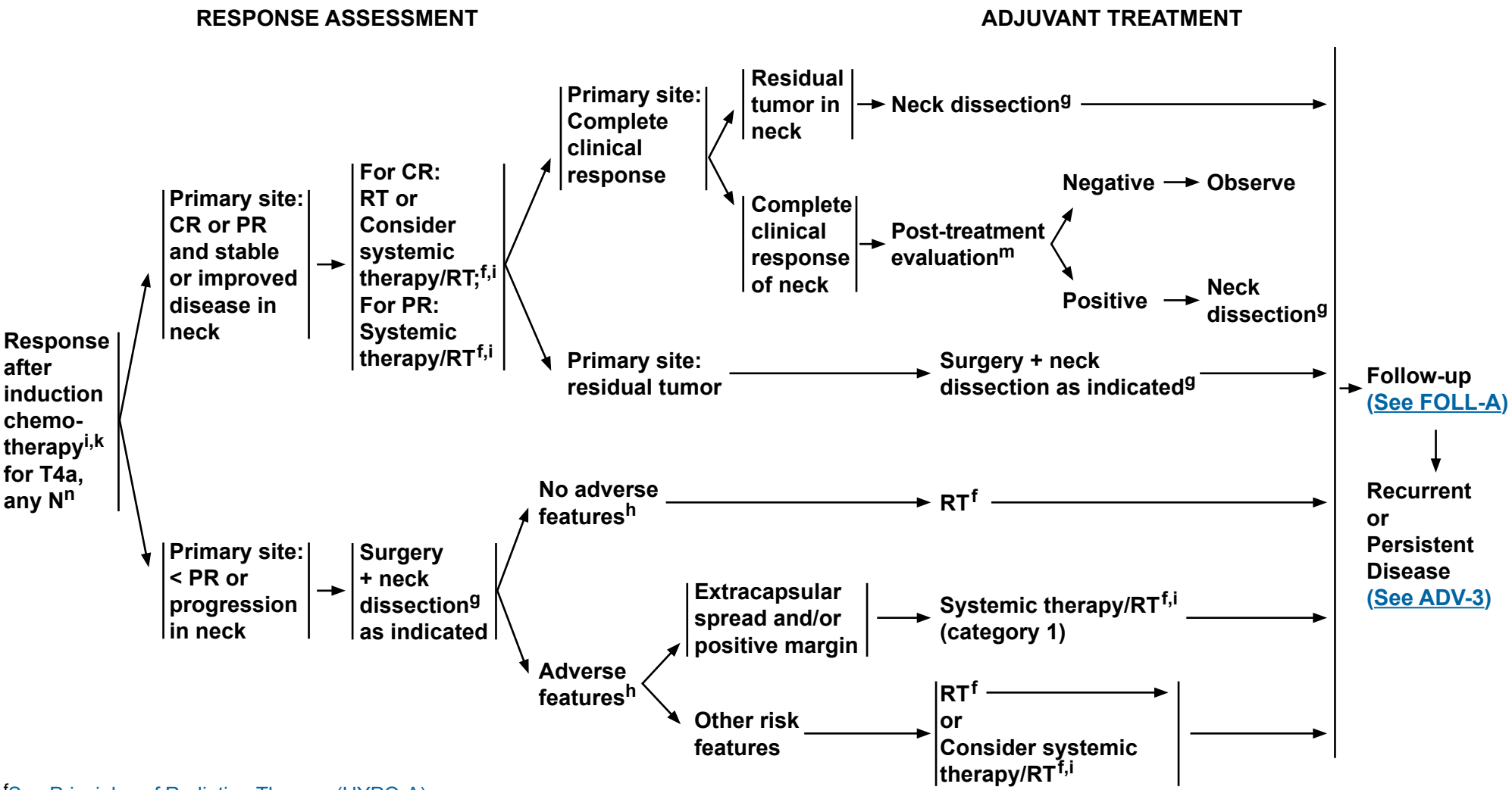

[f]See Principles of Radiation Therapy (HYPO-A).
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[h]Adverse features: extracapsular nodal spread, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism (lymphovascular invasion) (See Discussion).
[i]See Principles of Systemic Therapy (CHEM-A).
[k]In randomized clinical trials, assessment of response has been done after 2 or 3 cycles.
[m]See Post Chemoradiation or RT Neck Evaluation (FOLL-A 2 of 2).
[n]See Discussion on induction chemotherapy.

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

PRINCIPLES OF RADIATION THERAPY[1,2]

DEFINITIVE:

RT Alone

- **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[3]**
      - **66–70 Gy (2.0 Gy/fraction; 6 fractions/week accelerated)**
      - **69.96 Gy (2.12 Gy/fraction) daily Monday–Friday in 6–7 weeks[4]**
      - **Concomitant boost accelerated RT: 72 Gy/6 weeks (1.8 Gy/fraction, large field; 1.5 Gy boost as second daily fraction during last 12 treatment days)**
      - **Hyperfractionation: 81.6 Gy/7 weeks (1.2 Gy/fraction, twice daily)**
  - **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)[5]**

CONCURRENT CHEMORADIATION:[6,7]

- **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)[5]**

Either IMRT or 3-D conformal RT is recommended.

[1] See Radiation Techniques (RAD-A) and Discussion.

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

[3] 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.

[4] Eisbruch A, Harris J, Garden AS, et al. Multi-institutional trial of accelerated hypofractionated intensity-modulated radiation therapy for early-stage oropharyngeal cancer (RTOG 00-22). Int J Radiat Oncol Biol Phys 2010;76:1333-1338.

[5] Suggest 44–50 Gy in 3D conformal RT and sequentially planned IMRT or 54–63 Gy with IMRT dose painting technique (dependent on dose per fraction).

[6] See Principles of Systemic Therapy (CHEM-A).

[7] 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^2; 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, 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.

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

PRINCIPLES OF RADIATION THERAPY[1,2]

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 HYPO-3).**
    - ◊ **60–66 Gy (2.0 Gy/fraction; daily Monday–Friday) in 6–6.5 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)[5]**

POSTOPERATIVE CHEMORADIATION:

- **Concurrent single-agent cisplatin at 100 mg/m² every 3 weeks is recommended.[8-11]**

Either IMRT or 3-D conformal RT is recommended.

[1]See Radiation Techniques (RAD-A) and Discussion.
[2]Particular attention to speech and swallowing is needed during therapy.
[5]Suggest 44–50 Gy in 3D conformal RT and sequentially planned IMRT or 54–63 Gy with IMRT dose painting technique (dependent on dose per fraction).
[8]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.
[9]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.
[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]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.

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Cancer of the Nasopharynx

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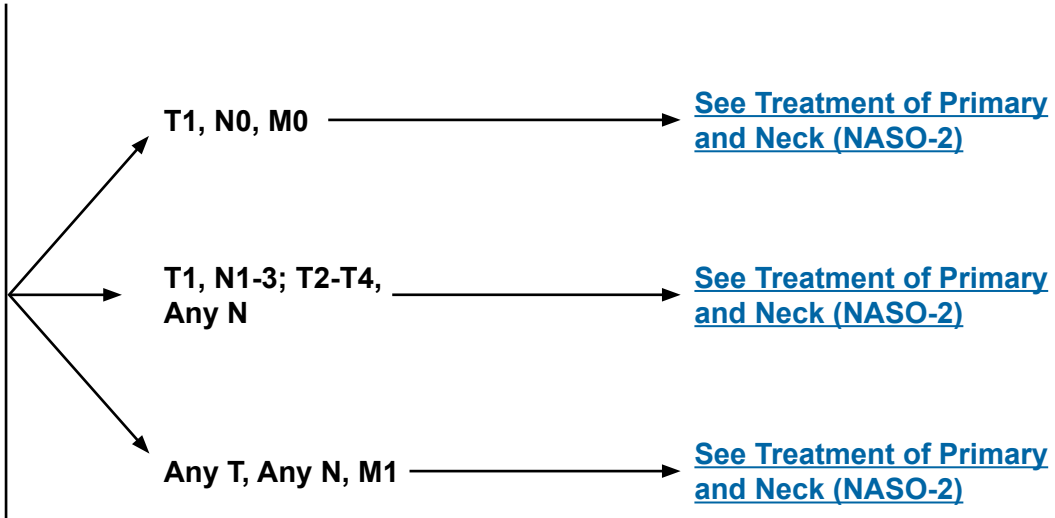
WORKUP

- **H&P[a,b] including a complete head and neck exam; mirror examination as clinically indicated**
- **Nasopharyngeal fiberoptic examination**
- **Biopsy of primary site or FNA of the neck**
- **MRI with contrast including base of skull, nasopharynx, and neck to the clavicles**
- **CT of skull base/neck with contrast as clinically indicated**
- **CT scan with contrast or FDG-PET/CT of the upper mediastinum/chest as clinically indicated**
- **Dental,[c] nutritional, speech and swallowing, and audiology evaluations as clinically indicated[d]**
- **Imaging for distant metastases (ie, chest, liver, bone) may include FDG-PET/CT and/or CT scan with contrast, especially for nonkeratinizing histology, endemic phenotype, or N2-3 disease; may be considered for stage III-IV disease**
- **Consider EBV/DNA testing**
- **Consider ophthalmologic and endocrine evaluation as clinically indicated.**

Multidisciplinary consultation as clinically indicated

CLINICAL STAGING



[a]H&P hould include documentation and quantification (pack years smoked) of tobacco use history. 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 the NCCN Guidelines for Smoking Cessation and www.smokefree.gov.
[b]Screen for depression (See NCCN Guidelines for Distress Management).
[c]See Principles of Dental Evaluation and Management (DENT-A).
[d]See Principles of Nutrition: Management and Supportive Care (NUTR-A).

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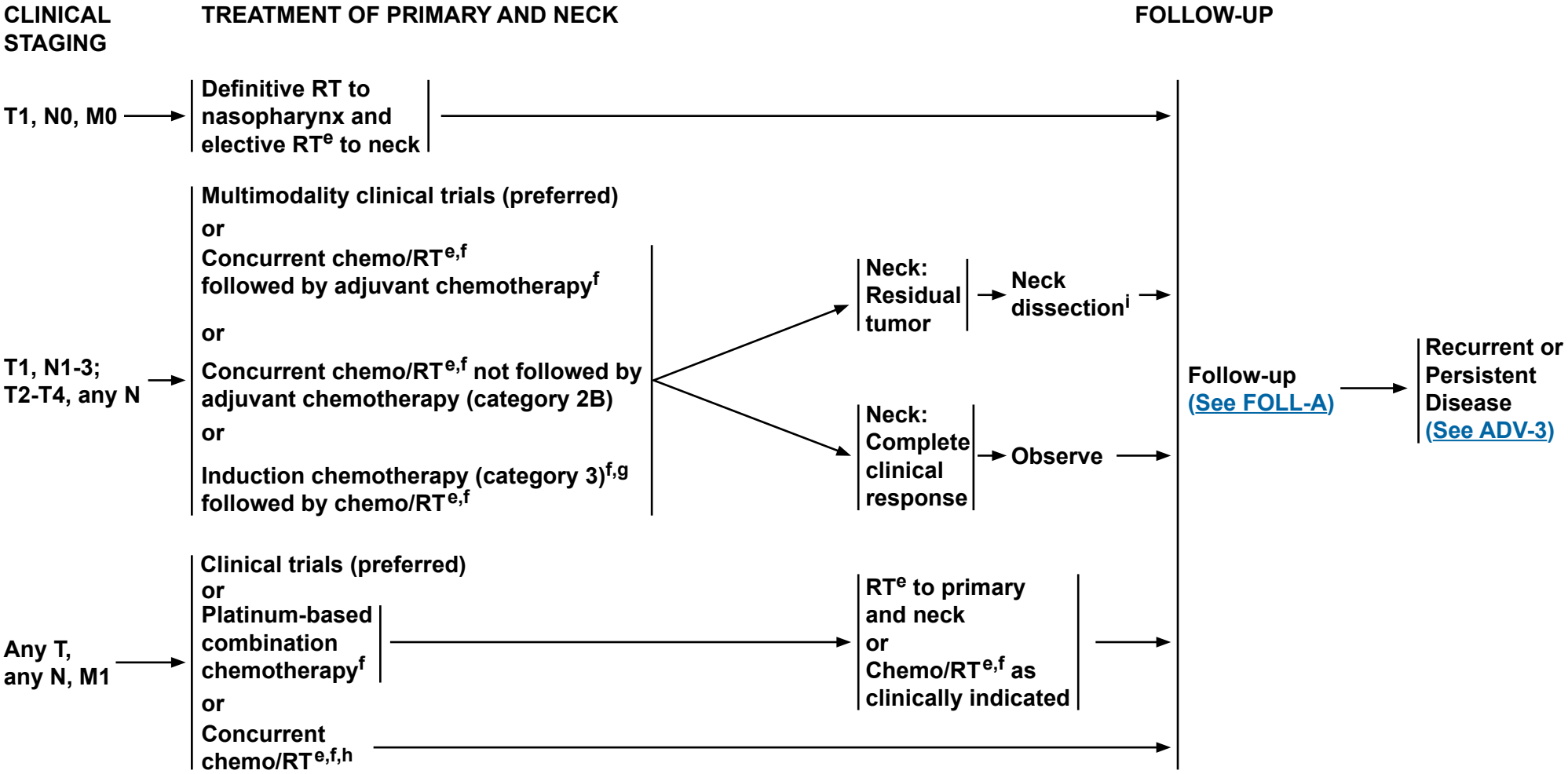

[e]See Principles of Radiation Therapy (NASO-A).
[f]See Principles of Systemic Therapy (CHEM-A).
[g]See Discussion on induction chemotherapy.
[h]Can be used for select patients with distant metastasis in limited site or with small tumor burden, or for patients with symptoms in the primary or any nodal site.
[i]See Principles of Surgery (SURG-A).

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

PRINCIPLES OF RADIATION THERAPY[1]

DEFINITIVE:
RT Alone (preferred if no chemotherapy is being used)
- **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))**
    - ◊ **66 Gy (2.2 Gy/fraction) to 70–70.2 Gy (1.8–2.0 Gy/fraction); daily Monday–Friday in 6–7 weeks[2,3]**
    - ◊ **69.96 Gy (2.12 Gy/fraction) daily Monday–Friday in 6–7 weeks[4]**
- **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)[5]**

CONCURRENT CHEMORADIATION:[6]
(preferred for patients eligible for chemotherapy)
- **PTV**
  - **High risk: typically 70–70.2 Gy (1.8–2.0 Gy/fraction); daily Monday–Friday in 7 weeks[2]**
  - **Low to intermediate risk: 44–50 Gy (2.0 Gy/fraction) to 54–63 Gy (1.6–1.8 Gy/fraction)[5]**

IMRT is preferred over 3-D conformal RT in cancer of the nasopharynx to minimize dose to critical structures.

[1]See Radiation Techniques (RAD-A) and Discussion.
[2]Care should be taken to avoid critical neural structures; therefore, 1.8 Gy/fraction can be considered.
[3]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.
[4]Lee NY, Zhang Q, Pfister DG, et al. Addition of bevacizumab to standard chemoradiation for locoregionally advanced nasopharyngeal carcinoma (RTOG 0615): a phase 2 multi-institutional trial. Lancet Oncol 2012;13:172-180.
[5]Suggest 44–50 Gy in 3D conformal RT and sequentially planned IMRT or 54–63 Gy with IMRT dose painting technique (dependent on dose per fraction).
[6]See Principles of Systemic Therapy (CHEM-A).

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Cancer of the Glottic Larynx

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WORKUP[a]

- H&P[b,c] including a complete head and neck exam; mirror and fiberoptic examination as clinically indicated
- Biopsy of primary site or FNA of the neck
- Chest imaging as clinically indicated
- CT with contrast and thin cuts through larynx and/or MRI with contrast of primary and neck
- Consider FDG-PET/CT for stage III-IV disease
- EUA with endoscopy
- Preanesthesia studies
- Dental evaluation as clinically indicated[d]
- Nutrition, speech and swallowing evaluation/therapy, and audiogram as clinically indicated[e]
- 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	See Treatment (GLOT-2)
Amenable to larynx-preserving (conservation) surgery) (T1-T2 or Select T3)	See Treatment (GLOT-2)
T3 requiring (amenable to) total laryngectomy (N0-1)	See Treatment of Primary and Neck (GLOT-3)
T3 requiring (amenable to) total laryngectomy (N2-3)	See Treatment of Primary and Neck (GLOT-4)
T4a disease	See Treatment of Primary and Neck (GLOT-6)
T4b, any N or Unresectable nodal disease or Unfit for surgery	See Treatment of Very Advanced Head and Neck Cancer (ADV-1)
Metastatic (M1) disease at initial presentation	See Treatment of Very Advanced Head and Neck Cancer (ADV-2)

[a]Complete workup may not be indicated for Tis, T1, but history and physical examination are required. Direct laryngoscopy and biopsy under anesthesia are generally recommended

[b]H&P hould include documentation and quantification (pack years smoked) of tobacco use history. 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 the NCCN Guidelines for Smoking Cessation and www.smokefree.gov.

[c]Screen for depression (See NCCN Guidelines for Distress Management).

[d]See Principles of Dental Evaluation and Management (DENT-A).

[e]See Principles of Nutrition: Management and Supportive Care (NUTR-A).

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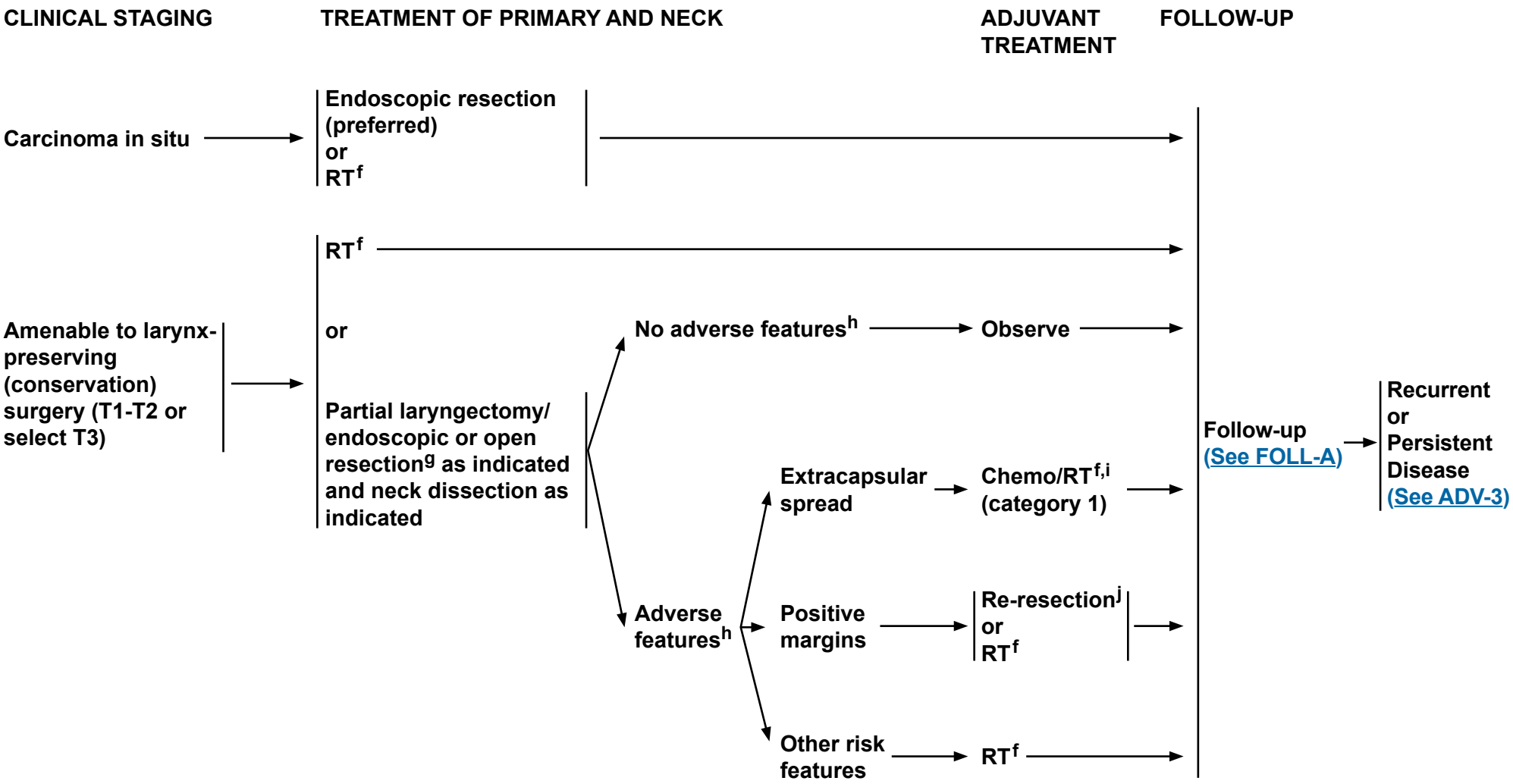

[f]See Principles of Radiation Therapy (GLOT-A).
[g]See Principles of Surgery (SURG-A).
[h]Adverse features: extracapsular nodal spread, positive margins, pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism (lymphovascular invasion) (See Discussion).
[i]See Principles of Systemic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

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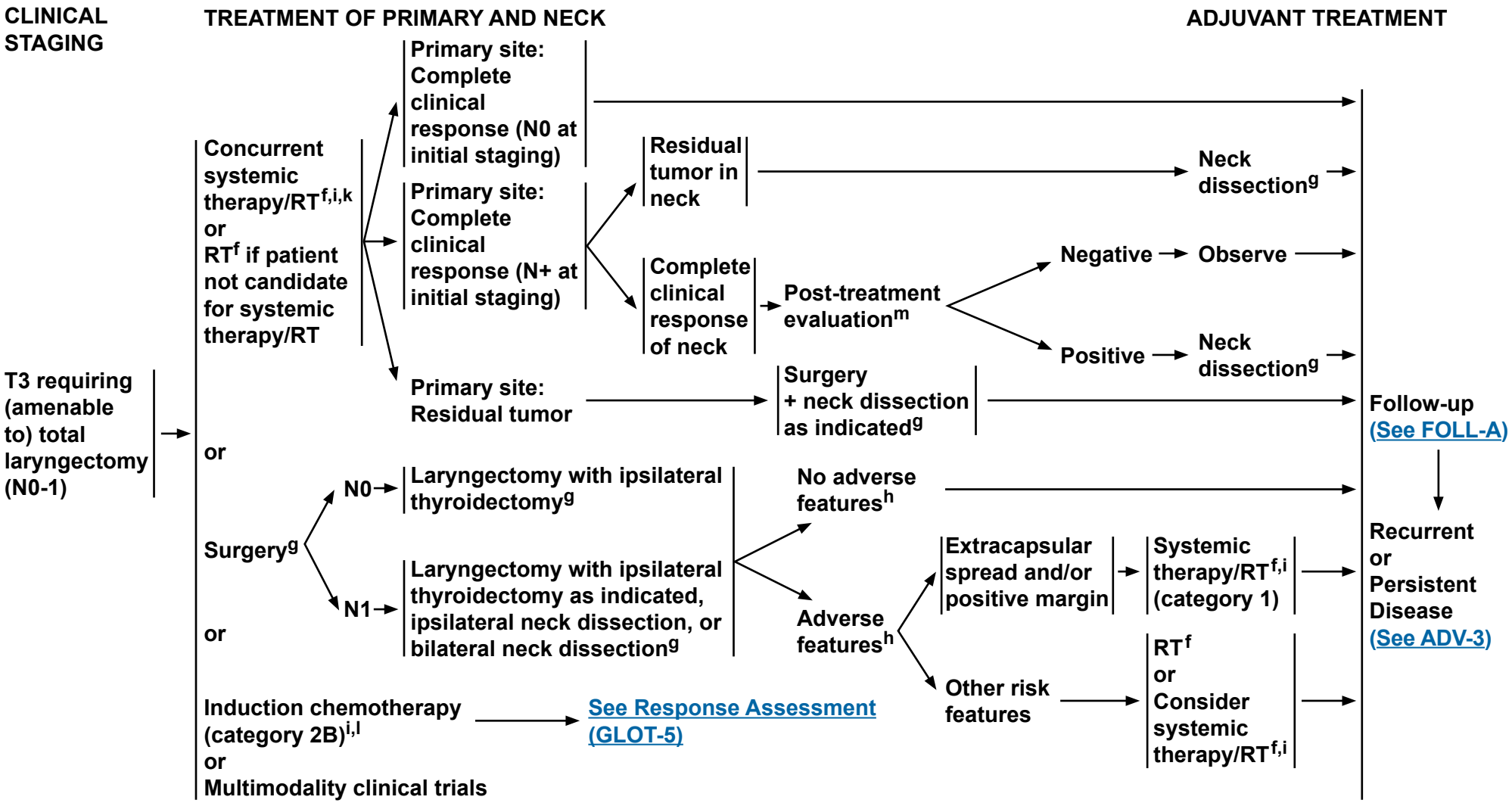

[f] See Principles of Radiation Therapy (GLOT-A).
[g] See Principles of Surgery (SURG-A).
[h] Adverse features: extracapsular nodal spread, positive margins, pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism (lymphovascular invasion) (See Discussion).
[i] See Principles of Systemic Therapy (CHEM-A).
[k] When using concurrent systemic therapy/RT, the preferred agent is cisplatin (category 1).
[l] See Discussion on induction chemotherapy.
[m] See Post Chemoradiation or RT Neck Evaluation (FOLL-A 2 of 2).

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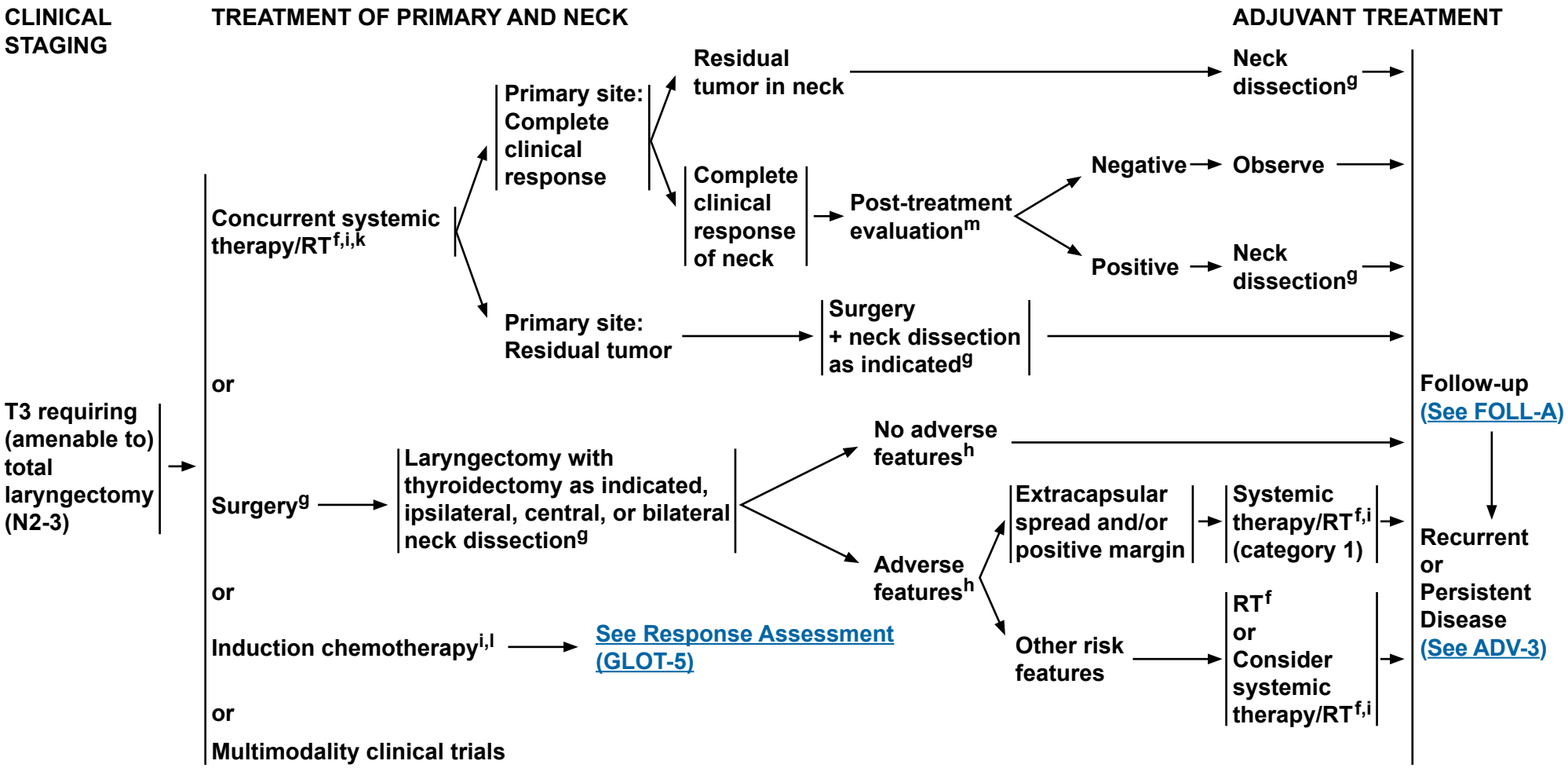

[f] See Principles of Radiation Therapy (GLOT-A).
[g] See Principles of Surgery (SURG-A).
[h] Adverse features: extracapsular nodal spread, positive margins, pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism (lymphovascular invasion) (See Discussion).
[i] See Principles of Systemic Therapy (CHEM-A).
[k] When using concurrent systemic therapy/RT, the preferred agent is cisplatin (category 1).
[l] See Discussion on induction chemotherapy.
[m] See Post Chemoradiation or RT Neck Evaluation (FOLL-A 2 of 2).

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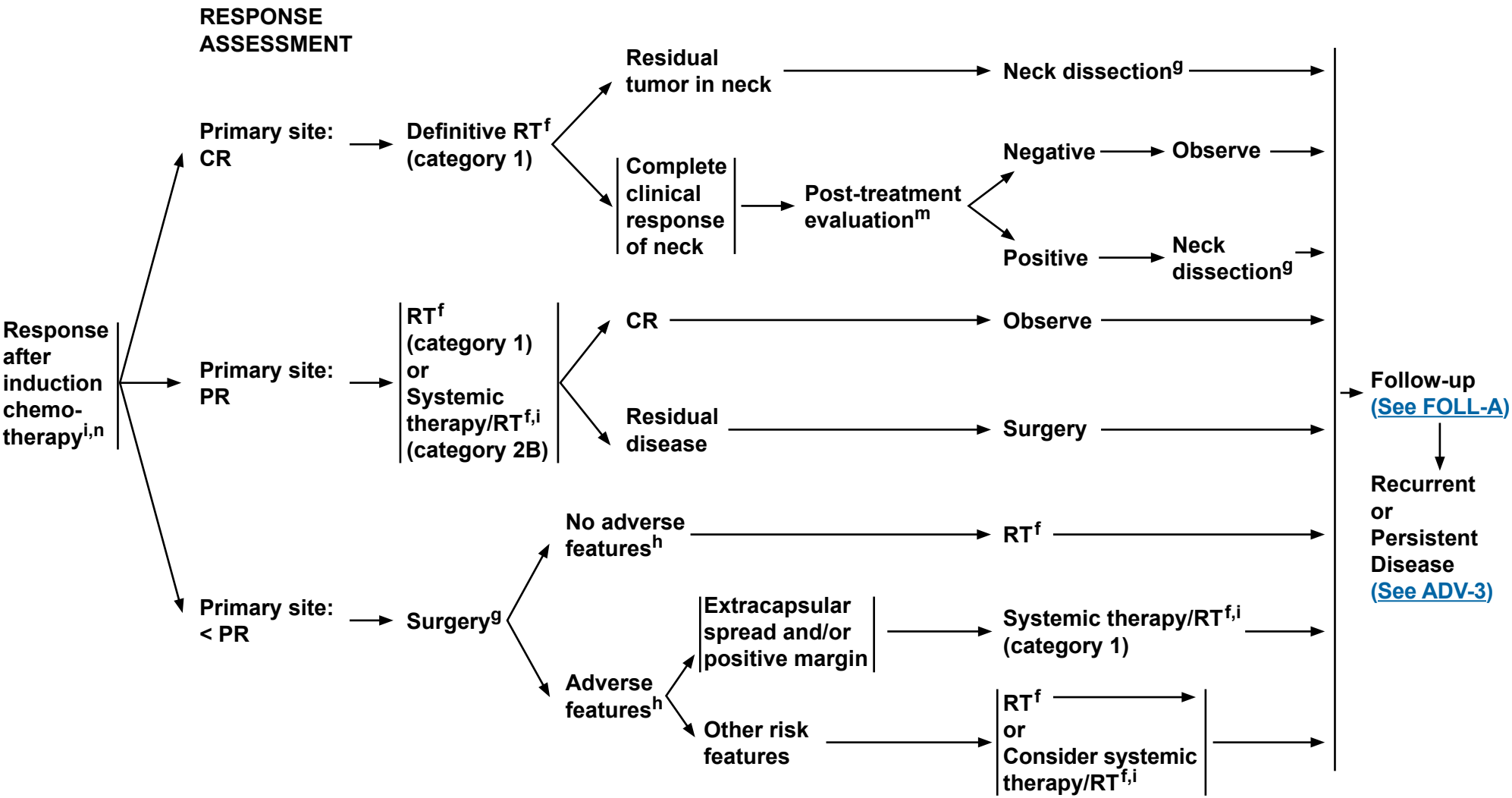

[f] See Principles of Radiation Therapy (GLOT-A).
[g] See Principles of Surgery (SURG-A).
[h] Adverse features: extracapsular nodal spread, positive margins, pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism (lymphovascular invasion) (See Discussion).
[i] See Principles of Systemic Therapy (CHEM-A).
[m] See Post Chemoradiation or RT Neck Evaluation (FOLL-A 2 of 2).
[n] In randomized clinical trials, assessment of response has been done after 2 or 3 cycles.

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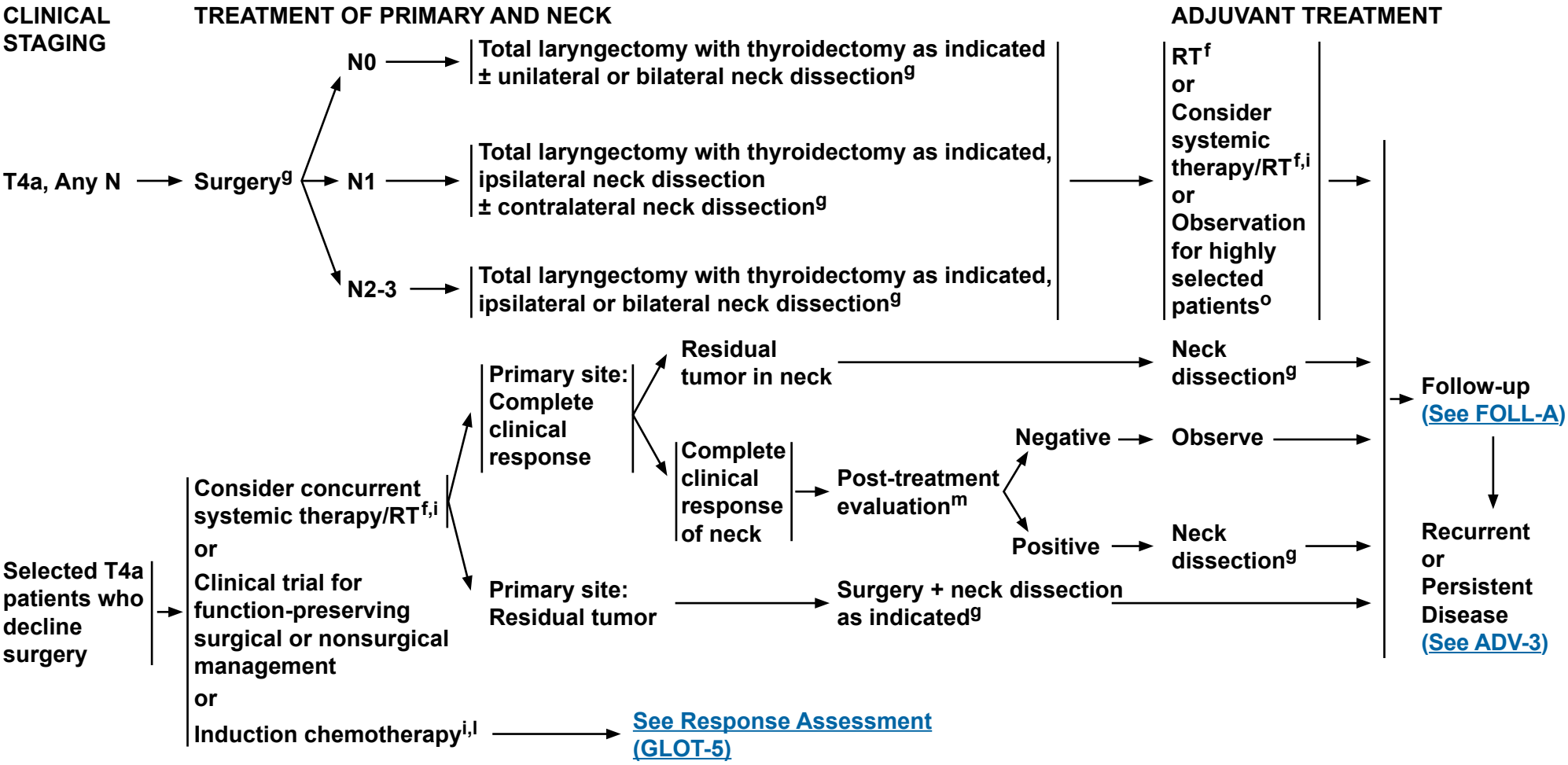

[f] See Principles of Radiation Therapy (GLOT-A).
[g] See Principles of Surgery (SURG-A).
[i] See Principles of Systemic Therapy (CHEM-A).
[m] See Post Chemoradiation or RT Neck Evaluation (FOLL-A 2 of 2).
[l] See Discussion on induction chemotherapy.

[o] 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.

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PRINCIPLES OF RADIATION THERAPY[1]

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[2]**
        - **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)[3]**

Either IMRT or 3-D conformal RT is recommended.

CONCURRENT CHEMORADIATION:[4,5]

- **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)[3]**

[1] See Radiation Techniques (RAD-A) and Discussion.

[2] 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.

[3] Suggest 44–50 Gy in 3D conformal RT and sequentially planned IMRT or 54–63 Gy with IMRT dose painting technique (dependent on dose per fraction).

[4] See Principles of Systemic Therapy (CHEM-A).

[5] 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^2 ; 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.

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

PRINCIPLES OF RADIATION THERAPY[1]

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 6–6.5 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)[3]**

POSTOPERATIVE CHEMORADIATION:

- **Concurrent single-agent cisplatin at 100 mg/m^2 every 3 weeks is recommended.[6-9]**

Either IMRT or 3-D conformal RT is recommended.

[1] See Radiation Techniques (RAD-A) and Discussion.

[3] Suggest 44–50 Gy in 3D conformal RT and sequentially planned IMRT or 54–63 Gy with IMRT dose painting technique (dependent on dose per fraction).
[6] 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.
[7] 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.
[8] 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.
[9] 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.

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Cancer of the Supraglottic Larynx

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WORKUP

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

Multidisciplinary consultation as indicated

CLINICAL STAGING

Amenable to larynx-preserving (conservation) surgery (Most T1-2, N0; Selected T3)	See Treatment of Primary and Neck (SUPRA-2)
Requiring (amenable to) total laryngectomy (T3, N0)	See Treatment of Primary and Neck (SUPRA-3)
T4a, N0	See Treatment of Primary and Neck (SUPRA-8)
Node-positive disease	See Clinical Staging (SUPRA-4)
T4b, any N or Unresectable nodal disease or Unfit for surgery	See Treatment of Very Advanced Head and Neck Cancer (ADV-1)
Metastatic (M1) disease at initial presentation	See Treatment of Very Advanced Head and Neck Cancer (ADV-2)

[a]H&P should include documentation and quantification (pack years smoked) of tobacco use history. 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 the NCCN Guidelines for Smoking Cessation and www.smokefree.gov.
[b]Screen for depression (See NCCN Guidelines for Distress Management).
[c]See Principles of Dental Evaluation and Management (DENT-A).
[d]See Principles of Nutrition: Management and Supportive Care (NUTR-A).

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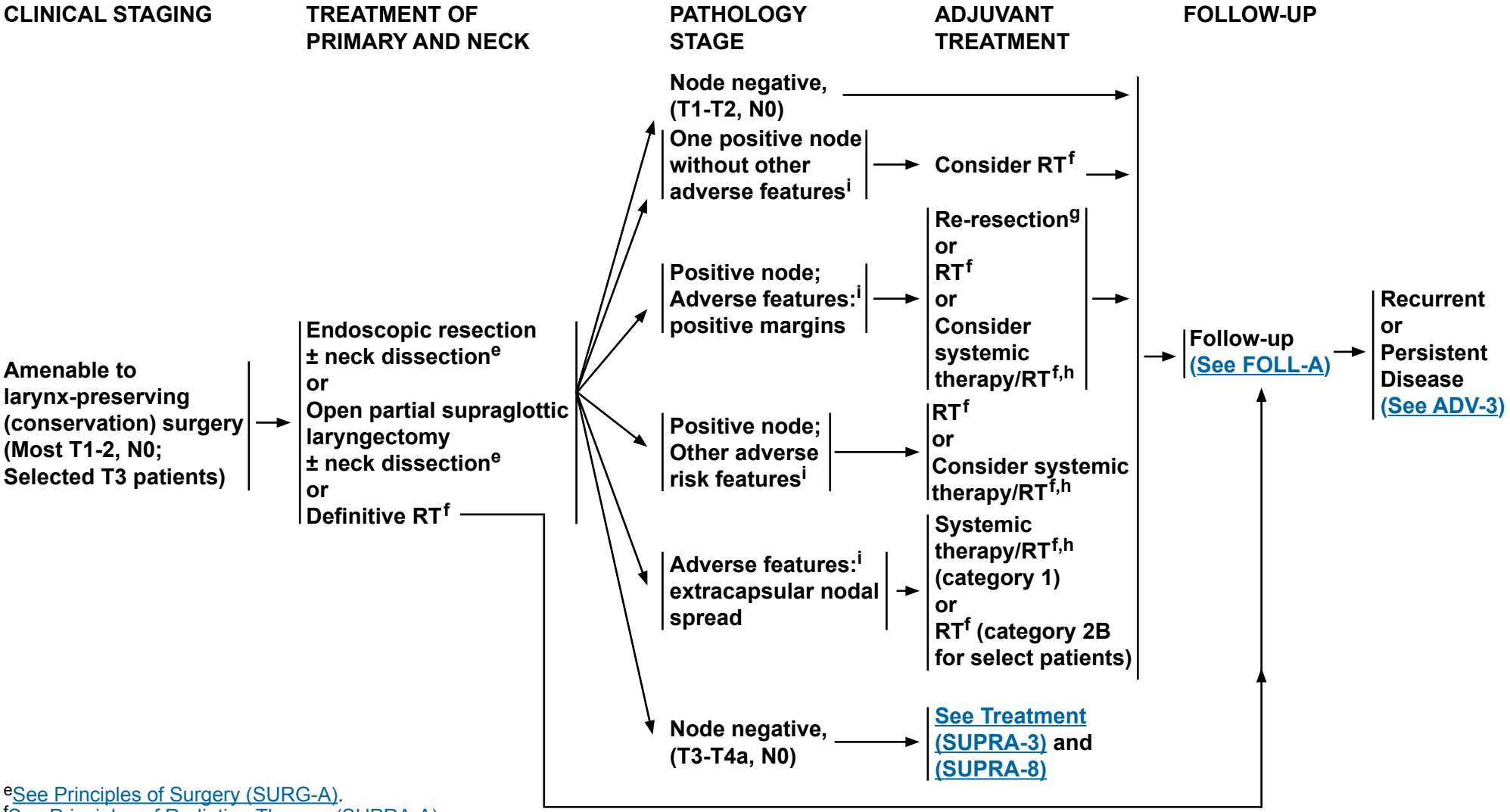

[e] See Principles of Surgery (SURG-A).
[f] See Principles of Radiation Therapy (SUPRA-A).
[g] In highly select patients, re-resection to achieve negative margins, if feasible.
[h] See Principles of Systemic Therapy (CHEM-A).
[i] Adverse features: extracapsular nodal spread, positive margins, pT4 primary, N2 or N3 nodal disease, perineural invasion, and vascular embolism (lymphovascular invasion) (See Discussion).

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

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Cancer of the Supraglottic Larynx

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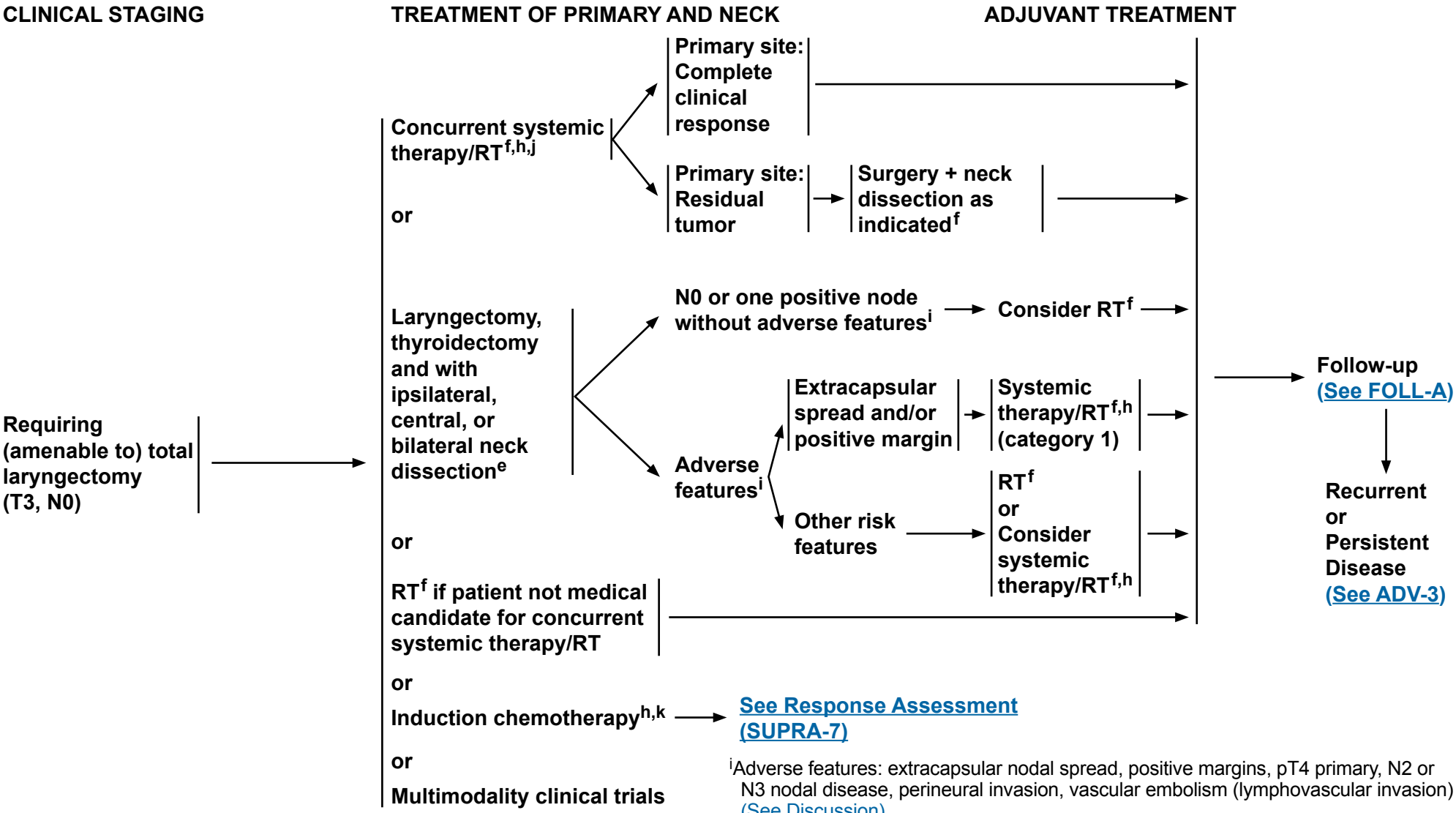
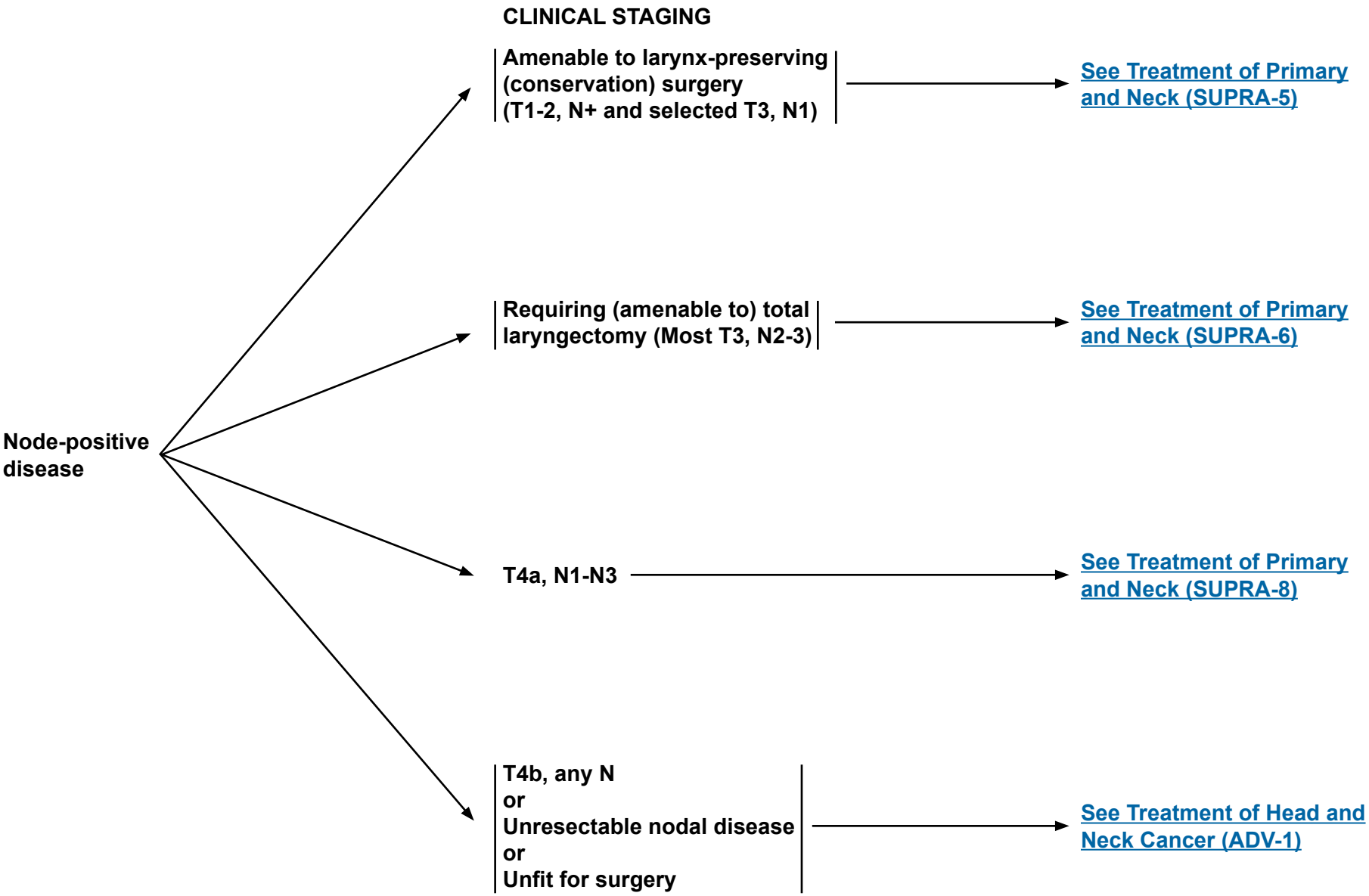


[e] See Principles of Surgery (SURG-A).
[f] See Principles of Radiation Therapy (SUPRA-A).
[h] See Principles of Systemic Therapy (CHEM-A).

[i] Adverse features: extracapsular nodal spread, positive margins, pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism (lymphovascular invasion) (See Discussion).
[j] When using concurrent systemic therapy/RT, the preferred agent is cisplatin (category 1). See Principles of Systemic Therapy (CHEM-A).
[k] See Discussion on induction chemotherapy.

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



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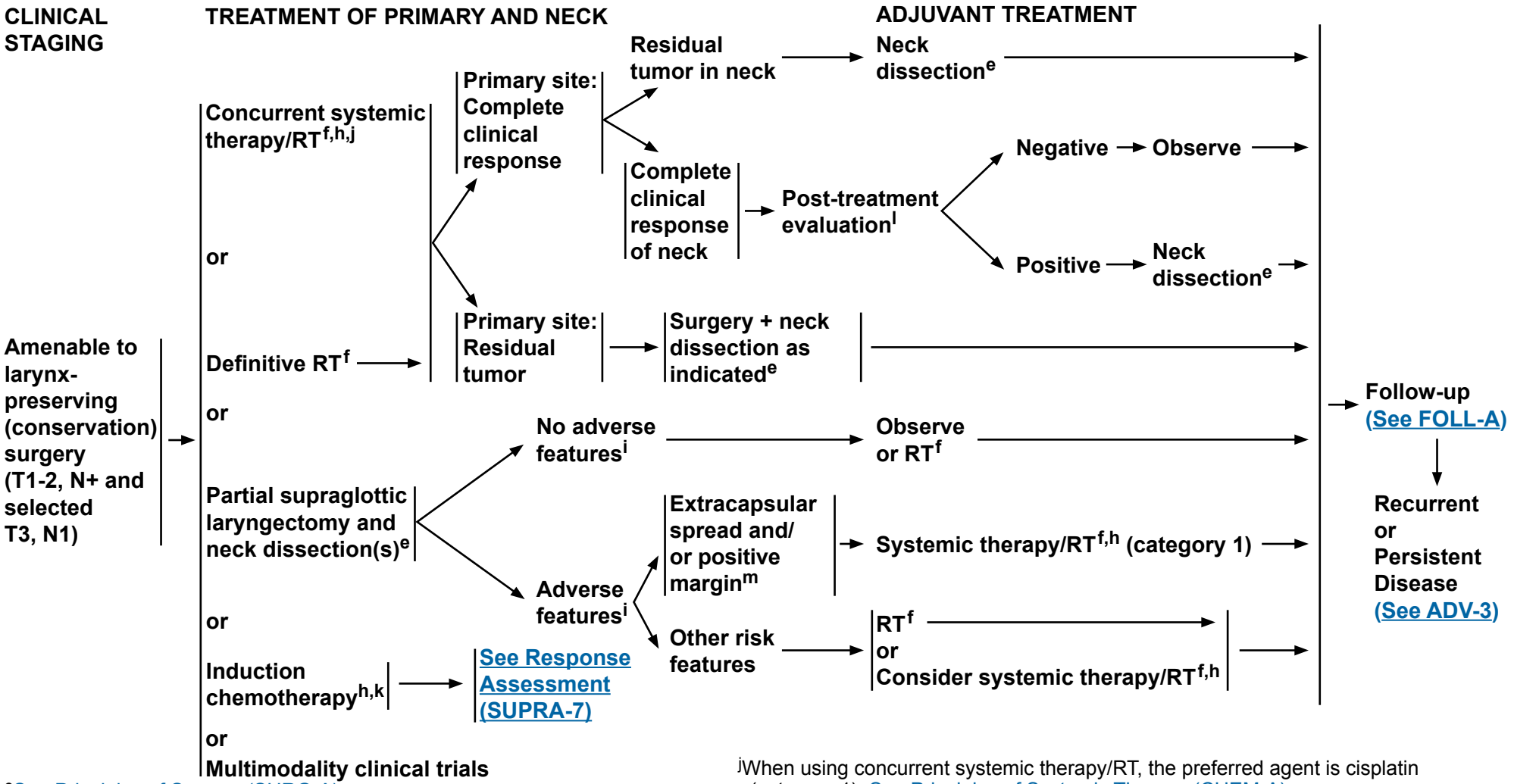

[e] See Principles of Surgery (SURG-A).
[f] See Principles of Radiation Therapy (SUPRA-A).
[h] See Principles of Systemic Therapy (CHEM-A).
[i] Adverse features: extracapsular nodal spread, positive margins, pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism (lymphovascular invasion) (See Discussion).
[j] When using concurrent systemic therapy/RT, the preferred agent is cisplatin (category 1). See Principles of Systemic Therapy (CHEM-A).
[k] See Discussion on induction chemotherapy.
[l] See Post Chemoradiation or RT Neck Evaluation (FOLL-A 2 of 2).
[m] In highly select patients, re-resection (if negative margins are feasible and can be achieved without total laryngectomy) where it would potentially change the subsequent indication for chemotherapy.

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

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Cancer of the Supraglottic Larynx

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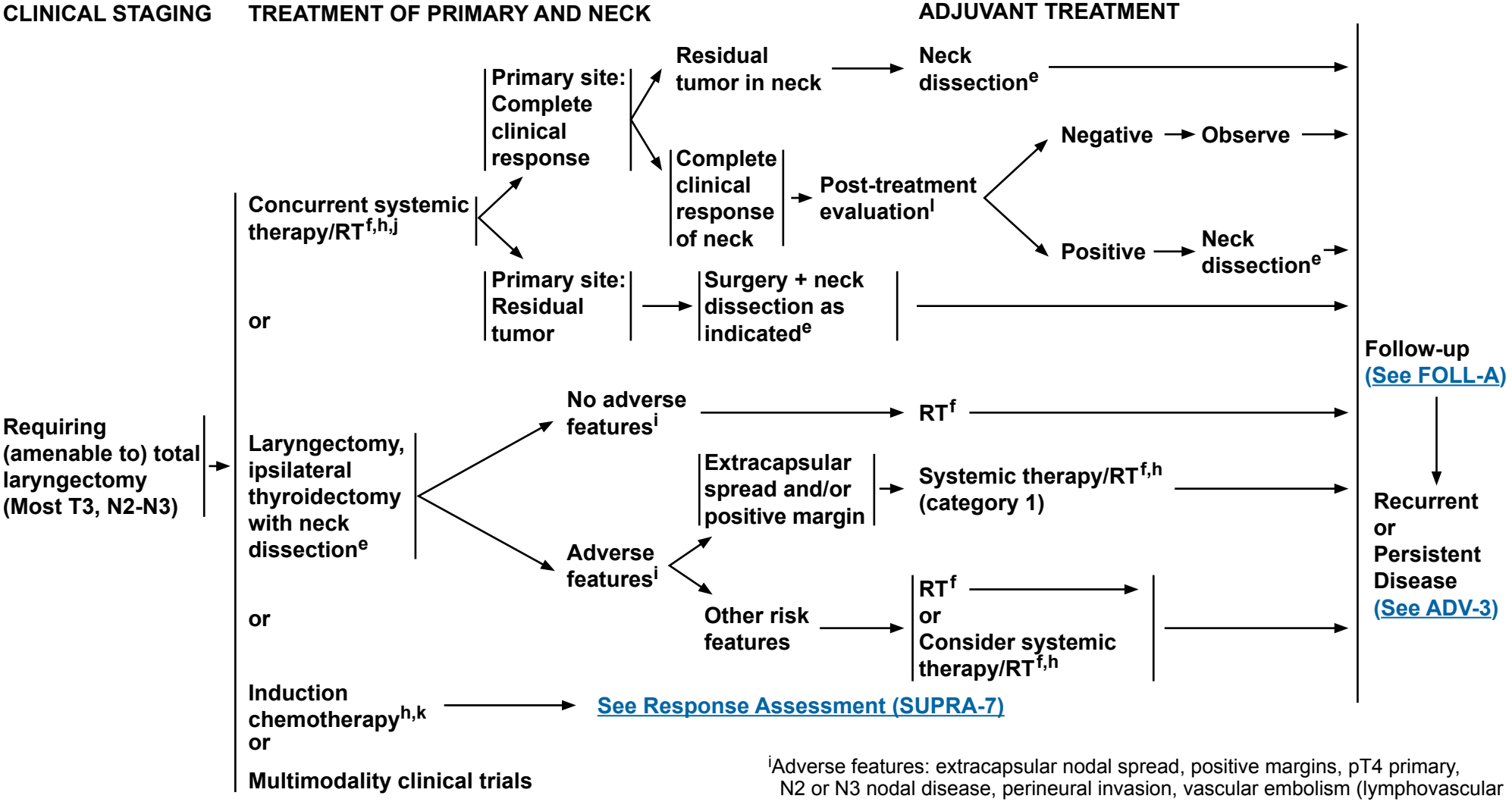

[i]Adverse features: extracapsular nodal spread, positive margins, pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism (lymphovascular invasion) (See Discussion).

[e]See Principles of Surgery (SURG-A).
[f]See Principles of Radiation Therapy (SUPRA-A).
[h]See Principles of Systemic Therapy (CHEM-A).
[j]When using concurrent systemic therapy/RT, the preferred agent is cisplatin (category 1). See Principles of Systemic Therapy (CHEM-A).
[k]See Discussion on induction chemotherapy.
[l]See Post Chemoradiation or RT Neck Evaluation (FOLL-A 2 of 2).

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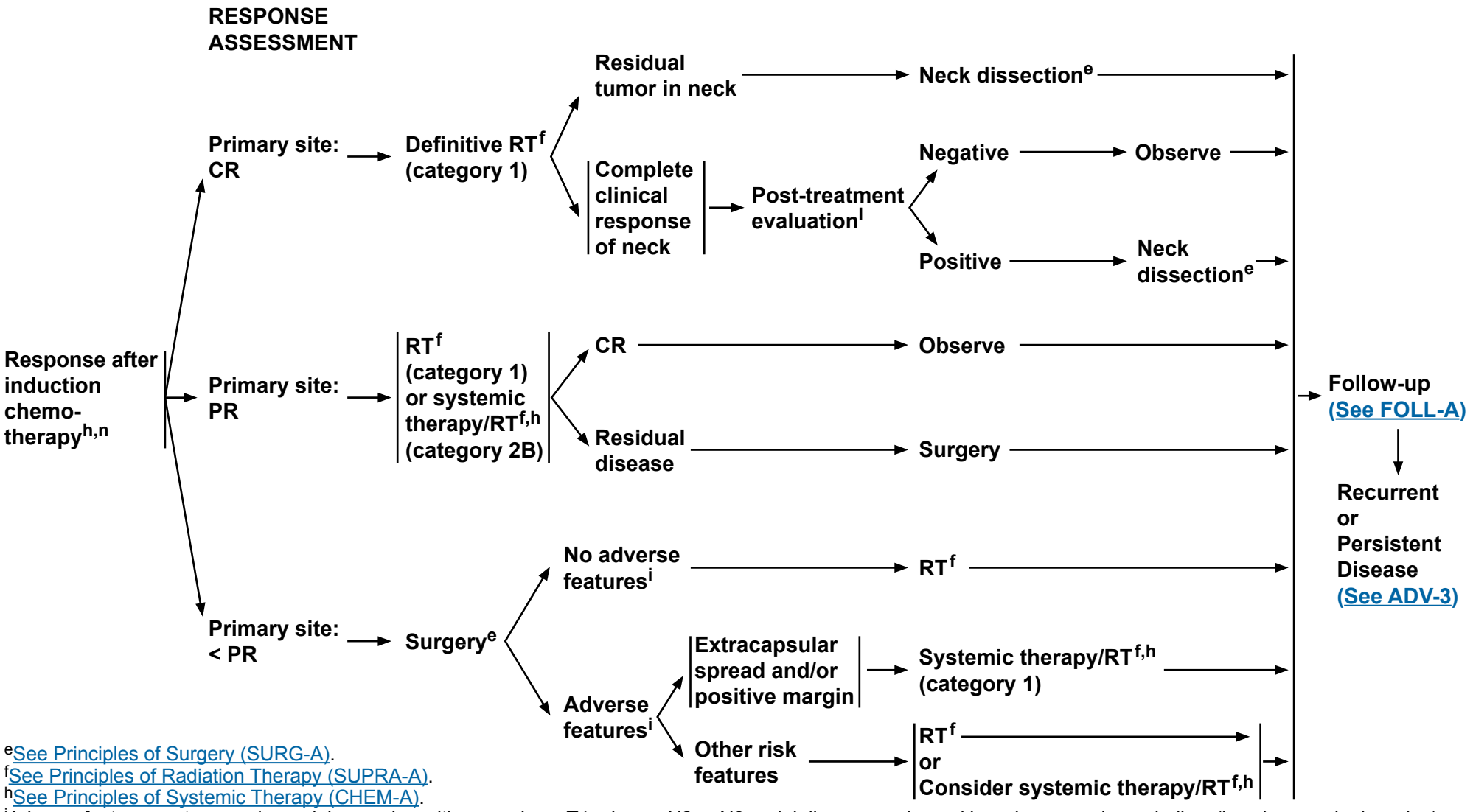
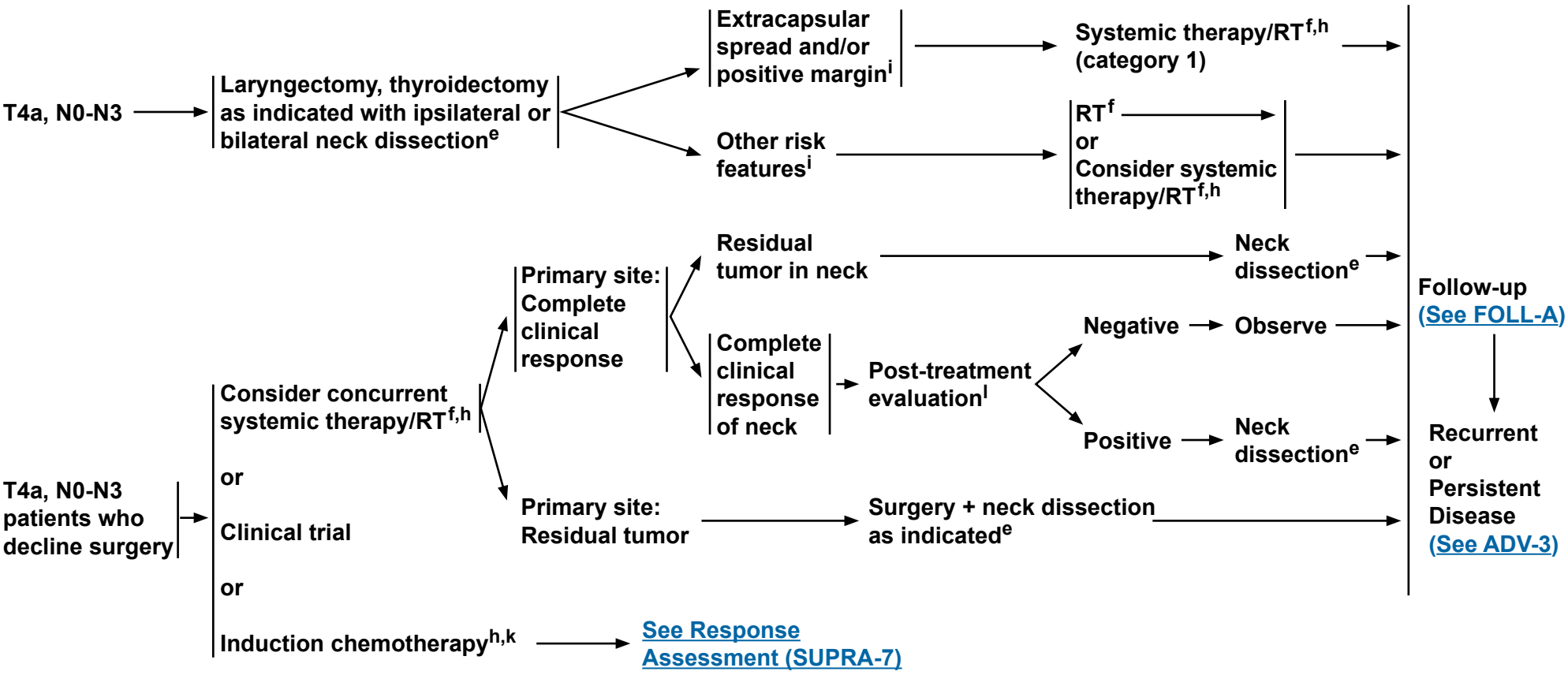
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



[e]See Principles of Surgery (SURG-A).
[f]See Principles of Radiation Therapy (SUPRA-A).
[h]See Principles of Systemic Therapy (CHEM-A).
[i]Adverse features: extracapsular nodal spread, positive margins, pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism (lymphovascular invasion) (See Discussion).
[l]See Post Chemoradiation or RT Neck Evaluation (FOLL-A 2 of 2).
[n]n randomized clinical trials, assessment of response has been done after 2 or 3 cycles.

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



[e] See Principles of Surgery (SURG-A).
[f] See Principles of Radiation Therapy (SUPRA-A).
[h] See Principles of Systemic Therapy (CHEM-A).
[k] See Discussion on induction chemotherapy.
[i] Adverse features: extracapsular nodal spread, positive margins, pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism (lymphovascular invasion) (See Discussion).
[l] See Post Chemoradiation or RT Neck Evaluation (FOLL-A 2 of 2).

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

PRINCIPLES OF RADIATION THERAPY[1]

DEFINITIVE:

RT Alone

- **T1-2, N0: 66–70 Gy conventional (2.0 Gy/fraction)[2]**
- **T2-3, N0-1:**
  - **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[3]**
        - **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)[4]**

Either IMRT or 3-D conformal RT is recommended.

CONCURRENT CHEMORADIATION:[5,6]

- **PTV**
  - **High risk: typically 70 Gy (2.0 Gy/fraction)**
  - **Low to intermediate and low risk: 44–50 Gy (2.0 Gy/fraction) to 54–63 Gy (1.6–1.8 Gy/fraction)[4]**

[1] See Radiation Techniques (RAD-A) and Discussion.
[2] For select T1-2, N0 tumors, accelerated fractionation may be used.
[3] 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.
[4] Suggest 44–50 Gy in 3D conformal RT and sequentially planned IMRT or 54–63 Gy with IMRT dose painting technique (dependent on dose per fraction).
[5] See Principles of Systemic Therapy (CHEM-A).
[6] 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^2; 2–3 cycles of chemotherapy are used depending on the radiation fractionation scheme (RTOG) (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, 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.

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

PRINCIPLES OF RADIATION THERAPY[1]

POSTOPERATIVE:

RT

- **Preferred interval between resection and postoperative RT is ≤6 weeks.**
- **PTV**
  - **High risk: Adverse features such as positive margins (See footnote i on SUPRA-3).**
    - **60–66 Gy (2.0 Gy/fraction); daily Monday–Friday in 6–6.5 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)[4]**

POSTOPERATIVE CHEMORADIATION:

- **Concurrent single-agent cisplatin at 100 mg/m² every 3 weeks is recommended.[7-10]**

Either IMRT or 3-D conformal RT is recommended.

[1] See Radiation Techniques (RAD-A) and Discussion.
[4] Suggest 44–50 Gy in 3D conformal RT and sequentially planned IMRT or 54–63 Gy with IMRT dose painting technique (dependent on dose per fraction).
[7] 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.
[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, 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.
[10] 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.

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NCCN Guidelines Version 1.2016
Ethmoid Sinus Tumors

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WORKUP

- H&P[a,b] including a complete head and neck exam; mirror and fiberoptic examination as clinically indicated
- CT with contrast or MRI with contrast of skull base
- Dental consultation[c] as clinically indicated
- Chest imaging as clinically indicated
- Consider FDG-PET/CT for Stage III or IV

→ Biopsy

PATHOLOGY

- Squamous cell carcinoma
- Adenocarcinoma
- Minor salivary gland tumor[d]
- Esthesioneuroblastoma
- Undifferentiated carcinoma (sinonasal undifferentiated carcinoma [SNUC], small cell, or sinonasal neuroendocrine carcinoma [SNEC])[e]

→ See Primary Treatment (ETHM-2)

Mucosal melanoma
(See NCCN Guidelines for Mucosal Melanoma MM-1)

Sarcoma
(See NCCN Guidelines for Soft Tissue Sarcoma)

Lymphoma
(See NCCN Guidelines for Non-Hodgkin's Lymphomas)

[a]H&P should include documentation and quantification (pack years smoked) of tobacco use history. 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 the NCCN Guidelines for Smoking Cessation and www.smokefree.gov.
[b]Screen for depression (See NCCN Guidelines for Distress Management).
[c]See Principles of Dental Evaluation and Management (DENT-A).
[d]Also see the NCCN Guidelines for Salivary Gland Tumors (SALI-1).
[e]For sinonasal undifferentiated carcinoma (SNUC), small cell or sinonasal neuroendocrine carcinoma (SNEC) histologies, systemic therapy should be a part of the overall treatment. Consider referral to a major medical center that specializes in these diseases.

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

NCCN Guidelines Version 1.2016
Ethmoid Sinus Tumors

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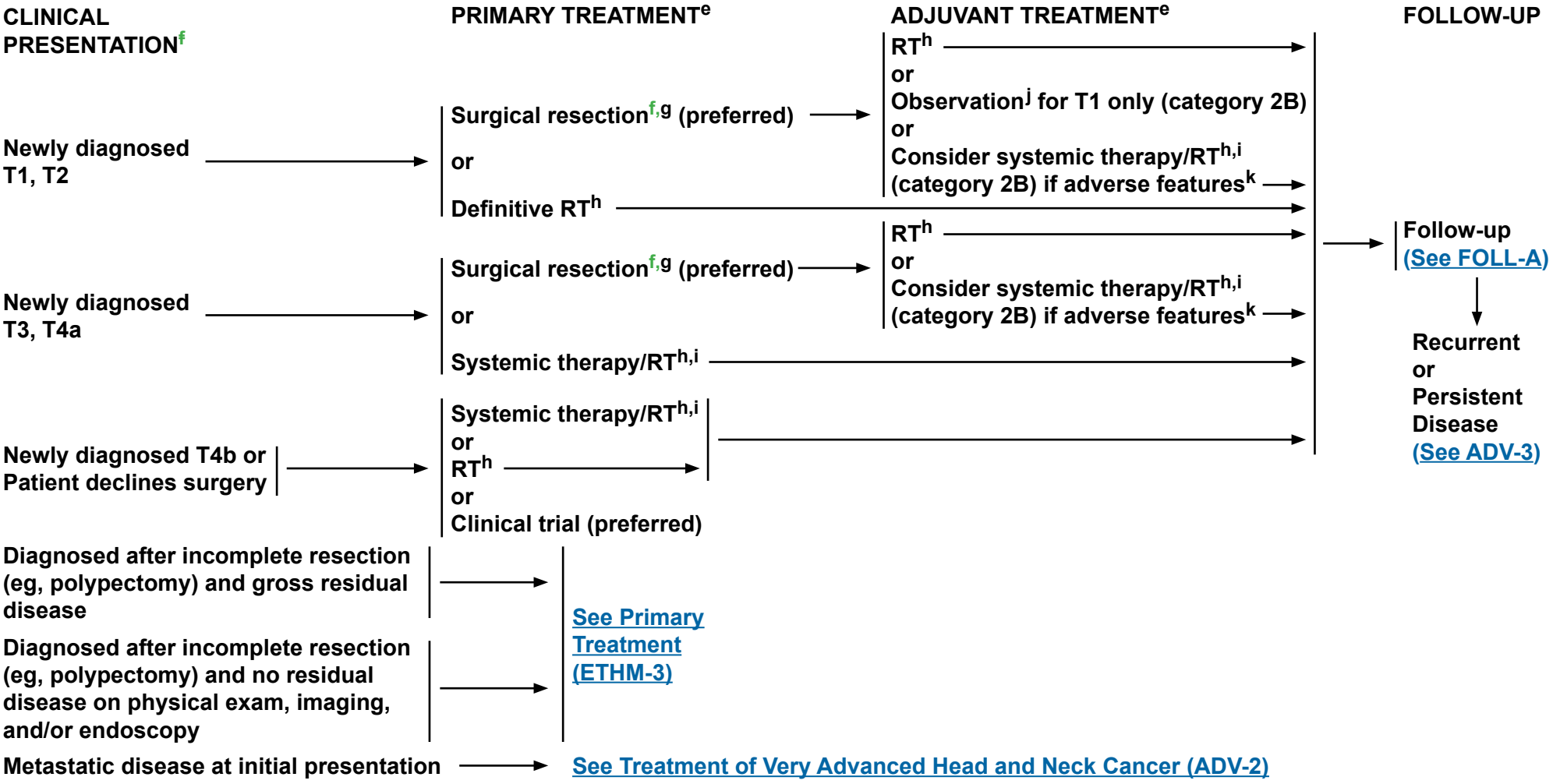

[e]For sinonasal undifferentiated carcinoma (SNUC), small cell or sinonasal neuroendocrine carcinoma (SNEC) histologies, systemic therapy should be a part of the overall treatment. Consider referral to a major medical center that specializes in these diseases.

[f]N+ neck disease is uncommon in ethmoid cancers, but, if present, requires neck dissection and appropriate risk-based adjuvant therapy.

[g]See Principles of Surgery (SURG-A).

[h]See Principles of Radiation Therapy (ETHM-A). For minor salivary gland tumors, see SALI-A.

[i]See Principles of Systemic Therapy (CHEM-A).

[j]Pathologic features: negative margins, central tumors, and low-grade tumors.

[k]Adverse features include positive margins and intracranial extension (See Discussion).

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

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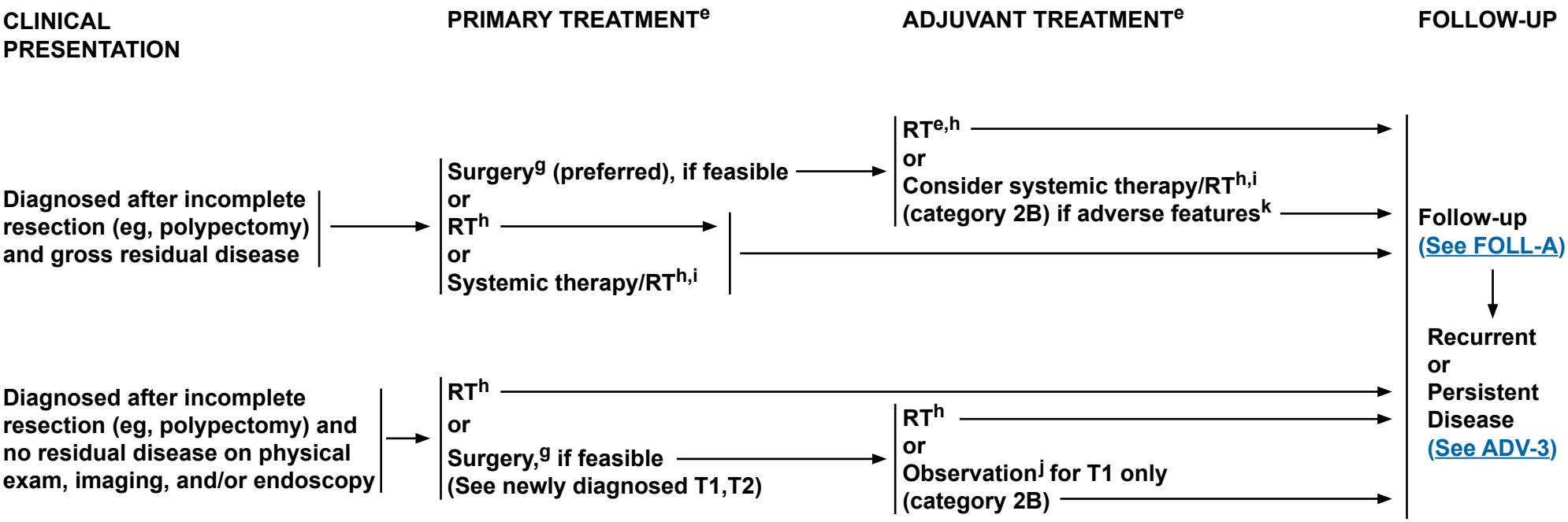

[e]For sinonasal undifferentiated carcinoma (SNUC), small cell or sinonasal neuroendocrine carcinoma (SNEC) histologies, systemic therapy should be a part of the overall treatment. Consider referral to a major medical center that specializes in these diseases.
[g]See Principles of Surgery (SURG-A).
[h]See Principles of Radiation Therapy (ETHM-A). For minor salivary gland tumors, see SALI-A.
[i]See Principles of Systemic Therapy (CHEM-A).
[j]Pathologic features: negative margins, favorable histology, central tumors, and low-grade tumors.
[k]Adverse features include positive margins and intracranial extension (See Discussion).

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PRINCIPLES OF RADIATION THERAPY[1]

DEFINITIVE:

RT Alone

- **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 70–70.2 Gy (1.8–2.0 Gy/fraction); daily Monday-Friday in 6–7 weeks[2,3]**
      - **– 66–70 Gy (2.0 Gy/fraction; 6 fractions/week accelerated)**
      - **– Concomitant boost accelerated RT: 72 Gy/6 weeks (2 Gy once daily and then 1.8 Gy/fraction, large field; 1.5 Gy boost as second daily fraction during last 12 treatment days)**
      - **– Hyperfractionation: 81.6 Gy/7 weeks (1.2 Gy/fraction, twice daily)**
  - **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)[4,5]**

CONCURRENT CHEMORADIATION:[6]

- **PTV**
  - **High risk: typically 70–70.2 Gy (1.8–2.0 Gy/fraction); daily Monday–Friday in 7 weeks[2]**
  - **Low to intermediate risk:**
    - ◊ **44–50 Gy (2.0 Gy/fraction) to 54–63 Gy (1.6–1.8 Gy/fraction)[4,5]**

POSTOPERATIVE:

RT

- **Preferred interval between resection and postoperative RT is ≤6 weeks**
- **PTV**
  - **High risk: Adverse features such as positive margins (See footnote k on ETHM-2)**
    - ◊ **60–66 Gy (1.8–2.0 Gy/fraction); daily Monday–Friday in 6–6.5 weeks[2]**
  - **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)[4,5]**

POSTOPERATIVE CHEMORADIATION

- **Concurrent single-agent cisplatin**

IMRT is preferred over 3-D conformal RT for maxillary sinus or paranasal/ethmoid sinus tumors to minimize dose to critical structures. The role of proton therapy is being investigated.

[1] See Radiation Techniques (RAD-A) and Discussion.
[2] In the paranasal sinus area, care should be taken to avoid critical neural structures; therefore, 1.8 Gy/fraction can be considered.
[3] 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.
[4] Suggest 44–50 Gy in 3-D conformal RT and sequentially planned IMRT or 54–63 Gy with IMRT dose painting technique (dependent on dose per fraction).
[5] Treatment to sites of suspected subclinical spread is not consistently performed at all institutions. (Le QT, Fu KK, Kaplan MJ, et al. Lymph node metastasis in maxillary sinus carcinoma. Int J Radiat Oncol Biol Phys 2000;46:541-549.)
[6] See Principles of Systemic Therapy (CHEM-A).

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

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NCCN Guidelines Version 1.2016
Maxillary Sinus Tumors

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WORKUP

- H&P[a,b] including a complete head and neck exam; mirror and fiberoptic examination as clinically indicated
- Complete head and neck CT with contrast and/or MRI with contrast
- Dental[c]/prosthetic consultation as clinically indicated
- Chest imaging as clinically indicated
- Consider FDG-PET/CT for Stage III or IV

→ Biopsy[d]

PATHOLOGY

- Squamous cell carcinoma
- Adenocarcinoma
- Minor salivary gland tumor[e]
- Esthesioneuroblastoma
- Undifferentiated carcinoma (SNUC, small cell, or SNEC)[f]

→ T1-2, N0, All histologies → See Primary Treatment (MAXI-2)

→ T3-4, N0, Any T, N+, All histologies → See Primary Treatment (MAXI-3)

Mucosal melanoma
(See NCCN Guidelines for Mucosal Melanoma MM-1)

Sarcoma
(See NCCN Guidelines for Soft Tissue Sarcoma)

Lymphoma
(See NCCN Guidelines for Non-Hodgkin's Lymphomas)

[a]H&P should include documentation and quantification (pack years smoked) of tobacco use history. 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 the NCCN Guidelines for Smoking Cessation and www.smokefree.gov.

[b]Screen for depression (See NCCN Guidelines for Distress Management).

[c]See Principles of Dental Evaluation and Management (DENT-A).

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

[e]Also see the NCCN Guidelines for Salivary Gland Tumors (SALI-1).

[f]For sinonasal undifferentiated carcinoma (SNUC), small cell or sinonasal neuroendocrine carcinoma (SNEC) histologies, systemic therapy should be a part of the overall treatment. Consider referral to a major medical center that specializes in these diseases.

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

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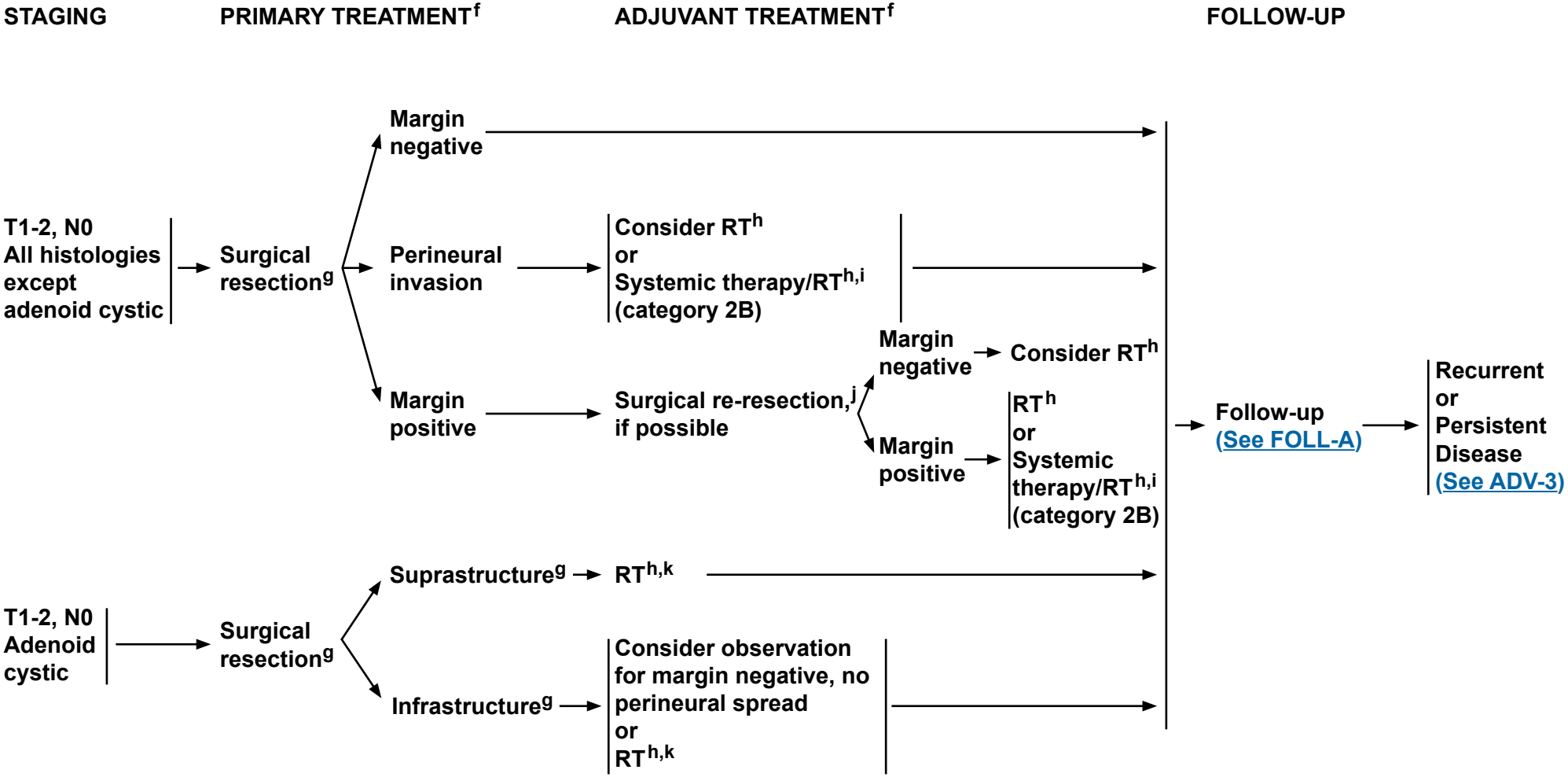

[f]For sinonasal undifferentiated carcinoma (SNUC), small cell or sinonasal neuroendocrine carcinoma (SNEC) histologies, systemic therapy should be a part of the overall treatment. Consider referral to a major medical center that specializes in these diseases.
[g]See Principles of Surgery (SURG-A).
[h]See Principles of Radiation Therapy (MAXI-A).
[i]See Principles of Systemic Therapy (CHEM-A).
[j]Consider re-resection to achieve negative margins, if feasible.
[k]For adenoid cystic tumors and minor salivary gland tumors, see SALI-A.

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

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Maxillary Sinus Tumors

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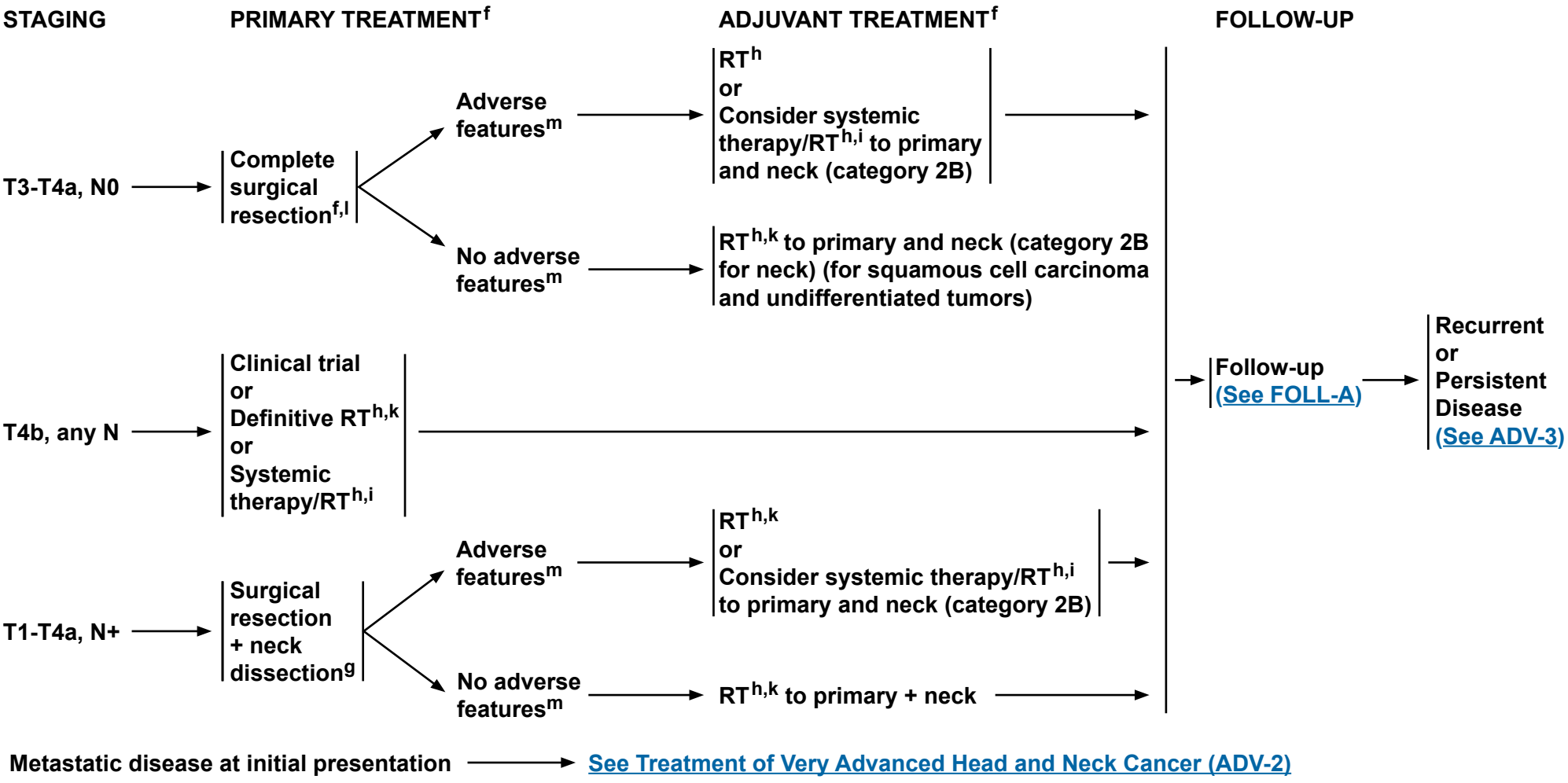

[f]For sinonasal undifferentiated carcinoma (SNUC), small cell or sinonasal neuroendocrine carcinoma (SNEC) histologies, systemic therapy should be a part of the overall treatment. Consider referral to a major medical center that specializes in these diseases.
[g]See Principles of Surgery (SURG-A).
[h]See Principles of Radiation Therapy (MAXI-A).
[i]See Principles of Systemic Therapy (CHEM-A).
[k]For adenoid cystic tumors and minor salivary gland tumors, see SALI-A.
[l]For surgical resection, consider preoperative RT or preoperative systemic therapy/RT in select patients (category 2B).
[m]Adverse features include positive margins or extracapsular nodal spread (See Discussion).

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

PRINCIPLES OF RADIATION THERAPY[1]

DEFINITIVE:

RT Alone

- 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 70–70.2 Gy (1.8–2.0 Gy/fraction) daily Monday–Friday in 6–7 weeks[2,3]
      - – 66–70 Gy (2.0 Gy/fraction; 6 fractions/week accelerated)
      - – Concomitant boost accelerated RT: 72 Gy/6 weeks (2 Gy once daily and then 1.8 Gy/fraction, large field; 1.5 Gy boost as second daily fraction during last 12 treatment days)
      - – Hyperfractionation: 81.6 Gy/7 weeks (1.2 Gy/fraction, twice daily)
  - 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)[4,5]

CONCURRENT CHEMORADIATION:[6]

- PTV
  - High-risk: typically 70–70.2 Gy (1.8–2.0 Gy/fraction); daily Monday–Friday in 7 weeks[2]
  - Low to intermediate risk:
    - ◊ 44–50 Gy (2.0 Gy/fraction) to 54–63 Gy (1.6–1.8 Gy/fraction)[4,5]

POSTOPERATIVE:

RT

- Preferred interval between resection and postoperative RT is ≤6 weeks
- PTV
  - High risk: Adverse features such as positive margins (See footnote m on MAXI-3)
    - ◊ 60–66 Gy (1.8–2.0 Gy/fraction); daily Monday–Friday in 6–6.5 weeks[2]
  - 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)[4,5]

POSTOPERATIVE CHEMORADIATION

- Concurrent single-agent cisplatin

IMRT is preferred over 3D conformal RT for maxillary sinus or paranasal/ethmoid sinus tumors to minimize dose to critical structures. The role of proton therapy is being investigated.

[1] See Radiation Techniques (RAD-A) and Discussion.
[2] In the paranasal sinus area, care should be taken to avoid critical neural structures; therefore, 1.8 Gy/fraction can be considered.
[3] 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.
[4] Suggest 44–50 Gy in 3D conformal RT and sequentially planned IMRT or 54–63 Gy with IMRT dose painting technique (dependent on dose per fraction).
[5] Treatment to sites of suspected subclinical spread is not consistently performed at all institutions. (Le QT, Fu KK, Kaplan MJ, et al. Lymph node metastasis in maxillary sinus carcinoma. Int J Radiat Oncol Biol Phys 2000;46:541-549) and (Jeremic B, Nguyen-Tan PF, Bamberg M. Elective neck irradiation in locally advanced squamous cell carcinoma of the maxillary sinus: a review. J Cancer Res Clin Oncol 2002;128:235-238.)
[6] See Principles of Systemic Therapy (CHEM-A).

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

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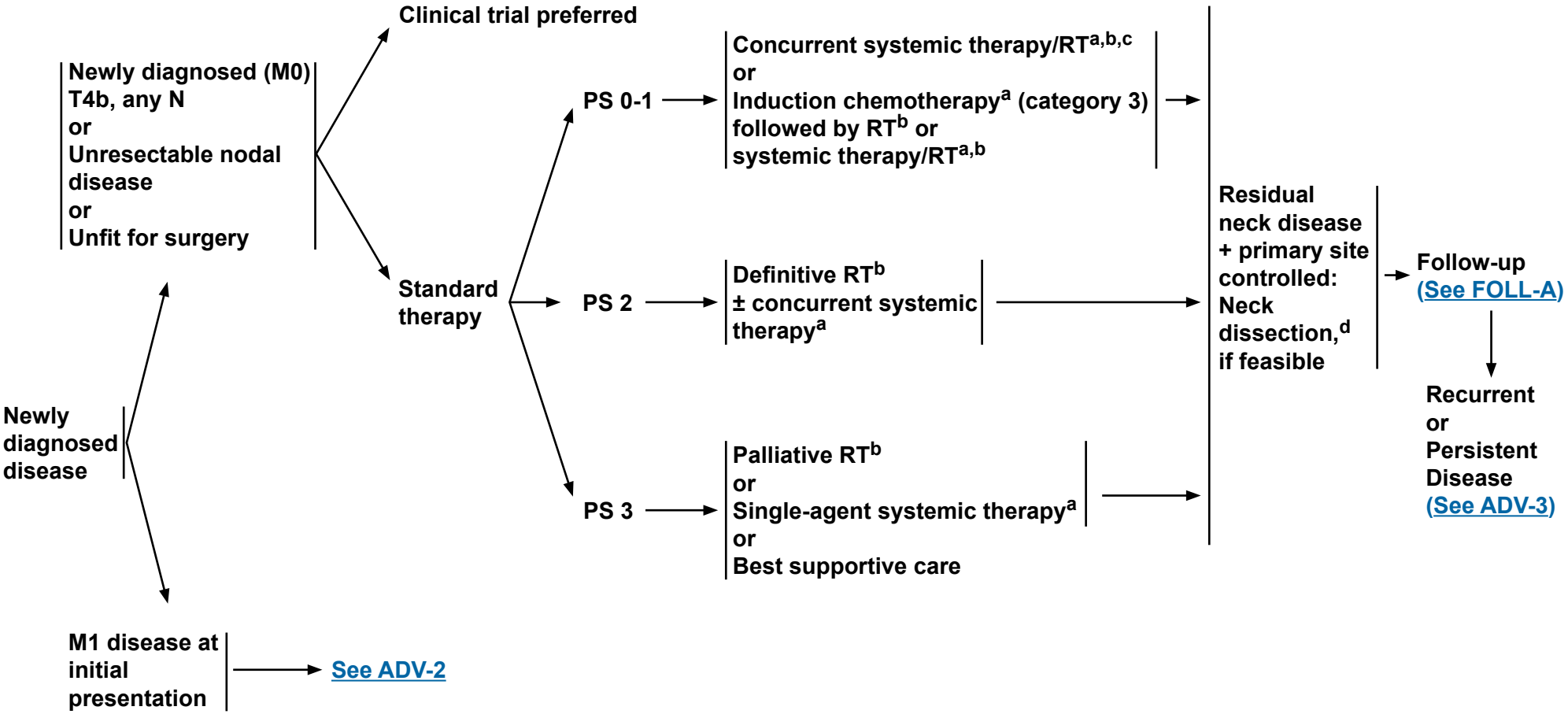
DIAGNOSIS

TREATMENT OF HEAD AND NECK CANCER



PS = Performance Status (Eastern Cooperative Oncology Group [ECOG])

[a] See Principles of Systemic Therapy (CHEM-A).
[b] See Principles of Radiation Therapy (ADV-A).
[c] When using concurrent systemic therapy/RT, the preferred agent is cisplatin (category 1). See Principles of Systemic Therapy (CHEM-A).
[d] See Principles of Surgery (SURG-A).

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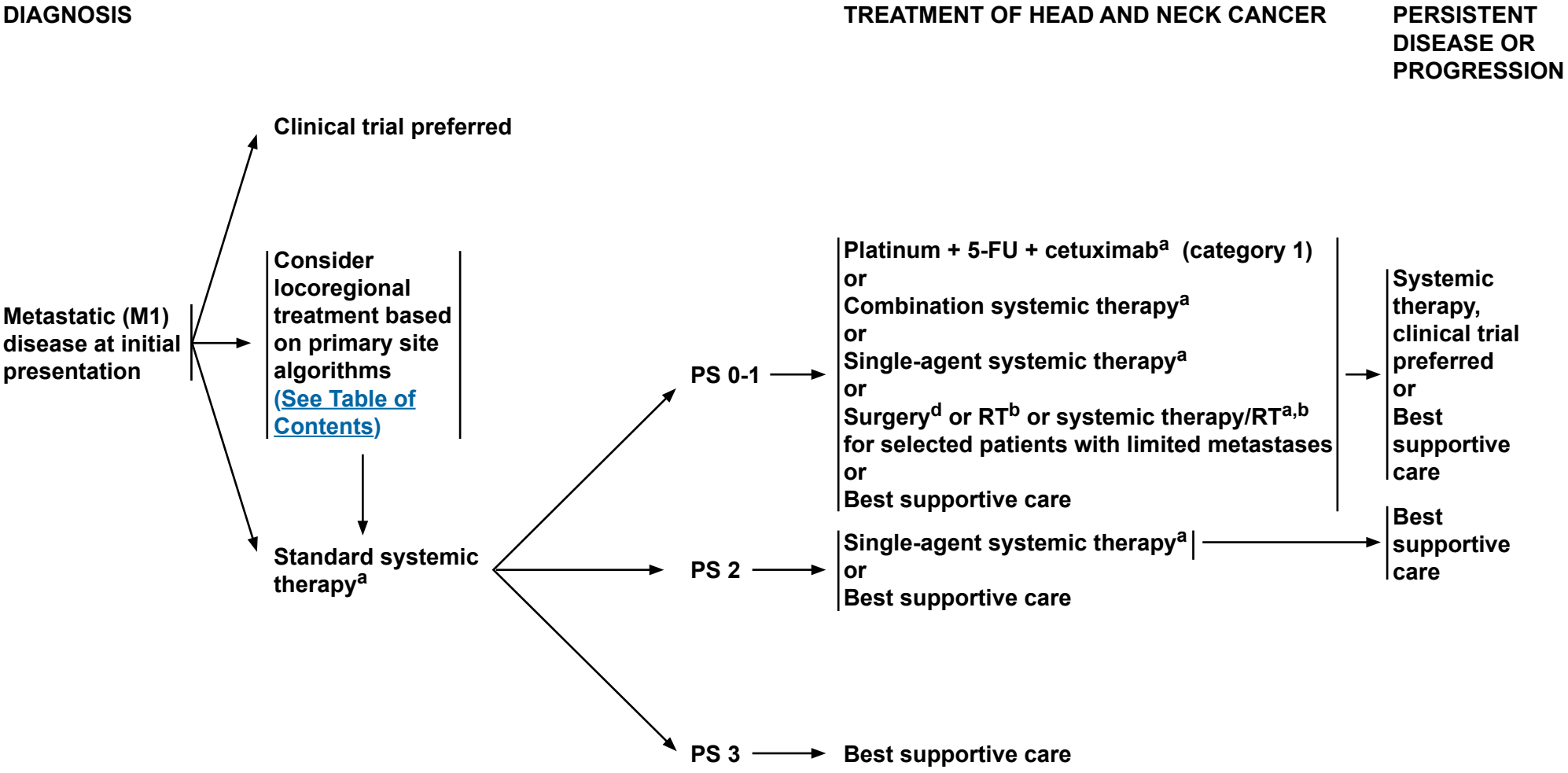

[a] See Principles of Systemic Therapy (CHEM-A).
[b] See Principles of Radiation Therapy (ADV-A).
[d] See Principles of Surgery (SURG-A).

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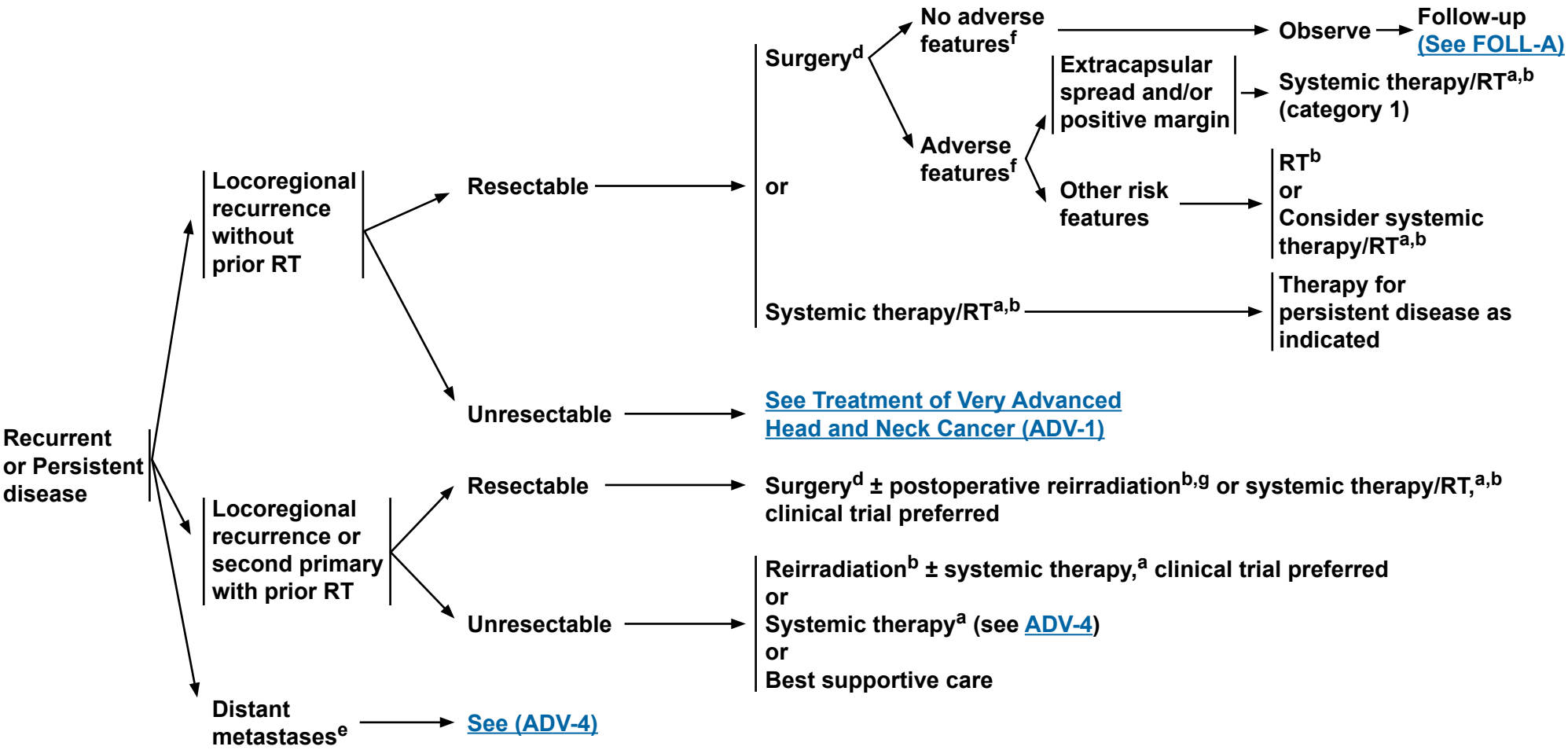
TREATMENT OF HEAD AND NECK CANCER



[a] See Principles of Systemic Therapy (CHEM-A).
[b] See Principles of Radiation Therapy (ADV-A).
[d] See Principles of Surgery (SURG-A).
[e] Consider palliative RT as clinically indicated (eg, bone metastases). (See RAD-A).
[f] Adverse features: extracapsular nodal spread, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, perineural invasion, and vascular embolism (lymphovascular invasion) (See Discussion).
[g] Reirradiation should be limited to a highly select subset of patients (Janot F, de Raucourt D, Benhamou E, et al. Randomized trial of postoperative reirradiation combined with chemotherapy after salvage surgery compared with salvage surgery alone in head and neck carcinoma. J Clin Oncol 2008;26:5518-5523).

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

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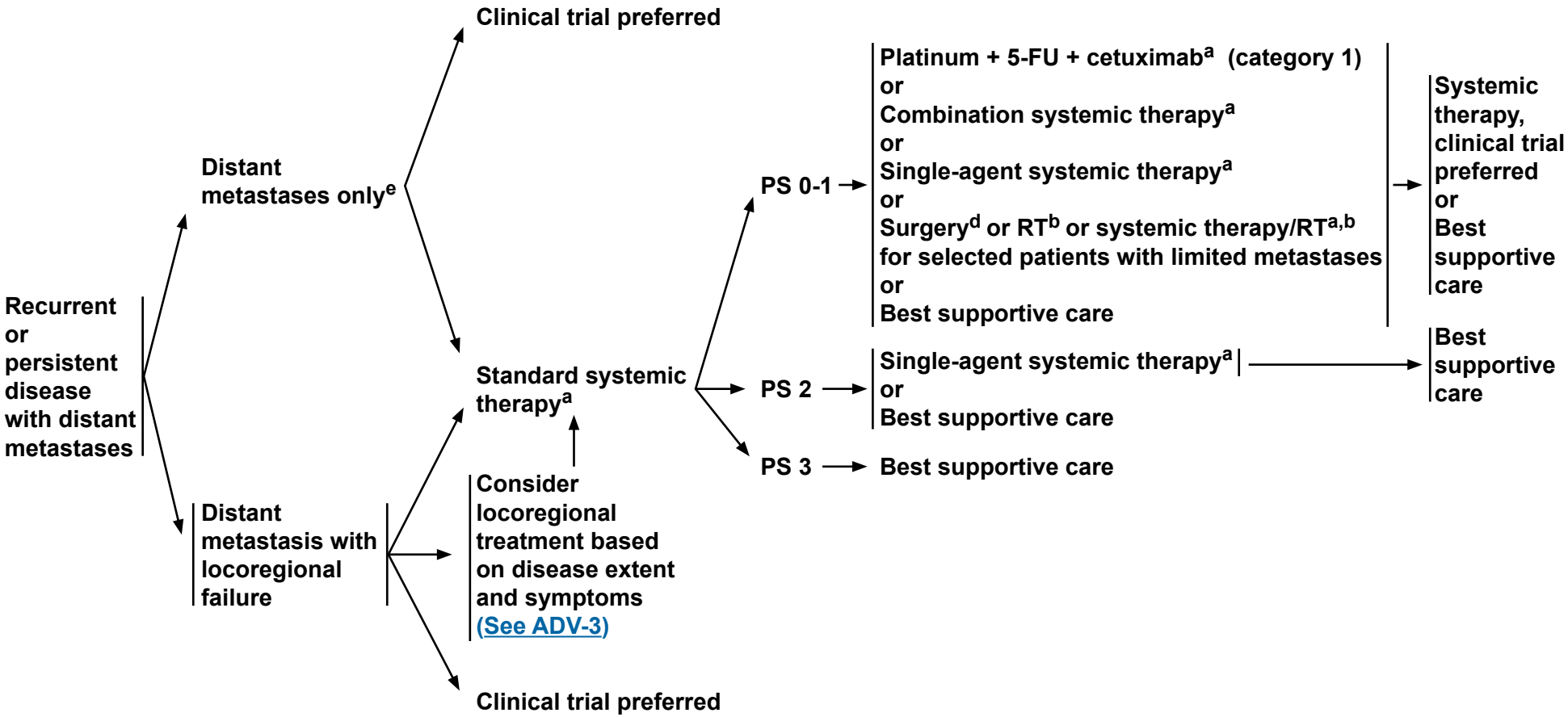
PERSISTENT DISEASE OR PROGRESSION



[a]See Principles of Systemic Therapy (CHEM-A).
[b]See Principles of Radiation Therapy (ADV-A).
[d]See Principles of Surgery (SURG-A).
[e]Consider palliative RT as clinically indicated (eg, bone metastases). (See RAD-A).

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PRINCIPLES OF RADIATION THERAPY[1,2]

CONCURRENT CHEMORADIATION[3] (preferred for patients eligible for chemotherapy):

- **PTV**
  - **High risk: typically 70 Gy (2.0 Gy/fraction)**
  - **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)[4]**

CHEMORADIATION:[3]

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^2; 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;13:145-53). 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.[5] 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.

[1] See Radiation Techniques (RAD-A) and Discussion.

[2] In general, the reirradiated population of head and neck cancer patients as described in the current literature represents a diverse but highly selected group of patients treated in centers where there is high level of expertise and systems in place for managing acute and long-term toxicities. When the goal of treatment is curative and surgery is not an option, reirradiation strategies can be considered for patients who: develop locoregional failures or second primaries at ≥6 months after the initial radiotherapy; can receive additional doses of radiotherapy of at least 60 Gy; and can tolerate concurrent chemotherapy. Organs at risk for toxicity should be carefully analyzed through review of dose volume histograms, and consideration for acceptable doses should be made on the basis of time interval since original radiotherapy, anticipated volumes to be included, and patient's life expectancy. (McDonald M, Lawson J, Garg M, et al. ACR appropriateness criteria retreatment of recurrent head and neck cancer after prior definitive radiation. Expert panel on radiation oncology-head and neck cancer. Int J Radiat Oncol Biol Phys 2011;80:1292-1298.)

[3] See Principles of Systemic Therapy (CHEM-A).

[4] Suggest 44–50 Gy in 3-D conformal RT and sequentially planned IMRT or 54–63 Gy with IMRT dose painting technique (dependent on dose per fraction).

[5] RTOG 0522: a randomized phase III trial of concurrent accelerated radiation and cisplatin versus concurrent accelerated radiation, cisplatin, and cetuximab [followed by surgery for selected patients] for stage III and IV head and neck carcinomas. Clin Adv Hematol Oncol 2007;5:79-81.

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

Continue

PRINCIPLES OF RADIATION THERAPY[1,2]

DEFINITIVE:

RT Alone

- **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:**
      - **– 70–72 Gy (2.0 Gy/fraction) daily Monday–Friday in 7–7.5 weeks[6]**
      - **– 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: 81.6 Gy/7 weeks (1.2 Gy/fraction, twice daily)**
      - **– Modified fractionation: total dose >70 Gy and treatment course <7 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)[4]**

Either IMRT or 3-D conformal RT is recommended.

POSTOPERATIVE:

RT

- **Preferred interval between resection and postoperative RT is ≤6 weeks.**
- **PTV**
  - **High risk: Adverse features such as positive margins (See footnote f on ADV-3)**
    - ◊ **60–66 Gy (2.0 Gy/fraction); daily Monday–Friday in 6–6.5 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)[4]**

POSTOPERATIVE CHEMORADIATION:

- **Concurrent single-agent cisplatin at 100 mg/m^2 every 3 weeks is recommended.[7-9]**

[1] See Radiation Techniques (RAD-A) and Discussion.

[2] In general, the reirradiated population of head and neck cancer patients as described in the current literature represents a diverse but highly selected group of patients treated in centers where there is high level of expertise and systems in place for managing acute and long-term toxicities. When the goal of treatment is curative and surgery is not an option, reirradiation strategies can be considered for patients who: develop locoregional failures or second primaries at ≥6 months after the initial radiotherapy; can receive additional doses of radiotherapy of at least 60 Gy; and can tolerate concurrent chemotherapy. Organs at risk for toxicity should be carefully analyzed through review of dose volume histograms, and consideration for acceptable doses should be made on the basis of time interval since original radiotherapy, anticipated volumes to be included, and patient's life expectancy. (McDonald M, Lawson J, Garg M, et al. ACR appropriateness criteria retreatment of recurrent head and neck cancer after prior definitive radiation. Expert panel on radiation oncology-head and neck cancer. Int J Radiat Oncol Biol Phys 2011;80:1292-1298.)

[4] Suggest 44–50 Gy in 3D conformal RT and sequentially planned IMRT or 54–63 Gy with IMRT dose painting technique (dependent on dose per fraction).

[6] 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.

[7] 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.

[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, 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.

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

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Occult Primary

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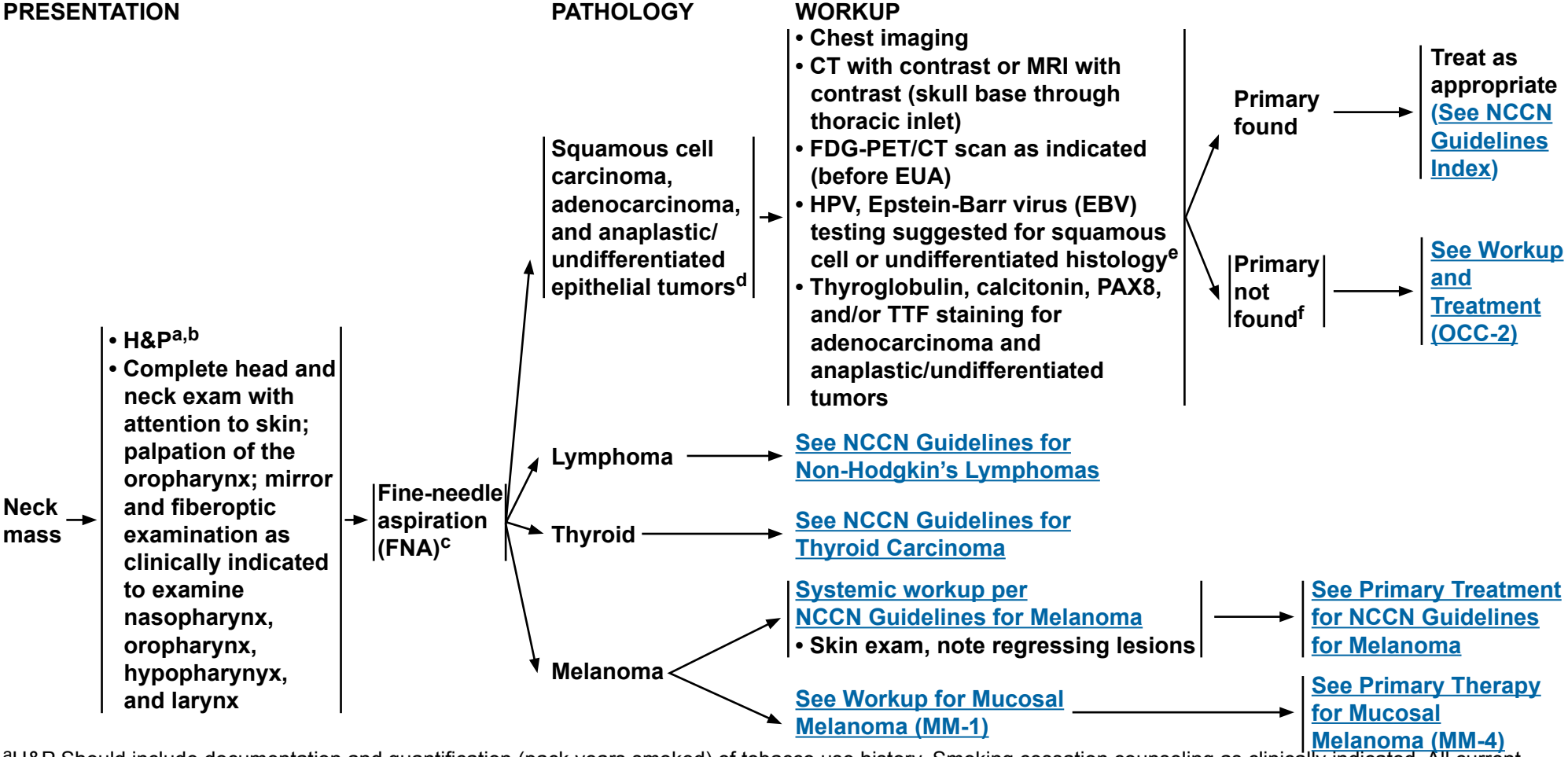

[a]H&P Should include documentation and quantification (pack years smoked) of tobacco use history. Smoking cessation counseling as clinically indicated. All current smokers should be advised to quit smoking, and former smokers should be advised to remain abstinent from smoking. For additional cessation support and resources, smokers can be referred to the NCCN Guidelines for Smoking Cessation and www.smokefree.gov.

[b]Screen for depression (See NCCN Guidelines for Distress Management).

[c]Repeat FNA, core, or open biopsy may be necessary for uncertain or non-diagnostic histologies. Patient should be prepared for neck dissection at time of open biopsy, if indicated.

[d]Determined with appropriate immunohistochemical stains.

[e]Whether HPV or EBV positive status may help to define the radiation fields is being investigated (See Principles of Surgery [SURG-A 2 of 8] and Discussion).

[f]Strongly consider referral to a high-volume, multidisciplinary cancer center.

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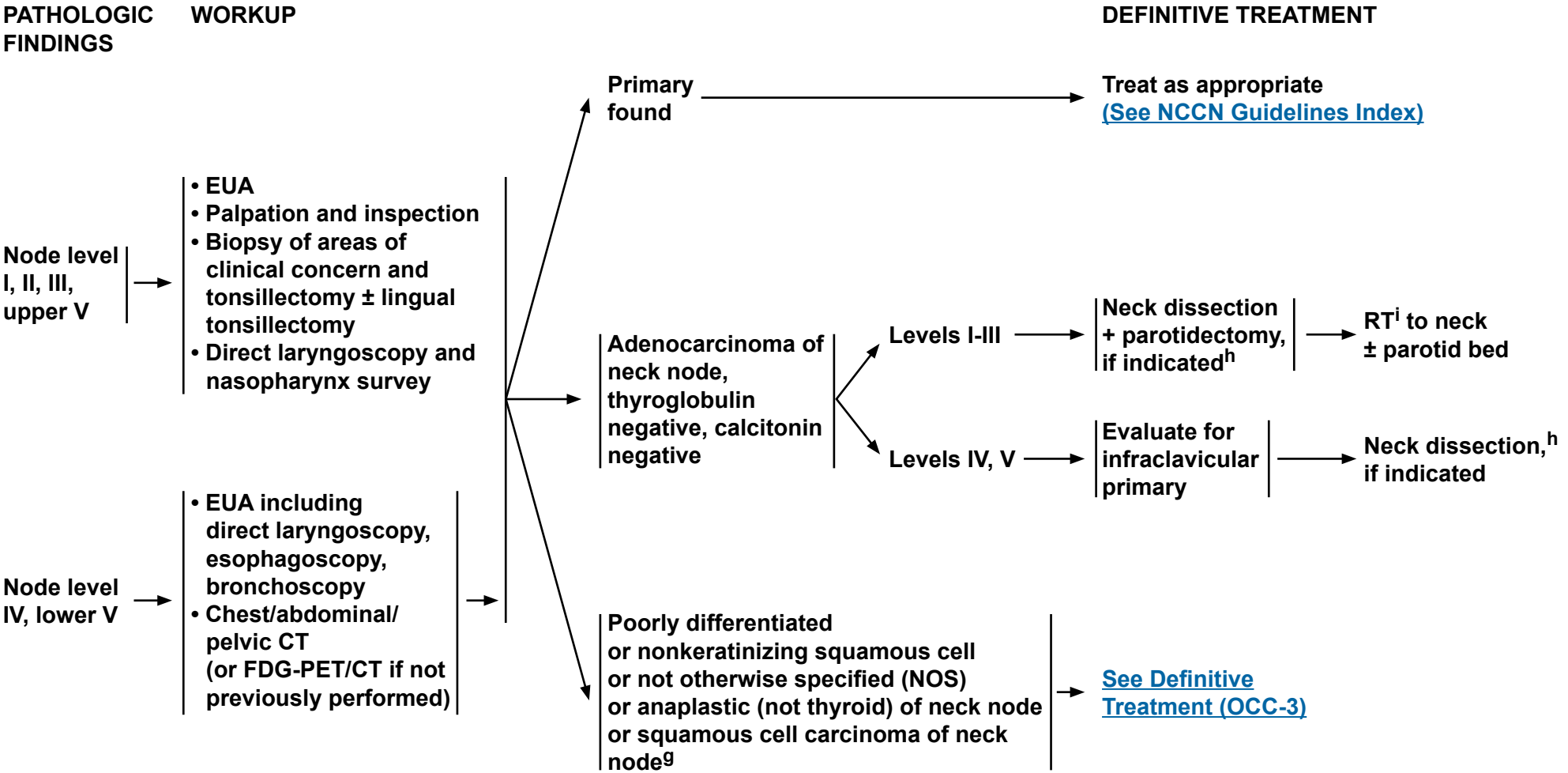

[g]HPV and EBV testing are suggested if not yet done.
[h]See Principles of Surgery (SURG-A).
[i]See Principles of Radiation Therapy (OCC-A).

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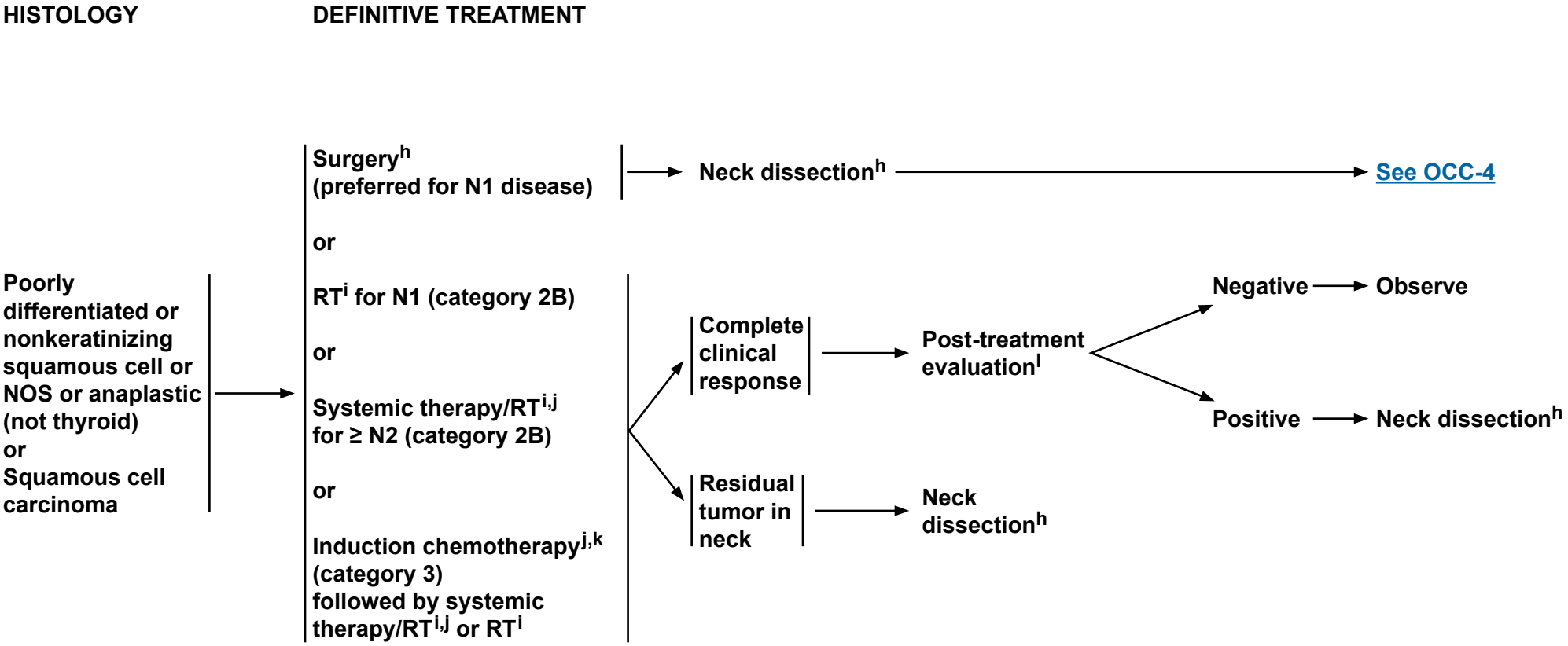

[h] See Principles of Surgery (SURG-A).
[i] See Principles of Radiation Therapy (OCC-A).
[j] See Principles of Systemic Therapy (CHEM-A).
[k] See Discussion on induction chemotherapy.
[l] See Post Chemoradiation or RT Neck Evaluation (FOLL-A 2 of 2).

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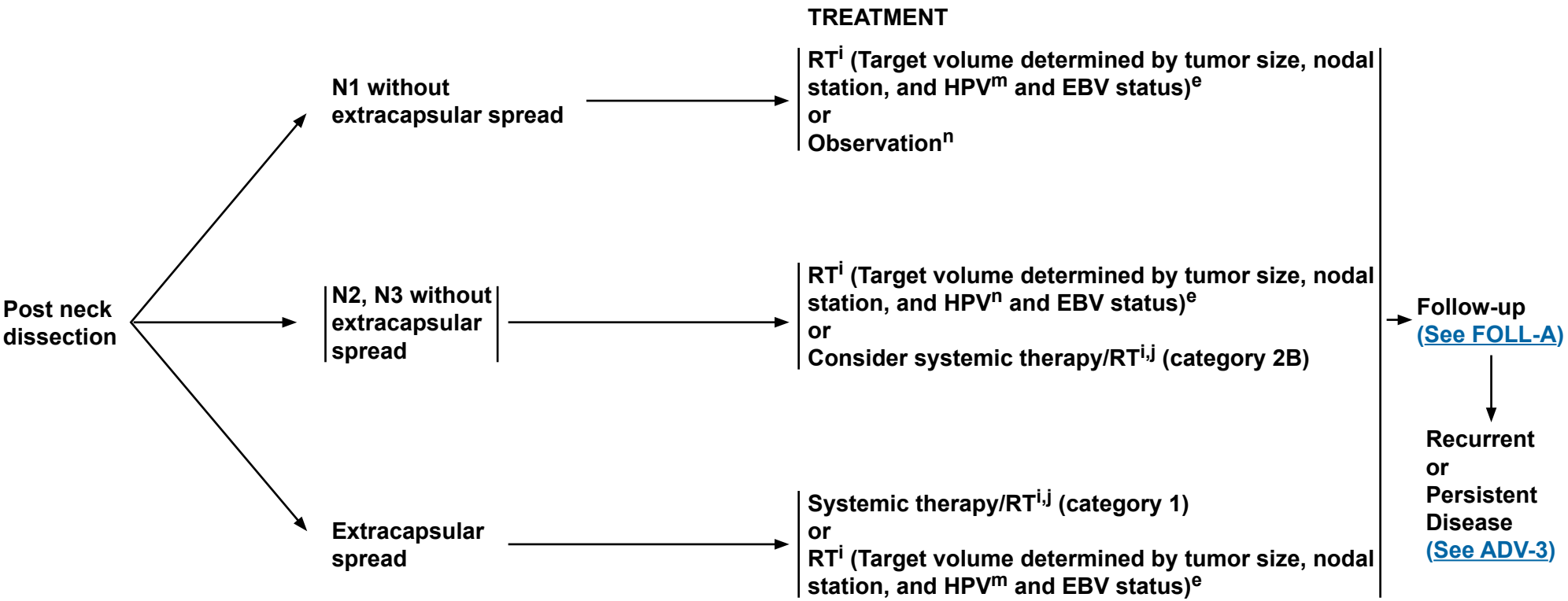

[e]Whether HPV or EBV positive status may help to define the radiation fields is being investigated (See Principles of Surgery [SURG-A 2 of 9] and Discussion).
[i]See Principles of Radiation Therapy (OCC-A).
[j]See Principles of Systemic Therapy (CHEM-A).
[m]Either immunohistochemistry for analysis of p16 expression or HPV in situ hybridization for detection of HPV DNA in tumor cell nuclei 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.
[n]Observation: Regular comprehensive exam performed by a head and neck oncologist 1 month after surgery followed by regular exams every 3 months through year 2, every 6 months for 3 years, then annually thereafter. Imaging consisting of CT/MRI or FDG-PET should be performed as clinically indicated.

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PRINCIPLES OF RADIATION THERAPY[1,2]

DEFINITIVE:

RT Alone

- **PTV**
  - **High risk: Involved lymph nodes (this includes possible local subclinical infiltration 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[3]**
      - **Mucosal dosing: 50–66 Gy (2.0 Gy/fraction) to putative mucosal sites, depending on field size. Consider higher dose to 60–66 Gy to particularly suspicious areas**
  - **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)[4]**

CONCURRENT CHEMORADIATION:[5,6]

- **PTV**
  - **High risk: typically 70 Gy (2.0 Gy/fraction)**
  - **Mucosal dosing: 50–60 Gy (2.0 Gy/fraction) to putative mucosal primary sites, depending on field size and use of chemotherapy. Consider higher dose to 60–66 Gy to particularly suspicious areas**
  - **Low to intermediate risk: 44–50 Gy (2.0 Gy/fraction) to 54–63 Gy (1.6–1.8 Gy/fraction)[4]**

Either IMRT or 3-D conformal RT is recommended when targeting the oropharynx to minimize the dose to critical structures, especially the parotid glands.

[1]For squamous cell carcinoma, adenocarcinoma, and poorly differentiated carcinoma.
[2]See Radiation Techniques (RAD-A) and Discussion.
[3]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.
[4]Suggest 44–50 Gy in 3-D conformal RT and sequentially planned IMRT or 54–63 Gy with IMRT dose painting technique (dependent on dose per fraction).
[5]See Principles of Systemic Therapy (CHEM-A).
[6]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^2; 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, 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.

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PRINCIPLES OF RADIATION THERAPY[1,2]

POSTOPERATIVE:

RT

- **Preferred interval between resection and postoperative RT is ≤6 weeks**
- **PTV**
  - **High risk: Adverse features such as extracapsular spread (See OCC-4)**
    - ◊ **Mucosal dose: 50–66 Gy (2.0 Gy/fraction) to putative mucosal sites, depending on field size. Consider higher dose to 60–66 Gy to particularly suspicious areas**
  - **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)[4]**

POSTOPERATIVE CHEMORADIATION:

- **Concurrent single-agent cisplatin at 100 mg/m^2 every 3 weeks is recommended.[7-10]**

Either IMRT or 3-D conformal RT is recommended when targeting the oropharynx to minimize the dose to critical structures, especially the parotid glands.

[1]For squamous cell carcinoma, adenocarcinoma, and poorly differentiated carcinoma.
[2]See Radiation Techniques (RAD-A) and Discussion.
[4]Suggest 44–50 Gy in 3-D conformal RT and sequentially planned IMRT or 54–63 Gy with IMRT dose painting technique (dependent on dose per fraction).
[7]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.
[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, 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.
[10]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.

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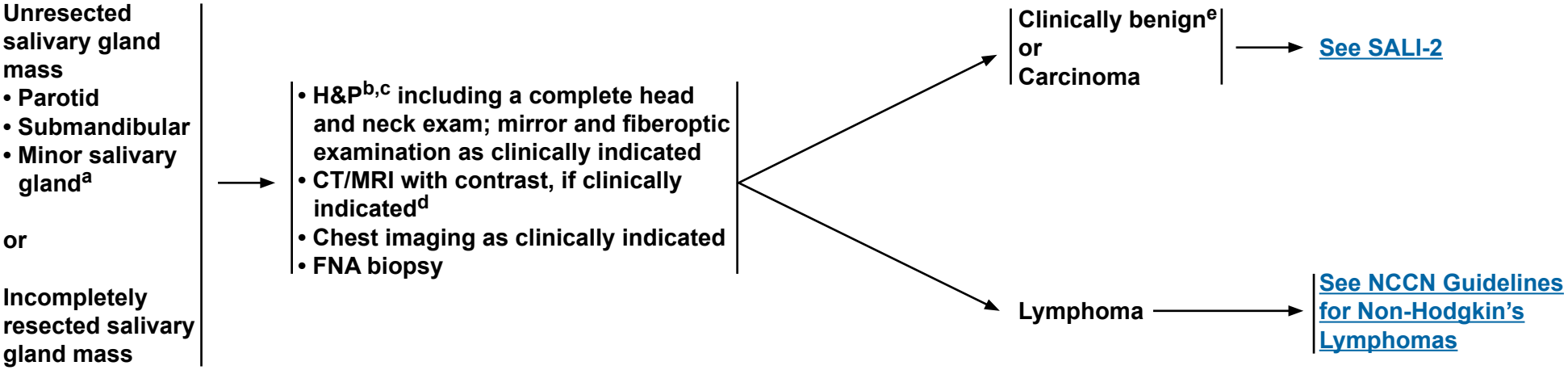
CLINICAL PRESENTATION

WORKUP



[a]Site and stage determine therapeutic approaches.
[b]H&P Should include documentation and quantification (pack years smoked) of tobacco use history. 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 the NCCN Guidelines for Smoking Cessation and www.smokefree.gov.
[c]Screen for depression (See NCCN Guidelines for Distress Management).
[d]For advanced cancer, this includes CT/MRI: base of skull to clavicles.
[e]Characteristics of a benign tumor include mobile superficial lobe, slow growth, painless, VII intact, and no neck nodes.

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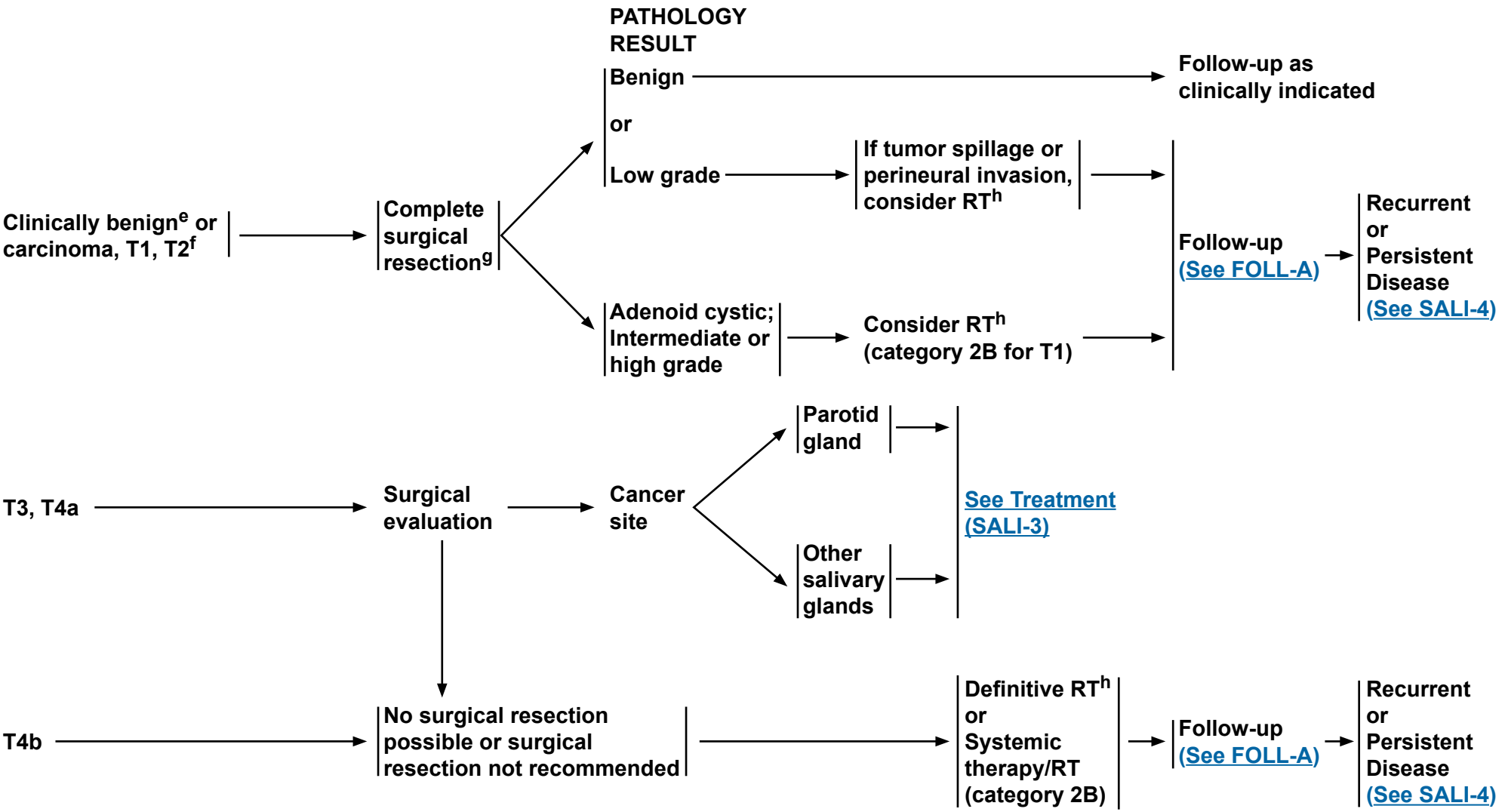

[e]Characteristics of a benign tumor include mobile superficial lobe, slow growth, no pain, VII intact, and no neck nodes.
[f]If incidental N+ disease is present go to SALI-3.
[g]Surgical resection of a clinically benign tumor includes: no enucleation of lateral lobe and intraoperative communication with pathologist if indicated.
[h]See Principles of Radiation Therapy (SALI-A).

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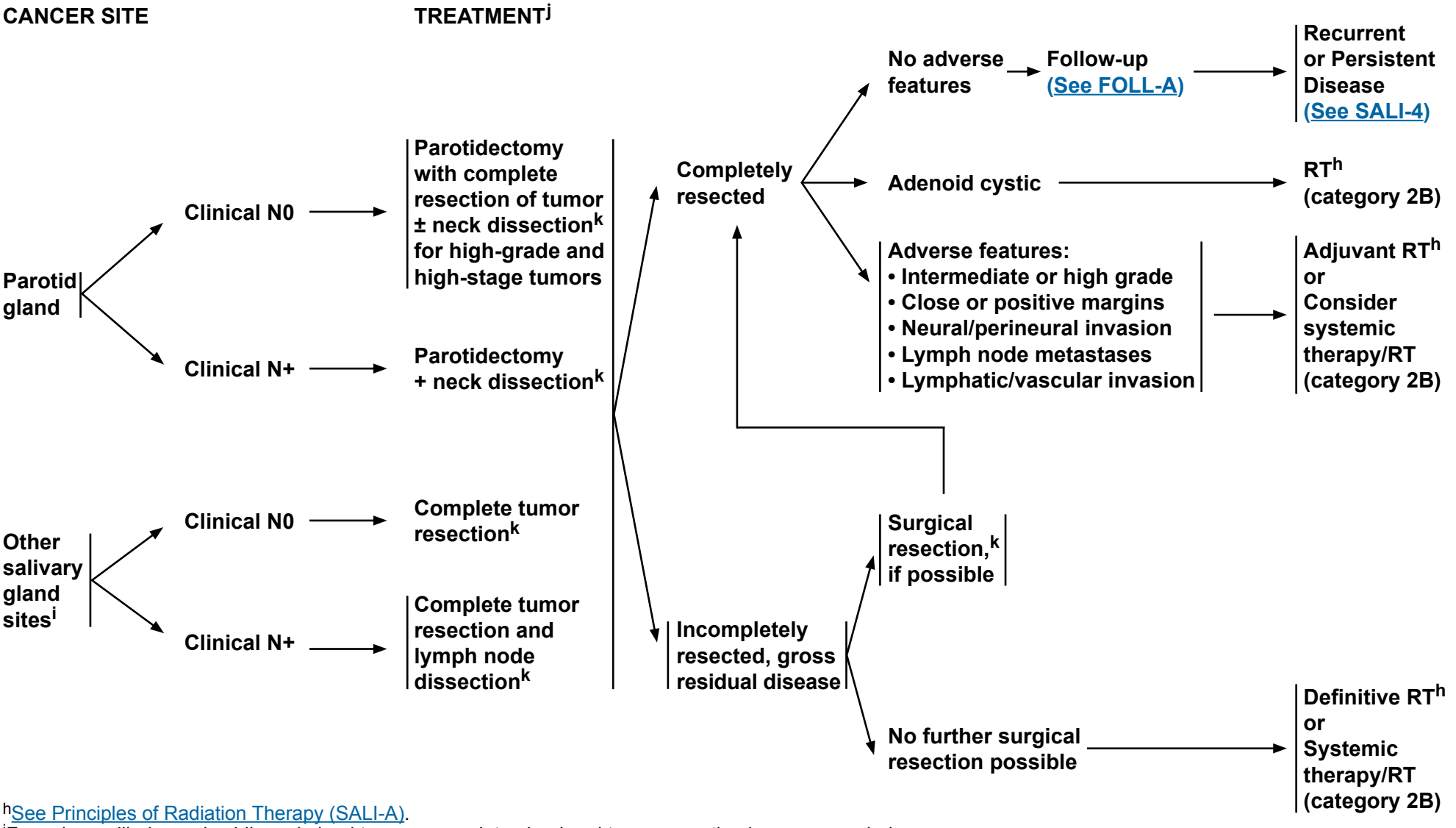

[h] See Principles of Radiation Therapy (SALI-A).
[i] For submandibular and sublingual gland tumors, complete gland and tumor resection is recommended.
[j] The facial nerve should be preserved if possible; strongly consider referral to a specialized center with reconstructive expertise.
[k] See Principles of Surgery (SURG-A).

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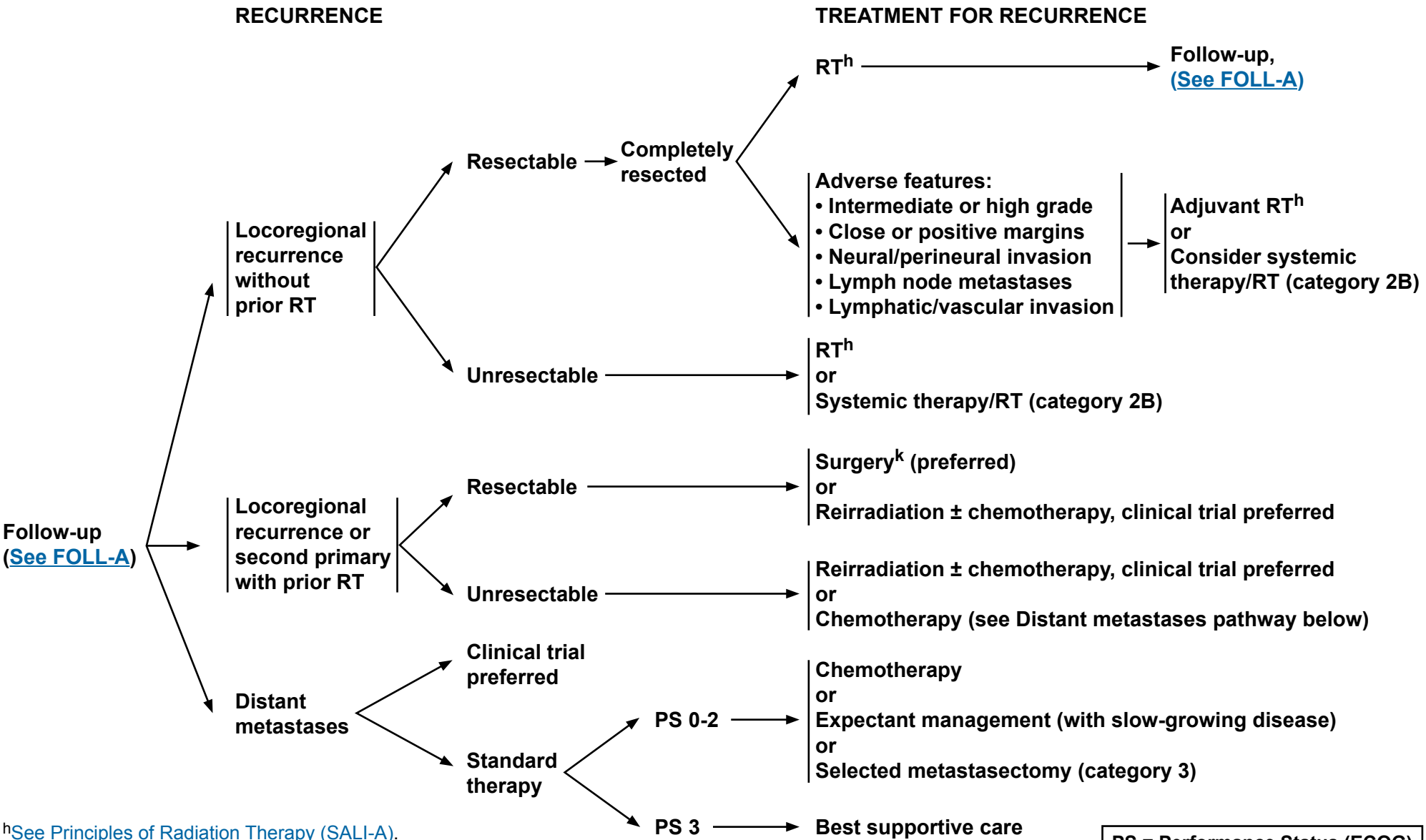

[h] See Principles of Radiation Therapy (SALI-A).
[k] See Principles of Surgery (SURG-A).

PS = Performance Status (ECOG)

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PRINCIPLES OF RADIATION THERAPY[1,2]

DEFINITIVE:

RT Alone

- **Photon or photon/electron therapy or highly conformal radiation therapy techniques**
- **PTV:**
  - **High risk: Primary tumor and involved lymph nodes (this includes possible local subclinical infiltration at the primary and at the high-risk level lymph node(s))**
    - ◊ **Fractionation:**
      - **66 Gy (2.0 Gy/fraction) to 70–70.2 Gy (1.8–2.0 Gy/fraction); daily Monday–Friday in 6–7 weeks[3]**
  - **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)[4]**

POSTOPERATIVE:

RT

- **Preferred interval between resection and postoperative RT is ≤6 weeks**
- **Photon or photon/electron therapy**
- **PTV**
  - **High risk: Adverse features such as positive margins (see SALI-3)**
    - ◊ **60–66 Gy (2.0 Gy/fraction); daily Monday–Friday in 6–7 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)[4]**

Either IMRT or 3-D conformal RT is recommended.

[1]See Radiation Techniques (RAD-A) and Discussion.
[2]Neutrons are still used in selected patients. Pfister DG, Spencer S, Brizel DM, et al. NCCN Head and Neck Cancers, Version 1.2015. J Natl Compr Canc Netw 2015;13:847-856.
[3]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.
[4]Suggest 44–50 Gy in 3D conformal RT and sequentially planned IMRT or 54–63 Gy with IMRT dose painting technique (dependent on dose per fraction).

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PRESENTATION **WORKUP** **TREATMENT**

Biopsy confirms diagnosis of mucosal malignant melanoma

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

Sinus or nasal cavity mucosal melanoma → **See Primary Treatment (MM-2)**

Oral cavity, oropharynx, larynx, or hypopharynx mucosal melanoma → **See Primary Treatment (MM-3)**

[a]H&P should include documentation and quantification (pack years smoked) of tobacco use history. 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 the NCCN Guidelines for Smoking Cessation and www.smokefree.gov.
[b]Screen for depression (See NCCN Guidelines for Distress Management).

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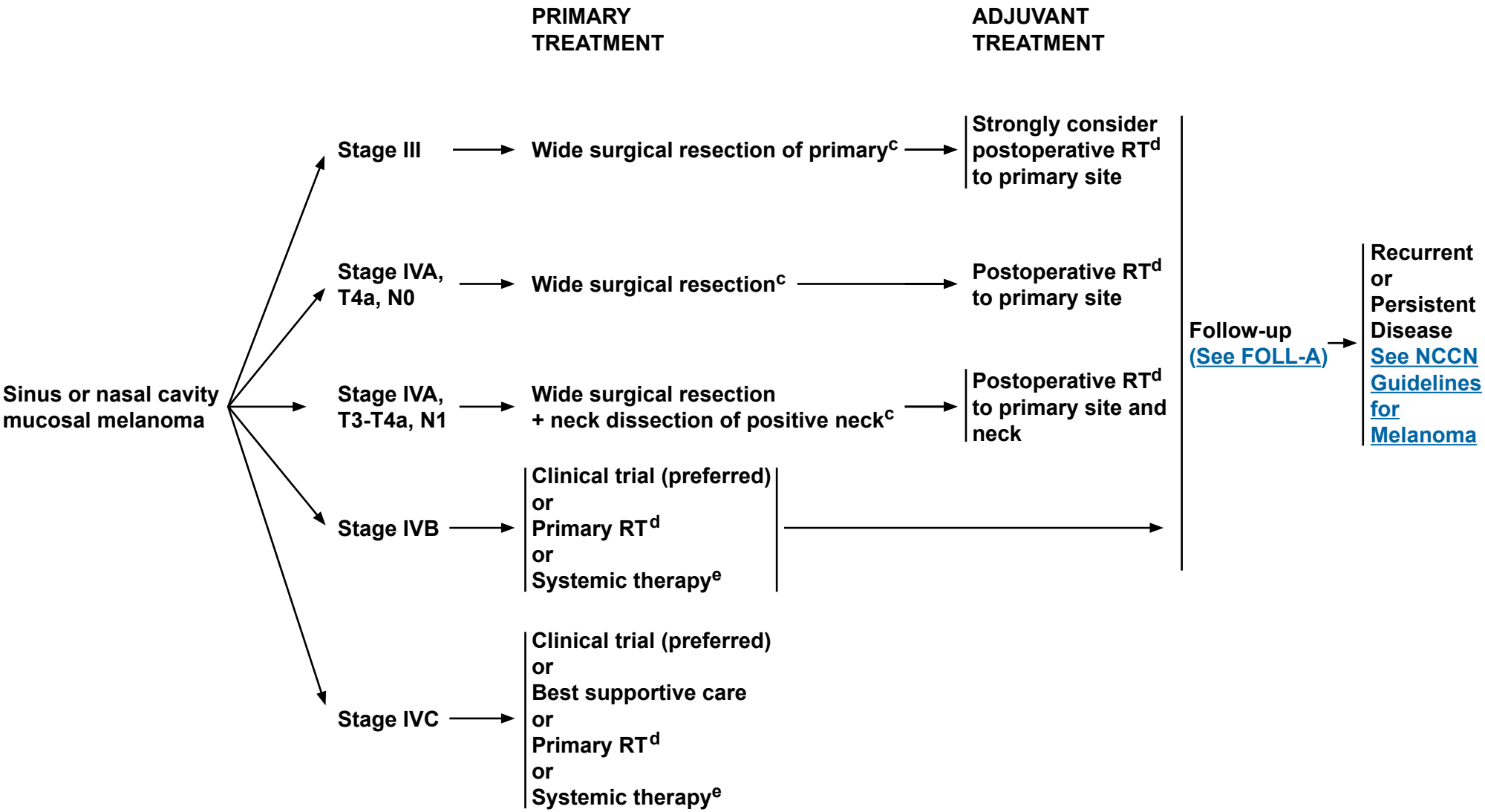

[c] See Principles of Surgery (SURG-A).
[d] See Principles of Radiation Therapy (MM-A).
[e] See Systemic Therapy for Metastatic or Unresectable Disease (page ME-E) from the NCCN Guidelines for Melanoma.

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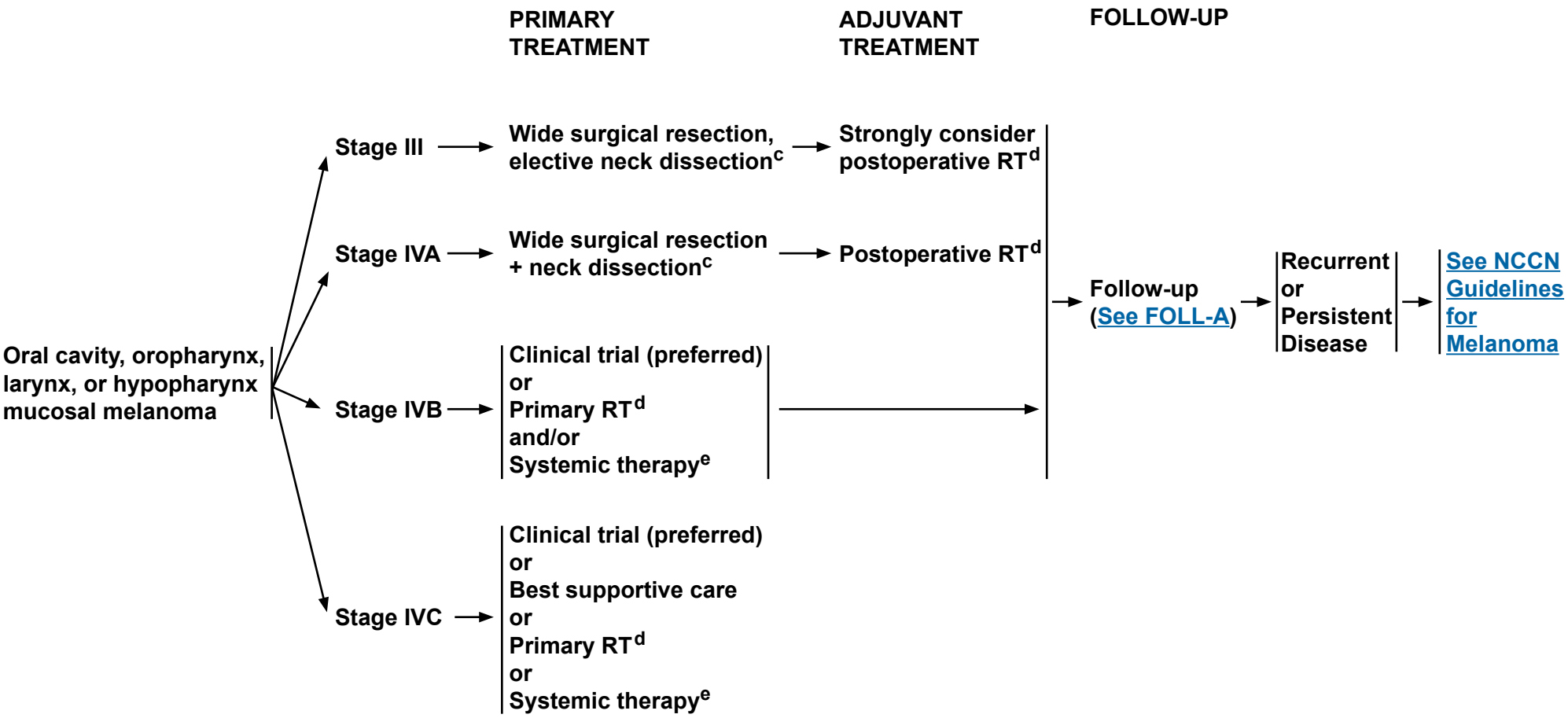

[c] See Principles of Surgery (SURG-A).
[d] See Principles of Radiation Therapy (MM-A).
[e] See Systemic Therapy for Metastatic or Unresectable Disease (page ME-E) from the NCCN Guidelines for Melanoma.

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PRIMARY THERAPY FOR OCCULT PRIMARY- MELANOMA (Also see NCCN Guidelines for Occult Primary)

Nodal basin → **Nodal dissection[c]** → **± RT to nodal bed[d]** → **± Adjuvant systemic therapy, per NCCN Guidelines for Melanoma**

[c] See Principles of Surgery (SURG-A).
[d] See Principles of Radiation Therapy (MM-A).

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PRINCIPLES OF RADIATION THERAPY[1]

DEFINITIVE:

RT Alone (Unresectable Locally Advanced Melanoma):

- **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)**
    - ◊ **66 Gy (2.2 Gy/fraction) to 70 Gy (2.0 Gy/fraction) daily Monday–Friday in 6–7 weeks**
  - **Low to intermediate risk: Sites suspected of subclinical spread**
    - ◊ **44–50 Gy (2.0 Gy/Fraction) to 54–63 Gy (1.6–1.8Gy/fraction)**
- **Palliative RT doses and schedules may be considered**

POSTOPERATIVE:

RT:

- **Preferred interval between resection and postoperative RT is <6 weeks.**
- **PTV**
  - **High risk: adverse features >2 nodes, single node >3 cm, extracapsular nodes, recurrence in nodal basin after previous surgery[2]**
    - ◊ **60–66 Gy (2.0 Gy/fraction; daily Monday–Friday) in 6–6.5 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)**

[1] See Radiation Techniques (RAD-A) and Discussion.

[2] Optional dose schedules include 48–50 Gy (2.4–3.0 Gy/fraction) and 30–36 Gy (6 Gy/fraction). (Burmeister BH, Henderson MA, Ainslie J, et al. Adjuvant radiotherapy versus observation alone for patients at risk of lymph-node field relapse after therapeutic lymphadenectomy for melanoma: a randomised trial. Lancet Oncol 2012;13:589-597; Ballo MT, Bonnen MD, Garden AS, et al. Adjuvant irradiation for cervical node metastases from melanoma. Cancer 2003;97:1789-1796; and Moreno MA, Roberts DB, Kupferman ME, et al. Mucosal melanoma of the nose and paranasal sinuses, a contemporary experience from the M. D. Anderson Cancer Center. Cancer 2010;116:2215-2213).

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FOLLOW-UP RECOMMENDATIONS[1]
(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):[2]**
  - **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[3] (category 2B)**
  - **Further reimaging as indicated based on worrisome or equivocal signs/symptoms, smoking history, and areas inaccessible to clinical examination.**
- **Chest imaging as clinically indicated for patients with smoking history (See NCCN Guidelines for Lung Cancer Screening)**
- **Thyroid-stimulating hormone (TSH) every 6–12 mo if neck irradiated**
- **Speech/hearing and swallowing evaluation[4] and rehabilitation as clinically indicated**
- **Smoking cessation[5] and alcohol counseling as clinically indicated**
- **Dental evaluation[6]**
  - **Recommended for oral cavity and sites exposed to significant intraoral radiation treatment**
- **Consider EBV DNA monitoring for nasopharyngeal cancer**
- **Due to the inaccessibility of the nasopharynx, routine annual imaging may be indicated**
- **Nutritional evaluation and rehabilitation as clinically indicated until nutritional status is stabilized[4]**
- **Ongoing surveillance for depression (See NCCN Guidelines for Distress Management)**
- **For response assessment immediately after chemoradiation or RT (see FOLL-A 2 of 2)**

[1]Most recurrences are reported by the patient.
[2]For mucosal melanoma, a physical exam should include endoscopic inspection for paranasal sinus disease.
[3]For cancer of the oropharynx, hypopharynx, glottic larynx, supraglottic larynx, and nasopharynx: imaging is recommended for T3-4 or N2-3 disease only.
[4]See Principles of Nutrition (NUTR-A).
[5]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 the NCCN Guidelines for Smoking Cessation and www.smokefree.gov.
[6]See Principles of Dental Evaluation and Management (DENT-A).

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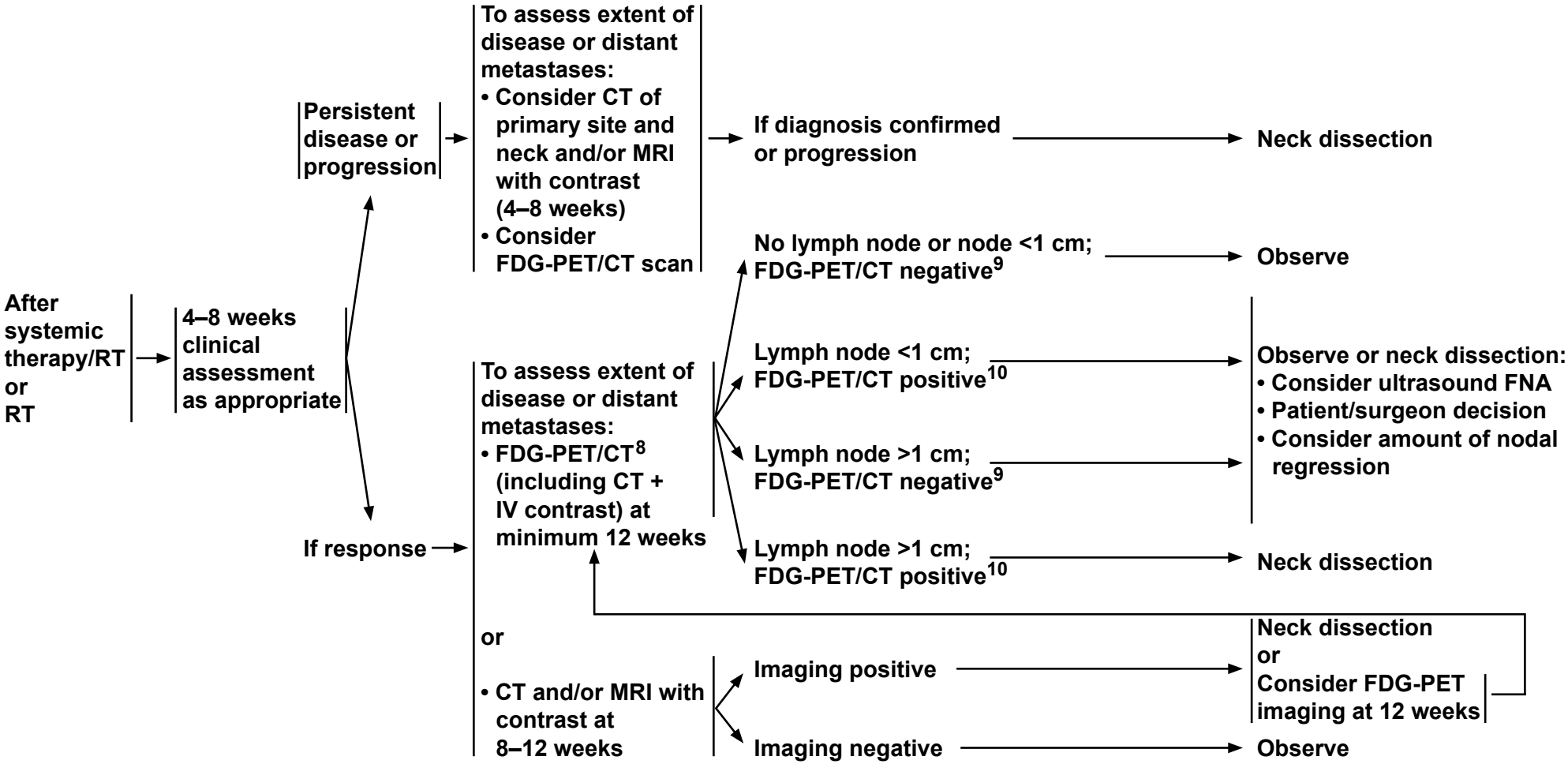
Continue

FOLLOW-UP RECOMMENDATIONS (POST CHEMORADIATION OR RT NECK EVALUATION)[7]



[7]Adapted with permission from Kutler DI, Patel SG, Shah JP. The role of neck dissection following definitive chemoradiation. Oncology 2004;18:993-998.
[8]If a FDG-PET/CT is performed and negative for suspicion of persistent cancer, further cross-sectional imaging is optional.
[9]PET negative = No or low-grade uptake, felt not suspicious for disease.
[10]PET positive = PET suspicious for disease.

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PRINCIPLES OF SURGERY

Evaluation

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

- **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 options, including those applicable if initial non-surgical treatment is unsuccessful.**
- **Participate in the multidisciplinary team discussions regarding patient treatment options with the goal of maximizing survival with preservation of form and function.**
- **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 an operation, the surgical procedure, margins, and reconstructive plan should be developed and designed to resect all gross tumors with adequate tumor-free surgical margins. The surgical procedure should not be modified based on any response observed as a result of prior therapy except in instances of tumor progression that mandate a more extensive procedure in order to encompass the tumor at the time of definitive resection.**

Integration of Therapy

- **It is critical that multidisciplinary evaluation and treatment be coordinated and integrated prospectively by all disciplines involved in patient care before the initiation of any treatment.**

Assessment of Resectability

Tumor involvement of the following sites is associated with poor prognosis or function* or with T4b cancer (ie, unresectable based on technical ability to obtain clear margins). None of these sites of involvement is an absolute contraindication to resection in selected patients in whom total cancer removal is possible:

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

*In selected cases, surgery might still be considered.

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PRINCIPLES OF SURGERY

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 appropriate resection 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, the risk of regional metastases and the need for adjuvant elective neck dissection also increases.**
- **Perineural invasion should be suspected when tumors are adjacent to motor or sensory nerves. The goal is total cancer resection. When gross invasion is present and the nerve can be resected without significant morbidity, the nerve should be dissected both proximally and distally and should be resected to obtain clearance of disease (See Surgical Management of Cranial Nerves page 4 of 8). 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 adequately 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 or marginal 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 (CT/MRI/Panorex). The extent of mandibular resection will depend on the degree of involvement accessed clinically and in the operating room.**
- **Medullary space invasion is an indication for segmental resection. Frozen section examination of available marrow may be considered to guide resection.**
- **For tumors of the larynx, the decision to perform either total laryngectomy or conservation laryngeal surgery (eg, transoral resection, hemilaryngectomy, supraglottic laryngectomy) will be decided by the surgeon but should adhere to the principles of complete tumor extirpation with curative intent and function preservation.**
- **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.**
- **Transoral robotic surgery (TORS) or laser-assisted resections of primary cancers in the oral cavity, larynx, and pharynx are increasingly used approaches for cancer resection in selected patients with limited disease and accessible tumors. Oncologic principles are similar to open procedures. Successful application of these techniques requires specialized skills and experience.**

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PRINCIPLES OF SURGERY

Margins

An overarching goal of oncologic surgery is complete tumor resection with histologic verification of tumor-free margins. Margin assessment may be in real time by frozen section or by assessment of formalin-fixed tissues. Tumor-free margins are an essential surgical strategy for diminishing the risk for local tumor recurrence. Conversely, positive margins increase the risk for local relapse and are an indication for postoperative adjuvant therapy. Clinical pathologic studies have demonstrated the significance of close or positive margins and their relationship with local tumor recurrence.[1] When there is an initial cut-through with an invasive tumor at the surgical margin, obtaining additional adjacent margins from the patient may also be associated with a higher risk for local relapse. Obtaining additional margins from the patient is subject to ambiguity regarding whether the tissue taken from the surgical bed corresponds to the actual site of margin positivity.[2] If positive surgical margins are reported, surgical re-resection and/or adjuvant therapy should be considered in selected patients.

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 the tongue and/or anterior tongue, mandible, larynx, or portions of the cervical esophagus.

- **Adequate resection is defined as clear resection margins with at least enough clearance from the gross tumor to obtain clear frozen section and permanent margins (often 1.5–2 cm of visible and palpable normal mucosa). However, for glottic cancers, a 1- to 2-mm margin is considered adequate. In general, frozen section examination of the margins will usually be undertaken intraoperatively, and, importantly, when a line of resection has uncertain clearance because of indistinct tumor margins, or there is suspected residual disease (ie, soft tissue, cartilage, carotid artery, mucosal irregularity). In transoral laser microsurgery, margins of 1.5–2.0 mm may be achieved with the goal of complete tumor resection with maximal normal tissue preservation. With this approach, adequacy of resection may be uncertain and is assessed under high magnification and confirmed intraoperatively by frozen sections.[3] Such margins would be considered "close" and may be inadequate for certain sites such as oral tongue.**
- **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.**
- **A positive margin is defined as carcinoma in situ or as invasive carcinoma at the margin of resection.**
- **The primary tumor should be marked in a fashion adequate for orientation by the surgical pathologist. The primary tumor should be assessed histologically for depth of invasion and for distance from the invasive portion of the tumor to the margin of resection, including the peripheral and deep margins. The pathology report should be template driven and describe how the margins were assessed. The report should provide information regarding the primary specimen to include the distance from the invasive portion of the tumor to the peripheral and deep margin. If the surgeon obtains additional margins from the patient, the new margins should refer back to the geometric orientation of the resected tumor specimen with a statement by the pathologist that this is the final margin of resection and its histologic status.**
- **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.**

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PRINCIPLES OF SURGERY

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, thorough efforts should be made to preserve the structure and function of the nerve (main trunk and/or branches)—even if otherwise adequate tumor margins are not achieved—recognizing that the surgeon should leave no gross residual disease.**
- **Adjuvant postoperative radiation or chemoradiation is generally prescribed when a microscopic residual or gross residual tumor is suspected.**
- **Direct nerve invasion by a tumor and/or preoperative paralysis of the nerve may warrant segmental resection (and sometimes 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

Neck Management

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

- **Tumor sites that frequently have bilateral lymphatic drainage (eg, base of tongue, palate, supraglottic larynx, deep pre-epiglottic space involvement) often should 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.**

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

- **Elective neck dissection should be based on risk of occult metastasis in the appropriate nodal basin. For oral cavity squamous cell carcinoma, sentinel lymph node biopsy or the primary tumor depth of invasion is currently the best predictor of occult metastatic disease and should be used to guide decision making. For tumors with a depth greater than 4 mm, elective dissection should be strongly considered if RT is not already planned. For a depth less than 2 mm, elective dissection is only indicated in highly selective situations. For a depth of 2–4 mm, clinical judgment (as to reliability of follow-up, clinical suspicion, and other factors) must be utilized to determine appropriateness of elective dissection. Recent randomized trial evidence supports the effectiveness of elective neck dissection in patients with oral cavity cancers >3 mm in depth of invasion.[4] Elective dissections are generally selective, preserving all major structures, unless operative findings dictate otherwise.**
- **The type of neck dissection (comprehensive or selective) is defined according to preoperative clinical staging, is determined at the discretion of the surgeon, and is 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 the 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. Subglottic laryngeal cancers are sites where elective level VI dissections are often considered appropriate.**

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PRINCIPLES OF SURGERY

Sentinel Lymph Node Biopsy

- **SLN biopsy is an alternative to elective neck dissection for identifying occult cervical metastasis in patients with early (T1 or T2) oral cavity carcinoma in centers where expertise for this procedure is available. Its advantages include reduced morbidity and an improved cosmetic outcome. Rates of detection of sentinel nodes in excess of 95% have been widely reported.[4-6] Patients with metastatic disease in their sentinel nodes must undergo a completion neck dissection while those without may be observed. Accuracy of sentinel node biopsy for nodal staging of early oral carcinoma has been tested extensively in multiple single-center studies and two multi-institutional trials against the reference standard of immediately performed neck dissection or subsequent extended follow-up with a pooled estimate of sensitivity of 0.93 and negative predictive values ranging from 0.88 to 1.[5-10] While direct comparisons with the policy of elective neck dissection are lacking, available evidence points towards comparable survival outcomes.[10]**
- **Sentinel node biopsy is a technically demanding procedure. Procedural success rates for sentinel node identification as well as accuracy of detecting occult lymphatic metastasis depend on technical expertise and experience. Hence, sufficient caution must be exercised when offering it as an alternative to elective neck dissection. This is particularly true in cases of floor-of-mouth cancer where accuracy of sentinel node biopsy has been found to be lower than for other locations such as the tongue.[4,5] Also, cancers of certain locations such as upper gingiva and hard palate may not lend themselves well technically to this procedure. Likewise, occult cervical metastases are uncommon in early lip cancer, but SLN has been shown to be feasible and effective in patients with lip cancers deemed to be at high risk of metastases generally based on tumor size or depth.[11]**

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PRINCIPLES OF SURGERY

Management of Recurrences

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

Surveillance

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

- **Tumor evaluations must be performed by specialists skilled in head and neck clinical examination.**
- **The frequency of evaluation is summarized elsewhere in the NCCN Guidelines for Head and Neck Cancers (See Follow-up Recommendations [FOLL-A 1 of 2]).**
- **For post chemoradiation or RT neck evaluations (See Follow-up Recommendations: [Post Chemoradiation or RT Neck Evaluation [FOLL-A 2 of 2]).**

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PRINCIPLES OF SURGERY
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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 or other 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] FDG-PET/CT or MRI with contrast can be used for fusion in treatment planning.

Intensity-Modulated Radiation Therapy

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 (eg, oral cavity, larynx, hypopharynx, salivary glands) is evolving and may be used at the discretion of treating physicians.

IMRT and Fractionation[10-12]

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

*For additional resources regarding the technical details of radiation, see the American College of Radiology Guidelines: http://www.acr.org/Quality-Safety/Standards-Guidelines/Practice-Guidelines-by-Modality/Radiation-Oncology.

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RADIATION TECHNIQUES*

Palliative Radiation

- Palliative radiation should be considered in the advanced cancer setting when curative-intent treatment is not appropriate.
- No general consensus exists for appropriate palliative RT regimens in head and neck cancer. For those who are either medically unsuitable for standard RT or who have widely metastatic disease, palliative RT should be considered for relief or prevention of locoregional symptoms if the RT toxicities are acceptable. RT regimens should be tailored individually; severe RT toxicities should be avoided when treatment is for palliation. Recommended RT regimens include:
  - 50 Gy in 20 fractions;[13]
  - 37.5 Gy in 15 fractions (if well tolerated, consider adding 5 additional fractions to 50 Gy);
  - 30 Gy in 10 fractions;
  - 30 Gy in 5 fractions:** give 2 fractions/week with ≥3 days between the 2 treatments; and[14]
  - 44.4 Gy in 12 fractions, in 3 cycles (for each cycle, give 2 fractions six hours apart for 2 days in a row, and treatments must exclude the spinal cord after second cycle).[15,16] Reassessment should be done at 1- to 3-week intervals.
- While the use of shorter treatment courses is encouraged, the dose tolerance of the spinal cord and neural structures must be evaluated carefully in light of fraction size.
- Carefully evaluate the patient's performance, treatment tolerance, tumor response, and/or any systemic progression. Other palliative/supportive care measures include analgesics, nutrition support, targeted therapy, or chemotherapy, if indicated (see the NCCN Guidelines for Supportive Care).

Reirradiation With 3-D Conformal RT, SBRT, or IMRT[17-24]

- It is strongly recommended that patients be evaluated by a multidisciplinary team at a high-volume head and neck center before reirradiation.
- Prior radiotherapy should be more than 6 months from the appearance of new disease.
- Before reirradiation, the patient should have a reasonable ECOG performance status of 0-1.
- The treatment team must be able to develop a reirradiation treatment plan that limits the cumulative dose of radiation to CNS tissues based on volume and the time interval between prior radiotherapy and anticipated retreatment.
- Research opportunities for reirradiation should be strongly considered in patients with unresectable head and neck cancer.

*For additional resources regarding the technical details of radiation, see the American College of Radiology Guidelines: http://www.acr.org/Quality-Safety/Standards-Guidelines/Practice-Guidelines-by-Modality/Radiation-Oncology.
**For end-stage disease, patients can be given more hypofractionated schedules because of the very limited prognosis.

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PRINCIPLES OF SYSTEMIC THERAPY

The choice of systemic therapy should be individualized based on patient characteristics (PS, goals of therapy).

- **The standard chemoradiotherapy approach for fit patients with locally advanced disease remains concurrent cisplatin and radiotherapy.**
- **Cisplatin-based induction chemotherapy can be used, followed by radiation-based locoregional treatment (ie, sequential chemoRT). However, an improvement in overall survival with the incorporation of induction chemotherapy compared to proceeding directly to state-of-the-art concurrent chemoRT (cisplatin preferred, category 1) has not been established. Randomized phase III studies comparing sequential chemotherapy/RT to concurrent chemotherapy/RT alone are ongoing and have not demonstrated a convincing survival benefit with the incorporation of induction chemotherapy.**
- **Cisplatin-based induction chemotherapy followed by high-dose, every-3-week cisplatin chemoradiotherapy is not recommended due to toxicity concerns.[1,2]**
- **After induction chemotherapy, multiple options can be used for the radiation-based portion of therapy. Radiotherapy alone versus radiotherapy plus weekly carboplatin or cetuximab are among the options.**

Squamous Cell Cancers

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

- **Primary systemic therapy + concurrent RT**
  - **High-dose cisplatin[3,4] (preferred) (category 1)**
  - **Cetuximab[5] (category 1)**
  - **Carboplatin/infusional 5-FU (category 1)[6,7]**
  - **5-FU/hydroxyurea[8]**
  - **Cisplatin/paclitaxel[8]**
  - **Cisplatin/infusional 5-FU[9]**
  - **Carboplatin/paclitaxel[10] (category 2B)**
  - **Weekly cisplatin 40 mg/m^2 (category 2B)[11,12]**
- **Postoperative chemoradiation**
  - **Cisplatin[13-17] (category 1 for high-risk non-oropharyngeal cancers)**

Nasopharynx:

- **Chemoradiation followed by adjuvant chemotherapy**
  - **Cisplatin + RT followed by cisplatin/5-FU[18,19] or carboplatin/5-FU[20] (category 2B for carboplatin/5-FU)**
- **Cisplatin + RT without adjuvant chemotherapy (category 2B)[21]**

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

- **Induction*/Sequential chemotherapy**
  - **Docetaxel/cisplatin/5-FU[22-24] (category 1 if induction is chosen)**
  - **Paclitaxel/cisplatin/infusional 5-FU[25]**
  - **Following induction, agents to be used with concurrent chemoradiation typically include weekly carboplatin or cetuximab.[1,26,27]**

Nasopharynx:

- **Induction (category 3)/Sequential chemotherapy**
  - **Docetaxel/cisplatin/5-FU[28]**
  - **Docetaxel/cisplatin (category 2B)[29]**
  - **Cisplatin/5-FU[23]**
  - **Cisplatin/epirubicin/paclitaxel**
  - **Following induction, agents to be used with concurrent chemoradiation typically include weekly cisplatin[19] or carboplatin[26]**

*The categories of evidence and consensus for induction therapy vary depending on site. (See disease-specific site in the Head and Neck Table of Contents)

Note: All recommendations are category 2A unless otherwise indicated.
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Continued on next page

PRINCIPLES OF SYSTEMIC THERAPY

- **The choice of systemic therapy should be individualized based on patient characteristics (PS, goals of therapy).**
- **Unless otherwise specified, regimens listed below can be used for either nasopharyngeal or non-nasopharyngeal cancer.**

Recurrent, Unresectable, or Metastatic (with no surgery or RT option)

- **Combination therapy**
  - **Cisplatin or carboplatin + 5-FU + cetuximab[30] (non-nasopharyngeal) (category 1)**
  - **Cisplatin or carboplatin + docetaxel[31] or paclitaxel[32]**
  - **Cisplatin/cetuximab[33] (non-nasopharyngeal)**
  - **Cisplatin/5-FU[32,34]**
  - **Cisplatin/docetaxel/cetuximab[35] (non-nasopharyngeal)**
  - **Cisplatin/paclitaxel/cetuximab[36,37] (non-nasopharyngeal)**
  - **Carboplatin/cetuximab[38] (nasopharyngeal)**
  - **Cisplatin/gemcitabine[39] (nasopharyngeal)**
  - **Gemcitabine/vinorelbine[40] (nasopharyngeal)**

- **Single agents**
  - **Cisplatin[33,41]**
  - **Carboplatin[42]**
  - **Paclitaxel[43]**
  - **Docetaxel[44,45]**
  - **5-FU[41]**
  - **Methotrexate[46,47]**
  - **Cetuximab[48] (non-nasopharyngeal)**
  - **Gemcitabine[49] (nasopharyngeal)**
  - **Capecitabine[50]**
  - **Vinorelbine[51,52] (non-nasopharyngeal)**
  - **Afatinib[53] (non-nasopharyngeal, second line) (category 2B)**

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See References on CHEM-A 3 of 5

PRINCIPLES OF SYSTEMIC THERAPY
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PRINCIPLES OF SYSTEMIC THERAPY
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PRINCIPLES OF NUTRITION: MANAGEMENT AND SUPPORTIVE CARE[1-3]

Most head and neck cancer patients lose weight as a result of their disease, health behaviors, and treatment-related toxicities. Nutritional management is very important in head and neck cancer patients to improve outcomes and to minimize significant temporary or permanent treatment-related complications (eg, severe weight loss). It is recommended that the multidisciplinary evaluation of head and neck cancer patients include a registered dietitian and a speech-language/swallowing therapist.

Assessment and Management

- **Nutrition**
  - **Close monitoring of nutritional status is recommended in patients who have: 1) significant weight loss (5% weight loss over prior 1 month, or 10% weight loss over 6 months); and/or 2) difficulty swallowing because of pain or tumor involvement prior to treatment. All patients should be evaluated for nutritional risks and should receive nutrition counseling by a registered dietitian and/or indicated treatment with various nutrition interventions, such as feeding tubes (eg, nasogastric [NG] tubes, percutaneous endoscopic gastrostomy [PEG] tubes) or intravenous nutrition support (but only if enteral support is not feasible).**
  - **Pre- and post-treatment functional evaluation including nutritional status should be undertaken using subjective and objective assessment tools. All patients should receive dietary counseling with the initiation of treatment, especially with radiotherapy-based treatments. Regular follow-up with the registered dietitian should continue at least until the patient has achieved a nutritionally stable baseline following treatment. For some patients with chronic nutritional challenges, this follow-up should be ongoing.**

- **Speech and Swallowing**
  - **A formal speech and swallowing evaluation at baseline is recommended: 1) for patients with speech and/or swallowing dysfunction; or 2) for patients whose treatment is likely to affect speech and/or swallowing. Patients with ongoing abnormal function should be seen regularly by speech-language pathologists. Dysphagia and swallowing function can be measured by clinical swallowing assessments or by videofluoroscopic swallowing studies. Patient quality-of-life evaluations should also include assessment for any changes in speech and communication; changes in taste; and assessment for xerostomia, pain, and trismus. Follow-up with the speech-language pathologist should continue at least until the patient has achieved a stable baseline following treatment. For some patients with chronic speech and swallowing challenges, this follow-up may need to be indefinite.**

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PRINCIPLES OF NUTRITION: MANAGEMENT AND SUPPORTIVE CARE[1-3]

Use of Alternative Routes for Nutrition (NG and PEG Tubes)

- **The panel does not recommend prophylactic PEG or NG tube placement in patients with very good PS and without significant pretreatment weight loss, significant airway obstruction, or severe dysphagia. However, these patients will need encouragement to monitor their caloric intake and to assess for changes in body weight during treatment. They also may need temporary tube feeding intervention during and/or after treatment.**

- **Prophylactic feeding tube placement should be strongly considered for patients with:**
  - **Severe weight loss prior to treatment, 5% weight loss over prior 1 month, or 10% weight loss over 6 months;**
  - **Ongoing dehydration or dysphagia, anorexia, or pain interfering with the ability to eat/drink adequately;**
  - **Significant comorbidities that may be aggravated by poor tolerance of dehydration, lack of caloric intake, or difficulty swallowing necessary medications;**
  - **Severe aspiration; or mild aspiration in elderly patients or in patients who have compromised cardiopulmonary function; or**
  - **Patients for whom long-term swallowing disorders are likely, including those anticipated to receive large fields of high-dose radiation to the mucosa and adjacent connective tissues. However, consideration of other risk factors for swallowing dysfunction must be taken into account as well.**

- **To maintain swallowing function during and following treatment (eg, radiation), patients who may have feeding tube placement should be encouraged to intake orally if they can swallow without aspiration or any other compromises. Alterations in swallowing function can occur long after treatment (especially after radiation-based treatment) and should be monitored for the lifetime of the patient.**

[1]Ehrsson YT, Langius-Eklöf A, Laurell G. Nutritional surveillance and weight loss in head and neck cancer patients. Support Care Cancer 2012;20:757-765.
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[3]Langius JA, van Dijk AM, Doornaert P, et al. More than 10% weight loss in head and neck cancer patients during radiotherapy is independently associated with deterioration in quality of life. Nutr Cancer 2013;65:76-83.

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

PRINCIPLES OF 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, which ~~increasing~~ increases their susceptibility to demineralization[1] 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[2] and with reduced risk for dental caries long term for some patients.[3] Radiation-related caries and other dental hard tissue changes can appear within the first 3 months following RT.[4,5]

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.

- **Effect on salivary glands**
  - **Dry mouth strategies**
    - ◊ **Increased hydration**
    - ◊ **Salivary substitutes (eg, calcium phosphate-containing solutions, gels containing lysozyme, lactoferrin, and peroxidase)**
    - ◊ **Alcohol-free mouthwash**
    - ◊ **Salivary stimulation**
      - **– Gustatory stimulants (eg, xylitol chewing gum, sorbitol/malic acid lozenges, xylitol lozenges)**
      - **– Cholinergic agonists (pilocarpine, cevimeline)[6,7]**
  - **Dental caries prevention**
    - ◊ **Diet counseling**
    - ◊ **High potency topical fluoride – continue long term after therapy**
      - **– Daily 1.1% NaF gel or SNF_2 gel, brush on or in custom dental trays or**
      - **– Daily 1.1% NaF dentifrice or**
      - **– Fluoride varnish application, three times per year**
      - **– Calcium phosphate artificial saliva rinse**
    - ◊ **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[3,8,9]**
    - ◊ **If yes, should be completed at least 2 weeks prior to 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[4,5]**
  - **Maintain range of motion**
    - ◊ **Tongue blades and gentle stretching**
    - ◊ **Custom mouth-opening devices for rehabilitation of trismus and jaw motion**

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

PRINCIPLES OF DENTAL EVALUATION AND MANAGEMENT

Goals of Pre-RT Dental/Oral Evaluation—(continued):

2. Examination and assessment of patient with treatment plan[4]

- **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 re-evaluation and reinforcement of preventive protocol, during last week of RT**
  - **Evaluate for oral candidiasis and treat appropriately with antifungal agents**

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**

Goals of Dental Management Post-treatment:

1. **Manage xerostomia**
2. **Prevent and minimize trismus**
3. **Prevent and treat dental caries**
4. **Prevent post-radiation osteonecrosis**
5. **Prevent and manage oral candidiasis**
6. **Consultation with treating radiation oncologist is recommended before considering implants or extraction.**

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

Continued on next page

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

PRINCIPLES OF DENTAL EVALUATION AND MANAGEMENT
(References)

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[9]Lee IJ, Koom WS, Lee CGet al. Risk factors and dose-effect relationship for mandibular osteoradionecrosis in oral and oropharyngeal cancer patients. Int J Radiat Oncol Biol Phys 2009; 75:1084-1091.

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

Table 1
American Joint Committee on Cancer (AJCC)
TNM Staging Classification for the Lip and Oral Cavity
(7th ed., 2010)
(Nonepithelial tumors such as those of lymphoid tissue, soft tissue, bone, and cartilage are not included)

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*
T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3	Tumor more than 4 cm in greatest dimension
T4a	Moderately advanced local disease* (lip) Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face, that is, chin or nose (oral cavity) Tumor invades adjacent structures (eg, through cortical bone [mandible or maxilla] into deep [extrinsic] muscle of tongue [genioglossus, hyoglossus, palatoglossus, and styloglossus], maxillary sinus, skin of face)
T4b	Very advanced local disease Tumor invades masticator space, pterygoid plates, or skull base and/or encases internal carotid artery

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

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N2a	Metastasis in single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node more than 6 cm in greatest dimension

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

Histologic Grade (G)

GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

Continued...

Table 1 — Continued
American Joint Committee on Cancer (AJCC)
TNM Staging Classification for the Lip and Oral Cavity
(7th ed., 2010)
(Nonepithelial tumors such as those of lymphoid tissue, soft tissue, bone, and cartilage are not included)

Anatomic Stage/Prognostic Groups			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
Stage IVB	Any T	N3	M0
	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

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Table 2
American Joint Committee on Cancer (AJCC)
TNM Staging System for the Pharynx (7th ed., 2010)
(Nonepithelial tumors such as those of lymphoid tissue, soft tissue, bone, and cartilage are not included)

Primary Tumor (T)

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma *in situ*

Nasopharynx

T1 Tumor confined to the nasopharynx, or tumor extends to oropharynx and/or nasal cavity without parapharyngeal extension*
T2 Tumor with parapharyngeal extension*
T3 Tumor involves bony structures of skull base and/or paranasal sinuses
T4 Tumor with intracranial extension and/or involvement of cranial nerves, hypopharynx, orbit, or with extension to the infratemporal fossa/masticator space

*Note: Parapharyngeal extension denotes posterolateral infiltration of tumor.

Oropharynx

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

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

Hypopharynx

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

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

Continued...

Table 2 — Continued

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

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

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

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

Regional Lymph Nodes (N)†:
Oropharynx and Hypopharynx

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

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

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

Continued...

Table 2 — Continued

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

Anatomic Stage/Prognostic Groups: Nasopharynx

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T1	N1	M0
	T2	N0	M0
	T2	N1	M0
Stage III	T1	N2	M0
	T2	N2	M0
	T3	N0	M0
	T3	N1	M0
	T3	N2	M0
Stage IVA	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IVB	Any T	N3	M0
Stage IVC	Any T	Any N	M1

Anatomic Stage/Prognostic Groups: Oropharynx, Hypopharynx

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
Stage IVB	T4b	Any N	M0
	Any T	N3	M0
Stage IVC	Any T	Any N	M1

Histologic Grade (G)

GX Grade cannot be assessed
G1 Well differentiated
G2 Moderately differentiated
G3 Poorly differentiated
G4 Undifferentiated

Table 3

American Joint Committee on Cancer (AJCC) TNM Staging System for the Larynx (7th ed., 2010)

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

Primary Tumor (T)

TX Primary tumor cannot be assessed

T0 No evidence of primary tumor

Tis Carcinoma *in situ*

Supraglottis

T1 Tumor limited to one subsite of supraglottis with normal vocal cord mobility

T2 Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (eg, mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx

T3 Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, pre-epiglottic space, paraglottic space, and/or inner cortex of thyroid cartilage

T4a Moderately advanced local disease
Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)

T4b Very advanced local disease
Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Continued on next page

Glottis

T1 Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility

T1a Tumor limited to one vocal cord

T1b Tumor involves both vocal cords

T2 Tumor extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility

T3 Tumor limited to the larynx with vocal cord fixation and/or invasion of paraglottic space, and/or inner cortex of the thyroid cartilage

T4a Moderately advanced local disease
Tumor invades through the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)

T4b Very advanced local disease
Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Subglottis

T1 Tumor limited to the subglottis

T2 Tumor extends to vocal cord(s) with normal or impaired mobility

T3 Tumor limited to larynx with vocal cord fixation

T4a Moderately advanced local disease
Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)

T4b Very advanced local disease
Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Table 3 — Continued

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

Regional Lymph Nodes (N)*

NX	Regional lymph nodes cannot be assessed N0; no regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N2a	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node, more than 6 cm in greatest dimension

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

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

Anatomic Stage/Prognostic Groups

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
Stage IVB	T4b	Any N	M0
	Any T	N3	M0
Stage IVC	Any T	Any N	M1

Histologic Grade (G)

GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

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

Primary Tumor (T)

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ

Maxillary Sinus

T1 Tumor limited to maxillary sinus mucosa with no erosion or destruction of bone
T2 Tumor causing bone erosion or destruction including extension into the hard palate and/or middle nasal meatus, except extension to posterior wall of maxillary sinus and pterygoid plates
T3 Tumor invades any of the following: bone of the posterior wall of maxillary sinus, subcutaneous tissues, floor or medial wall of orbit, pterygoid fossa, ethmoid sinuses
T4a Moderately advanced local disease
Tumor invades anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid or frontal sinuses
T4b Very advanced local disease
Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve (V_2), nasopharynx, or clivus

Nasal Cavity and Ethmoid Sinus

T1 Tumor restricted to any one subsite, with or without bony invasion
T2 Tumor invading two subsites in a single region or extending to involve an adjacent region within the nasoethmoidal complex, with or without bony invasion
T3 Tumor extends to invade the medial wall or floor of the orbit, maxillary sinus, palate, or cribriform plate
T4a Moderately advanced local disease
Tumor invades any of the following: anterior orbital contents, skin of nose or cheek, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid or frontal sinuses
T4b Very advanced local disease
Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than (V_2), nasopharynx, or clivus

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2 Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N2a Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
N2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3 Metastasis in a lymph node, more than 6 cm in greatest dimension

Distant Metastasis (M)

M0 No distant metastasis
M1 Distant metastasis

Continued on next page

Table 4 — Continued

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

Anatomic Stage/Prognostic Groups			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
Stage IVB	T4b	Any N	M0
	Any T	N3	M0
Stage IVC	Any T	Any N	M1

Histologic Grade (G)

GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

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Table 5
American Joint Committee on Cancer (AJCC)
TNM Staging System for the Major Salivary Glands (7th ed., 2010)
(Parotid, Submandibular, and Sublingual)

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 2 cm or less in greatest dimension without extraparenchymal extension*
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension without extraparenchymal extension*
T3	Tumor more than 4 cm and/or tumor having extraparenchymal extension*
T4a	Moderately advanced disease Tumor invades skin, mandible, ear canal, and/or facial nerve
T4b	Very advanced disease Tumor invades skull base and/or pterygoid plates and/or encases carotid artery

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

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N2a	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node, more than 6 cm in greatest dimension

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

Anatomic Stage/Prognostic Groups

Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
Stage IVB	T4b	Any N	M0
	Any T	N3	M0
Stage IVC	Any T	Any N	M1

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Table 6
American Joint Committee on Cancer (AJCC)
TNM Staging System for Mucosal Melanoma of the Head and Neck
(7th ed., 2010)

Primary Tumor (T)

T3	Mucosal disease
T4a	Moderately advanced disease Tumor involving deep soft tissue, cartilage, bone, or overlying skin
T4b	Very advanced disease Tumor involving brain, dura, skull base, lower cranial nerves (IX, X, XI, XII), masticator space, carotid artery, prevertebral space, or mediastinal structures

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Regional lymph node metastases present

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

Anatomic Stage/Prognostic Groups

Stage III	T3	N0	M0
Stage IVA	T4a	N0	M0
	T3-T4a	N1	M0
Stage IVB	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

Histologic Grade (G)

GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

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Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 05/29/14

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.

Table of Contents

Overview

The NCCN Guidelines for Head and Neck Cancers address tumors arising in the lip, oral cavity, pharynx, larynx, and paranasal sinuses; occult primary cancer, salivary gland cancer, and mucosal melanoma are also addressed.[1,2] The *Updates* section in the algorithm briefly describes the new changes for 2014, which include revisions to the *Principles of Radiology* for each site and to the *Principles of Surgery*. A new section on *Principles of Dental Evaluation and Management* was added for the 2014 update (see this Discussion and the algorithm). A brief overview of the epidemiology and management of head and neck (H&N) cancers is provided in the following section. A recent review discusses the progress that has been made during the last 10 years in understanding the epidemiology, pathogenesis, and management of H&N cancers.[3]

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.

Incidence and Etiology

In 2014, it is estimated that about 55,070 new cases of oral cavity, pharyngeal, and laryngeal cancers will occur, which account for about 3% of new cancer cases in the United States.[4] An estimated 12,000 deaths from H&N cancers will occur during the same time period.[4] 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, hypopharynx, and larynx. 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.

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 the tongue).[5-11] The overall incidence of HPV-positive H&N cancers is increasing in the United States, while the incidence of HPV-negative (primarily tobacco- and alcohol-related) cancer is decreasing.[12] A strong causal relationship has been established between HPV type 16 and development of oropharyngeal cancer (see *HPV Testing* in this Discussion).[5] It has not yet been shown whether HPV vaccination will decrease the incidence of HPV-positive oropharyngeal cancer. Cancer of the oral tongue also seems to be increasing in young white women, (+1%/year among young women); however, the etiology is unclear.[13-15]

Staging

Stage at diagnosis predicts survival rates and guides management in patients with H&N cancers. The 2010 AJCC staging classification (7th edition) was used as a basis for NCCN's treatment recommendations for H&N cancers.[16,17] The TNM staging systems developed by the AJCC for the lip and oral cavity, pharynx (nasopharynx, oropharynx, and hypopharynx), larynx (glottis and supraglottis), paranasal sinuses (ethmoid and maxillary), major salivary glands (parotid, submandibular, and sublingual), and mucosal melanoma are shown in Tables 1 to 6, respectively (see the NCCN Guidelines for Head and Neck Cancers).[17] 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 in the NCCN Guidelines for

Head and Neck Cancers). Definitions for staging the primary tumor (T), based on its size, are uniform for the lip, oral cavity, and oropharynx. In contrast, T stage is based on subsite involvement and is specific to each subsite for the glottic larynx, supraglottic larynx, hypopharynx, and nasopharynx. In general, stage I or 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. 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).[16] These changes were deemed necessary, because a substantial proportion of advanced-stage malignancies of the H&N, although resectable, are being treated non-surgically. 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 it is anticipated that surgery will not improve prognosis (see *Resectable versus Unresectable Disease* in this Discussion). 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 (ie, lip, oral cavity, oropharynx, hypopharynx, larynx, paranasal sinuses, major salivary glands, mucosal melanoma). Of note, a designation of stage IV disease does not necessarily mean the disease is incurable, particularly in the absence of distant metastases. Mucosal melanomas are rare, very aggressive tumors that mainly affect the nasal cavity and paranasal sinuses. Thus, melanomas confined to the mucosa only are T3; those with moderately advanced lesions (involving underlying cartilage or bone) are T4a, and very advanced primary tumors are T4b (see Table 6 in the NCCN Guidelines for Head and Neck Cancers).

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, indications for chemotherapy). Single-modality treatment with surgery or radiation therapy (RT) 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 the following sites (ie, lip, oral cavity, pharynx, larynx, paranasal sinus) and for occult primary cancer is addressed in the algorithm. 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.[18,19] Follow-up for these sequelae should include a comprehensive H&N examination. Adequate nutritional support can help to prevent severe weight loss in patients receiving treatment for H&N cancers; therefore, patients should be encouraged to see a dietician.[20] A new section on *Principles of Dental Evaluation and Management* was added for the 2014 update (see this Discussion). Patients should also be encouraged to stop smoking (and remain abstinent) and to modify alcohol consumption if excessive, because these habits may decrease the efficacy of treatment and adversely affect other health outcomes.[21,22] Programs using behavioral counseling combined with medications that promote smoking cessation (approved by the FDA) can be very useful (www.smokefree.gov/). Patients are at risk for depression from H&N cancer and its sequela, so screening for depression is advised (see the NCCN Guidelines for Distress Management).[23-26] Specific components of patient support and follow-up are listed in the algorithm. Panel members also recommend referring to the NCCN Guidelines for Palliative Care, Distress Management, and Adult Cancer Pain as needed.

Comorbidity and Quality of Life

Comorbidity

Comorbidity refers to the presence of concomitant disease (in addition to H&N cancers) that may affect diagnosis, treatment, and prognosis.[27-29] 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,[29-36] and comorbidity also influences costs of care, utilization, and quality of life.[37-39] Traditional indices of comorbidity include the Charlson index[28] and the Kaplan-Feinstein index and its modifications.[29,40] The Adult Comorbidity Evaluation-27 (ACE-27) is specific for H&N cancers and has excellent emerging reliability and validity.[41,42]

Quality of Life

Health-related quality-of-life issues are paramount in H&N cancers. These tumors affect basic physiologic functions (ie, the ability to chew, swallow, and breathe), the senses (taste, smell, hearing), and uniquely human characteristics (ie, appearance, 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.[43]

An NIH–sponsored conference[44] 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);[45] 2) the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-HN35);[46] and 3) the Functional Assessment of Cancer Therapy Head and Neck module (FACT-H&N).[47] The Performance Status Scale is a clinician-rated performance scale that is widely used for patients with H&N cancers.[48]

Head and Neck Surgery

Principles of Surgery

All patients should be evaluated by an H&N surgical oncologist before treatment. In addition, 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 post-treatment neck evaluation) are discussed in the algorithm.[49,50] 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.[51,52] 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.[53,54] For the 2014 update, revisions to the *Principles of Surgery* section are described in the *Updates* section of the algorithm.

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 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. 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 (ie, those tumors that cannot be removed without causing unacceptable morbidity) should be distinguished from inoperable tumors in those 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 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. 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 RT alone or RT combined with chemotherapy may represent equivalent or preferable approaches to surgery in these individuals. Although such patients may not undergo surgery, their tumors should not be labeled as unresectable. Their disease is usually far less extensive than those 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.*[55] 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.

Selective neck dissections have been developed based on the common pathways for spread of H&N cancers to regional nodes.[56,57] Depending on the site, selective neck dissection is often recommended for N0 disease. To remove the nodes most commonly involved with metastases from the oral cavity, a selective neck dissection is recommended that includes the nodes found above the omohyoid muscle (levels I–III and sometimes the superior parts of level V).[55,58] Similarly, to remove the nodes most commonly involved with metastases from the pharynx and larynx, a selective neck dissection is recommended that includes the nodes in levels II to IV and level VI when appropriate.[55] 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).[59-61]

The chief role of selective neck dissections in these NCCN Guidelines is to determine which patients are candidates for possible adjuvant therapy (ie, chemotherapy/RT or RT), although selective neck dissections may be used as treatment when neck tumor burden is low.[62] 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.[63-65] In the 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.[49] 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 nonsurgically treated patients so that any local or regional recurrence is detected early, and salvage surgery (and neck dissection as indicated) is performed. After either RT or chemoradiation, post-treatment evaluation with imaging (ie, CT and/or MRI with contrast, PET-CT) guides the use of neck dissection.[66-69] 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.[67,70]

Note that 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]);[66,71] 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.[66,71,72] In patients who have a clinically negative neck, a negative PET-CT is 90% reliable and further imaging is optional.[73-75] 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.[66] 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 patients who can be safely observed without surgery to the neck.[76]

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;[77,78] long-term follow-up has been recently reported for one of the trials.[79] A combined analysis of data from the 2 trials has been done.[80]

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^2 every 3 weeks for 3 doses).[78] Note that long-term results from RTOG 9501 have recently been published.[79] 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.[77] 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.[81]

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, there was no survival advantage.[79,80] The NCCN Panel noted that the combined analysis was considered exploratory by the authors, because it was not part of the initial protocol design.[80] 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.[81-87] 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 oropharyngeal primary cancers with positive level 4 or 5 nodes—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 to RT alone, the NCCN Panel added *consider chemoradiation* for these features.[77]

Salvage Surgery

Patients with advanced carcinoma (any T, N2–3) who undergo nonsurgical treatment, such as concurrent chemotherapy and RT, need very close follow-up both to evaluate for local recurrence and to assess for ipsilateral or contralateral neck recurrence. 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 due to 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. Laryngectomy may be indicated to obtain clear surgical margins or to prevent aspiration (eg, in patients with advanced oropharyngeal cancer). After salvage laryngectomy, patients may have a higher incidence of pharyngocutaneous fistula and flaps may be advantageous (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).

Head and Neck Radiation Therapy

RT for H&N cancers has grown increasingly complex. The availability and technical precision of intensity-modulated RT (IMRT) has markedly increased, perhaps beyond our 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 NCCN Guidelines for Radiation Therapy 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. Guidelines from the American College of Radiology may be useful for technical details (http://www.acr.org/Quality-Safety).

Recent Updates

For the 2014 update, the NCCN Guidelines for Radiation Therapy were revised for each site, including extensive revisions for mucosal melanoma. In addition, for 2014, 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 the following sites: lip, oral cavity, oropharynx, hypopharynx, glottic larynx, supraglottic larynx, occult primary, salivary gland tumors, and mucosal melanoma. For sites of suspected subclinical spread (at low to intermediate risk of recurrence), the doses for intensity-modulated RT (IMRT) or 3-D conformal RT were clarified for the following sites: lip, oral cavity, oropharynx, hypopharynx, glottic larynx, supraglottic larynx, occult primary, salivary gland tumors, and mucosal melanoma.

A new section on *Palliative RT* was added in 2013 and revised for 2014 (see *Palliative RT* in this Discussion). 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: 1) high-risk sites; and 2) 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. 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).[88-90] 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.[88,91-95] When using hyperfractionation, high-risk sites generally require up to 81.6 Gy (1.2 Gy/fraction).[88,89]

In contrast, 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-D conformal RT or IMRT is used. For 3-D conformal RT and sequentially planned IMRT, suggest 44 to 50 Gy (2.0 Gy/fraction).[96,97] For IMRT, suggest 54 to 63 Gy (1.6-1.8 Gy/fraction).[97-99] Postoperative irradiation is recommended based on stage, histology, and surgical-pathologic findings. In general, postoperative RT 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 postoperative RT alone (60–66 Gy), or with chemotherapy, are recommended for the high-risk features of extracapsular disease and/or positive margins.[79,80] 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.[100-102] Especially in RT alone settings, schedules delivering at least 1000 cGy per week are recommended,[103-107] with the exception of salivary gland tumors, which may have slower cell kinetics. Trials in early-stage glottic laryngeal cancer have shown higher recurrence rates with daily fraction sizes <200 cGy where the cumulative weekly dose is <1000 cGy.[108,109]

Two large, randomized 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 in local control was observed in the hyperfractionation arm (38% vs. 56%; $P = .01$) and no increase in late complications was observed.[110] A long-term follow-up analysis has also shown a small survival advantage for hyperfractionation ($P = .05$).[111] 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 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.[112]

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.[88,89,113] 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 to standard fractionation.[89]

A meta-analysis of updated individual patient data from 15 randomized trials analyzed the effect of hyperfractionated or accelerated RT on survival of patients with H&N cancers.[114] Standard fractionation constituted the control arm in all of the trials in this meta-analysis.[90] An absolute survival benefit for altered fractionation of 3.4% at 5 years (HR 0.92; 95% CI, 0.86–0.97; *P*=.003) was reported. This benefit, however, was limited to patients younger than 60 years of age.[114] Hyperfractionation was associated with a benefit of 8% after 5 years.[115] However, the recent GORTEC 99-02 trial reported that altered fractionation did not improve outcomes when compared with conventional fractionation.[116,117] 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.[114,118,119]

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^2).[120] Other fraction sizes (eg, 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.[119,121-123] RTOG 0129 assessed accelerated fractionation with 2 cycles of concurrent cisplatin versus standard fractionation with 3 cycles of concurrent cisplatin. There was no significant difference in overall survival between the 2 arms.[120,124]

Concurrent chemoradiation increases acute toxicity compared to radiation alone, although an increase in late toxicity beyond that caused by RT alone is less clear.[125-127] Altered fractionation and/or multiagent chemotherapy may further increase the toxicity burden.[128] 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.[129,130] IMRT is an advanced form of conformal RT permitting more precise cancer targeting while reducing dose to normal tissues.[97,131-135] 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).[136-141]

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).[142,143] Although dose painting has been used to simplify radiation planning, hot spots associated with higher toxicity can

occur.[143,144] 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.[134,145]

IMRT is now widely used in H&N cancers and is the predominant technique used at NCCN Member Institutions.[146,147] It is useful in reducing long-term toxicity in oropharyngeal, paranasal sinus, and nasopharyngeal cancers by reducing the dose to one or more major salivary glands, temporal lobes, mandible, auditory structures (including cochlea), and optic structures.[98,137,138,148-155] Overall survival is similar between patients treated with IMRT and those receiving conventional RT.[149,156-158] In-field recurrences, low-grade mucositis in areas away from the cancer targets, and posterior neck hair loss can occur with IMRT.[159-162] The application of IMRT to other sites (eg, oral cavity, larynx, hypopharynx, salivary glands) is evolving.[163-170]

Numerous phase II studies show a decrease in late toxicity (xerostomia) without compromising tumor control for nasopharyngeal, sinonasal, and other sites. More recently, 3 randomized trials have supported the clinical benefits of IMRT in H&N cancers with regard to the reduction in xerostomia. Pow et al evaluated treatment of early-stage nasopharyngeal carcinoma with conventional RT techniques versus with IMRT.[137] The results showed a statistical improvement in salivary flow and in patient-reported quality-of-life parameters.[137] In the study by Kam et al, patients with nasopharyngeal carcinoma were randomly assigned to either IMRT or conventional 2-D RT.[138] At one year after treatment, patients in the IMRT arm had significantly lower rates of clinician-rated severe xerostomia than patients in the 2-D RT 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 there was no significant difference in patient-reported outcomes between the 2 arms. The authors concluded that other salivary glands may also be important and merit protection.

A recent review suggests that IMRT may be useful to preserve the optic pathway in patients with sinonasal malignancies.[148] Data from a phase III randomized trial (PARSPORT) indicate that IMRT decreases xerostomia when compared with conventional RT in patients with non-nasopharyngeal carcinoma.[156] In this trial, patients with T1–T4, N0–N3, M0 disease were treated to a total dose of 60 or 65 Gy in 30 fractions either with conventional RT (ie, parallel opposed technique) or with IMRT; 80 patients with oropharyngeal and 14 patients with hypopharyngeal tumors were included. Grade 2 or worse (LENT-SOMA scale) xerostomia 2 years after treatment was seen in 83% of patients receiving conventional RT versus 29% of patients in the IMRT group (P< .0001). No differences were seen in the rates of locoregional control or survival.

A new section on palliative RT was recently added to the NCCN Guidelines. Although several regimens are provided, no single regimen is preferred; specific regimens vary widely among NCCN Member Institutions.[171-173] Any palliative RT regimen that might cause severe toxicities should be avoided. More hypofractionated regimens may be useful for patients with end-stage disease.[174]

Brachytherapy

Brachytherapy has been used less often in recent years because of improved local control obtained with concurrent chemoradiation. However, brachytherapy still has a role for lip and oral cavity cancers.[175]

Follow-up After RT

For patients whose cancer has been treated with RT, the recommended follow-up 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.[176-178]

Principles of Nutrition and Supportive Care

A new section on *Principles of Nutrition* was recently added to the NCCN Guidelines. 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.[18,179,180] 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 had significant weight loss (>10% body weight) clearly need nutritional evaluation and close monitoring of their weight to prevent further weight loss.[181,182] In addition, all patients should receive nutritional evaluation before and after treatment to assess the need for interventions (eg, enteral support via feeding tubes).[183,184] 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.[185-187] Evaluation by a speech-language/swallowing therapist is valuable before and after treatment, because it can help mitigate potential problems.[188-190] Patients are also at risk for dental problems (see this Discussion).[18]

NCCN Panel Members agree that reactive feeding tube placement is appropriate in selected patients with H&N cancers.[180,184] There is no consensus 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).[180,182,191] The 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). The 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. 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.[192-194] In addition, 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.[192,193,195-202] Dental/oral evaluation and management can help decrease dental caries and associated problems such as dentoalveolar infection and osteoradionecrosis.[194,195,202-215]

The recommended dental/oral evaluations before, during, and after RT are described in detail in the algorithm and summarized here. A dental/oral treatment plan needs to 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.[203] Some of the strategies to decrease oral and dental complications include: 1) decrease dry mouth (eg, by using salivary substitutes and stimulation);[216-220] 2) decrease dental caries (eg, by using topical fluoride);[204,221-225] 3) decrease dentoalveolar infection (eg, with frequent evaluations to detect and treat disease promptly); 4) decrease osteoradionecrosis (eg, by extracting teeth before RT);[207] 5) decrease trismus of the masticatory muscles (eg, by using custom mouth opening devices to maintain range of motion);[226-228] and 6) need for evaluations during and after treatment to help minimize complications.[216,217,223,229,230]

During and after treatment, the goals of dental/oral management include: 1) managing xerostomia; 2) preventing trismus; and 3) detecting and treating oral candidiasis.[203] Additional goals after treatment include: 1) preventing and treating dental caries; 2) preventing postradiation osteonecrosis; and 3) preventing oral candidiasis.[203]

Cancer of the Lip

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

Workup and Staging

The workup for patients with squamous cell carcinoma of the lip consists of a complete H&N examination, biopsy, and other appropriate studies. Dental evaluation (dental panoramic x-ray), CT scan, or MRI is done as clinically indicated to better assess soft tissue or nodal spread or if bone invasion is suspected. A new section on *Principles of Dental Evaluation and Management* was added for the 2014 update (see this Discussion).

The AJCC TNM staging system reflects tumor size, extension, and nodal disease (see Table 1 in the NCCN Guidelines for Head and Neck Cancers).[16] This system does predict the risk for local recurrence. The location of the primary tumor also is predictive. Tumors in the upper lip and commissural areas have a higher incidence of lymph node metastases at the time of diagnosis. Systemic dissemination is rare, occurring in approximately 10% to 15% of patients, most often in those with uncontrolled locoregional disease.

Treatment

Treatment of the Primary

The treatment of lip cancer is governed by the stage of the disease. The choice of a local treatment modality is based on the expected functional and cosmetic outcome. In early-stage cancers (T1–2, N0), surgery is preferred and radiation is an option for local control.[231-233] Some very small or superficial cancers are managed more expeditiously with a surgical resection without resultant functional deformity or an undesired cosmetic result. A superficial cancer that occupies most of the lower lip, however, is best managed with RT.[234] Some advanced lip cancers can

cause a great deal of tissue destruction and secondary deformity; surgery is preferred in this clinical setting. Surgery is also preferred for advanced cancers with extension into the bone. Patients with resectable T3–T4a, N0; or any T, N1–3 disease who have a poor surgical risk should be treated as for very advanced disease.[234]

Management of the Neck

The management of the neck is also governed by stage and the location of the tumor. For example, the lymphatics of the upper lip are very extensive. Thus, tumors in this location are more apt to spread to deep superior jugular nodes. The position of the tumor along the lip also can be helpful in predicting the pattern of lymph node spread. A midline location can place a patient at higher risk for contralateral disease. For patients with advanced disease (T3, T4a) and an N0 neck, an ipsilateral or bilateral neck dissection is an option. When a patient presents with palpable disease, all appropriate nodal levels should be dissected. In patients who appear to have a complete response after either RT or chemoradiation, post-treatment evaluation with imaging can be used to guide the use of neck dissection.

Radiation Therapy

For the 2014 update, extensive revisions were made to the radiation guidelines (see *Head and Neck Radiation Therapy* in this Discussion). RT, when used as definitive treatment, may consist of external-beam RT with (or without) brachytherapy, depending on the size of the tumor. Brachytherapy should only be performed at centers with expertise. The NCCN algorithm provides recommendations for low-dose rate and high-dose rate brachytherapy.[235,236] The conventional fractionation dose required also depends on tumor size, but doses of 66 to 72 Gy are adequate to control the disease.

In the adjuvant setting, doses of 60 to 66 Gy are required, depending on the pathologic features. In both definitive and adjuvant settings, the neck is treated with doses that address adverse features, such as positive margins or invasion (perineural, vascular, and/or lymphatic).[237] The fraction size to the intermediate- and low-risk sites ranges from 44 Gy (2.0 Gy/fraction) to 60 Gy (1.6 Gy fraction.) For these sites of suspected subclinical spread, suggested doses are 44–54 Gy if 3-D conformal RT is used or 54–60 Gy if IMRT is used, depending on the dose/fraction (1.6–2.0 Gy/fraction).

Follow-up/Surveillance

Recommendations for surveillance are provided in the algorithm.

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. The area has a rich lymphatic supply, and initial regional node dissemination is to nodal groups at levels I to 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, many patients undergo either ipsilateral or bilateral neck dissection, which is guided by tumor thickness. If definitive RT is chosen for treatment of T1–2, N0 disease, the fraction size to the intermediate- and low-risk sites ranges from 44 Gy (2.0 Gy/fraction) to 60 Gy (1.6 Gy fraction). For these sites of suspected subclinical spread, suggested doses are 44–54 Gy if 3-D

conformal RT is used or 54–60 Gy if IMRT is used, depending on the dose/fraction (1.6–2.0 Gy/fraction).

Workup and Staging

Imaging studies to evaluate mandibular involvement and a careful dental evaluation (including jaw imaging, as clinically indicated) are particularly important for staging (see Table 1 in the NCCN Guidelines for Head and Neck Cancers) and planning therapy for oral cavity cancers in addition to a complete H&N examination, biopsy, and other appropriate studies. For patients who appear to have stage III to IV disease, PET-CT may alter management by upstaging patients.[238] Nutrition, speech, and swallowing evaluations are recommended for selected at-risk patients (see *Principles of Nutrition* in this Discussion). A new section on *Principles of Dental Evaluation and Management* was added for the 2014 update (see this Discussion).

Treatment

Surgery and RT represent the standards of care for early-stage and locally advanced resectable lesions in the oral cavity. The specific treatment is dictated by the TN stage and, if N0 at diagnosis, by the risk of nodal involvement. Multidisciplinary team involvement is particularly important for this site, because critical physiologic functions may be affected such as mastication, deglutition, and articulation of speech. Most panel members prefer surgical therapy for resectable oral cavity tumors, even for more advanced tumors. The functional outcome after primary surgical management is often quite good, given advances in reconstruction using microvascular techniques. Therefore, organ preservation using chemotherapy has received less attention for the initial management of patients with oral cavity cancers. Definitive RT may be offered to selected patients who are medically inoperable or refuse surgery. For the 2014 update, extensive revisions were made to the radiation guidelines (see *Head and Neck Radiation Therapy* in this Discussion).

For patients with early-stage oral cavity cancers, the recommended initial options are resection (preferred) of the primary or definitive RT. For the 2014 update, the option of using sentinel lymph node biopsy was added, which may be used to identify occult cervical metastases.[239-245] Patients may be spared the morbidity of an elective neck dissection if they do not have occult cervical metastases. However, sentinel lymph node biopsy should be done in centers with expertise in this technique; it is less accurate for floor of the mouth tumors.[239,240] Postsurgical adjuvant treatment options depend on whether adverse features are present. For patients with resected oral cavity cancers who have the adverse pathologic features of extracapsular nodal spread with [or without] a positive mucosal margin, postoperative chemotherapy/RT (preferred, category 1) is the recommended treatment. For patients with positive margins, options include: 1) re-resection; 2) RT; or 3) consider chemotherapy/RT (for T2 only). For patients with other risk features, options include RT or consider chemotherapy/RT.

For patients with advanced-stage, resected oral cavity cancers who have the adverse pathologic features of extracapsular nodal spread and/or a positive mucosal margin, recommended postoperative adjuvant options include: 1) chemotherapy/RT (preferred, category 1); 2) re-resection of positive margins (if technically feasible); or 3) RT.[77-81] For other risk features—such as pT3 or pT4 primary, N2 or N3 nodal disease, nodal disease in levels IV or V, perineural invasion, or vascular tumor embolism—clinical judgment should be used when deciding to either use RT alone or add chemotherapy to RT.

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.

Workup and Staging

A multidisciplinary consultation is encouraged including a registered dietitian and a speech-language/swallowing therapist (see *Principles of Nutrition* in this Discussion). Accurate staging (see Table 2 in the NCCN Guidelines for Head and Neck Cancers) depends on a complete H&N examination and appropriate imaging studies.[16,246] Tumor HPV testing is recommended for cancers of the oropharynx, because prior HPV infection is related to the development of a significant proportion of oropharyngeal cancers (see *HPV Testing* in this Discussion).[247]

HPV Testing

Studies have documented an increase in the incidence of HPV-related cancer, which is estimated at 60% to 70% of newly diagnosed cancers of the oropharynx in the United States and parts of the European Union.[12,248-251] HPV type 16 appears to be related to the development of oropharyngeal cancer.[5,252] Analyses of clinical trials indicate that patients with HPV-positive cancers have improved response to treatment and survival (overall and progression-free survival) when compared with HPV-negative tumors.[120,253-256] Consensus is increasing 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. Some clinicians have recently suggested that less-intense treatment may be adequate for HPV-positive oropharyngeal cancers (ie, deintensification); however, the available data supporting this assertion are limited, and this strategy is not currently recommended by the NCCN Panel.[257,258] The NCCN Panel believes that HPV status should not be a routine consideration in treatment selection at this time, except for cancers of unknown primary (see *Occult Primary Cancer* in this Discussion).[259] Additional studies are needed to understand the effect of HPV status on response to different therapies, treatment outcome, and patterns of failure. Recent studies have assessed the relation of HPV to other prognostic or predictive factors such as smoking history and stage.[260,261] Clinical trial groups are reporting retrospective analyses of response to therapy in HPV-related versus HPV-unrelated oropharyngeal cancers.[120,253,255,262] Panel members urge that patients with HPV-related cancers be enrolled in clinical trials evaluating biological and treatment-related questions.[263]

HPV testing options in a clinical setting include HPV in situ hybridization and a surrogate marker, p16 immunohistochemistry (which is a more widely available test that strongly correlates with HPV status and is similarly associated with improved prognosis).[120,254,255,264] Sufficient pathologic material for HPV testing can be obtained by fine-needle aspiration (FNA).[265] Panel members note that HPV testing may prompt questions about prognosis (ie, a favorable or a 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, gaining an understanding of the etiology for one's cancer can reduce 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. Of note, the following categories are treated as advanced cancer: 1) T4b, any N; 2) unresectable nodal disease; or 3) unfit for surgery.

Early-stage (T1–2, N0–1) oropharyngeal cancers may be treated with: 1) primary surgery—more specifically, transoral or open resection of the primary—(with or without neck dissection); or 2) definitive RT.[51,54,266] Panel members felt that the third option of RT plus systemic therapy (category 2B for systemic therapy) was only appropriate for T2, N1. Note that a category 2B recommendation indicates that most, but not all, panel members agree that the intervention is appropriate (>50% but <85%). Adjuvant chemotherapy/RT is recommended (category 1) for adverse pathologic features of extracapsular nodal spread with (or without) positive mucosal margins.[77,78,80]

For locally advanced resectable disease (T3–4a, N0–1; or any T, N2–3), 3 treatment options are recommended, in addition to enrollment in multimodality clinical trials. The 3 options are: 1) concurrent systemic therapy/RT (salvage surgery is used for managing residual or recurrent disease);[125] 2) transoral or open resection of the primary and neck (with appropriate adjuvant therapy [chemotherapy/RT or RT]); or 3) induction chemotherapy (category 3) (followed by RT or chemotherapy/RT), although panel members had a major disagreement for induction therapy.[51,54,267]

Concurrent systemic therapy/RT—with high-dose cisplatin as the preferred (category 1) systemic agent—is recommended for treatment of locally or regionally advanced (T3–4a, N0–1, or any T, N2–3) cancer of the oropharynx. Many panel members did not agree that induction chemotherapy should be recommended for locally or regionally advanced cancer of the oropharynx. This disagreement is reflected by the category 3 recommendations for oropharyngeal cancer (see *The Induction Chemotherapy Controversy* in this Discussion).[125,268-277] Note that a category 3 recommendation indicates that only a few panel members agree (<25%) that the intervention is appropriate; most disagree. Most panel members agree that concurrent systemic therapy with RT is the standard therapy for fit patients with locally advanced disease.

The Induction Chemotherapy Controversy

Defining the role of induction chemotherapy in the management of locally or regionally advanced H&N cancers has generated considerable discussion within the NCCN Panel in recent years. The algorithm for the management of advanced oropharyngeal cancer illustrates the lack of consensus among NCCN Member Institutions despite the extensive discussion. Thus, induction chemotherapy has a category 3 recommendation (ie, major disagreement) for the management of both locally and regionally advanced oropharyngeal cancer (ie, T3–4a, N0–1, any T, N2–3). However in other sites, category 2A and 2B recommendations for induction chemotherapy are common based on the update from RTOG 91-11.[278] For selected patients with hypopharyngeal and laryngeal cancers less than T4a in extent (for which total laryngectomy is indicated, if managed surgically), induction chemotherapy—used as part of a larynx preservation strategy—is category 2A.

Panel members feel that induction chemotherapy should only be done in centers with expertise in these regimens because of challenges associated with appropriate patient selection and management of treatment-related toxicities.[268] Residual toxicity from induction chemotherapy may also complicate the subsequent delivery of definitive RT or chemotherapy/RT. For laryngeal cancer, RT alone (category 1) is recommended after a complete or partial response with induction chemotherapy; chemotherapy/RT is a category 2B recommendation after a partial response.

A summary of the data helps provide some perspective on the NCCN Panel's recommendations. Most randomized trials of induction

chemotherapy followed by RT and/or surgery compared to locoregional treatment alone, which were published in the 1980s and 1990s, did not show an improvement in overall survival with the incorporation of chemotherapy.[273] However, a change in the pattern of failure with less distant metastases was noted in some studies.[279] Also, a correlation was noted between response to induction chemotherapy and subsequent durable response to radiation.[279,280] Thus, the concept developed that in selected patients, induction chemotherapy could facilitate organ preservation, avoid morbid surgery, and improve overall quality of life of the patient even though overall survival was not improved. Because total laryngectomy is among the procedures most feared by patients,[281] larynx preservation was the focus of initial studies.

Two randomized studies—the Veterans Affairs (VA) Laryngeal Cancer Study Group trial in advanced laryngeal cancer and the EORTC trial predominantly in advanced hypopharynx cancer—established the role of induction cisplatin/5-FU chemotherapy followed by definitive RT in responding patients as an alternative treatment to primary total laryngectomy and postoperative radiation, offering potential larynx preservation without compromise in survival (see *Cancer of the Larynx* and *Cancer of the Hypopharynx* in this Discussion).[279,280] Yet even in this setting, the role of induction chemotherapy decreased with time. Randomized trials and related meta-analyses indicated that concurrent systemic RT (with cisplatin being the best studied agent) offered superior locoregional tumor control and survival compared to radiation alone,[282-292] and shorter duration of therapy compared to induction therapy followed by radiation. Meta-analyses reported that concurrent systemic RT was more efficacious than an induction chemotherapy strategy.[273,277] In the larynx preservation setting, Intergroup 91-11 compared radiation alone, concurrent cisplatin/radiation, and induction cisplatin/5-FU followed by radiation; all arms had surgery for salvage. The concurrent arm had the highest larynx preservation rate (see *Cancer of the Larynx* in this Discussion).[293] A recent long-term follow-up of 91-11 confirmed that concomitant chemotherapy/RT improved the larynx preservation rate and that induction chemotherapy was not superior to RT alone.[278] However, overall survival did not differ among the treatment arms.

Nonetheless, interest in the role of induction chemotherapy was renewed several years ago for a few reasons. Advances in surgery, RT, and concurrent systemic therapy/RT have yielded improvements in local/regional control; thus, the role of distant metastases as a source of treatment failure has increased and induction chemotherapy allows greater drug delivery for this purpose.[294,295] Clinicians have increasing concern regarding the long-term morbidity of concurrent systemic therapy/RT, and thus have increasing interest in exploring alternative approaches that might have a more favorable side-effect profile.[296] Finally, a more effective triplet chemotherapy regimen has been identified for induction chemotherapy compared to the standard cisplatin/5-FU used in induction trials of the 1980s and 1990s, and in the related meta-analyses. Three phase III trials compared induction cisplatin plus infusional 5-FU with (or without) the addition of a taxane (docetaxel or paclitaxel) followed by the same locoregional treatment. Results showed significantly improved outcomes (response rates, disease-free survival, or overall survival depending on the trial) for patients in the 3-drug induction group compared to those receiving 2 drugs (cisplatin plus 5-FU).[271,272,275,276] A randomized trial in the larynx preservation setting similarly showed superior larynx preservation outcome when induction docetaxel/cisplatin/5-FU (TPF) and cisplatin/5-FU were compared.[297]

However, a clear advantage in overall survival has not yet been shown when adding induction chemotherapy to concurrent

chemoradiation.[270,298,299] More recently, both the DeCIDE and the PARADIGM trials did not convincingly show a survival advantage with the incorporation of induction chemotherapy.[298,299] In patients with stage III or IV squamous cell H&N cancers, a randomized phase II study compared: 1) induction TPF followed by concurrent cisplatin/5-FU with RT; versus 2) concurrent cisplatin/5-FU with RT alone; a higher radiologic complete response rate was reported with the incorporation of induction chemotherapy.[300] A follow-up and larger study is in progress.

After a complete or partial response with induction chemotherapy for patients with laryngeal cancer, RT alone is recommended (category 1);[278] chemotherapy/RT is a category 2B recommendation after a partial response.[297] After induction chemotherapy, panel members agree that weekly cetuximab or carboplatin are reasonable agents to use with concurrent radiation.[298,301-303] Of note, investigators in the DeCIDE trial used the combination of docetaxel/hydroxyurea/5-FU with RT after induction chemotherapy in this setting.[299] Because of toxicity concerns, high-dose cisplatin (100 mg/m^2 every 21 days × 3) is not recommended after induction cisplatin-based chemotherapy.[270,302] Thus, this highlights concerns that any efficacy gains of induction may be offset by the use of better tolerated—but potentially less effective—concurrent regimens or poorer patient compliance with the radiation-based part of treatment. Because of these uncertainties, enrollment of patients in appropriate clinical trials is particularly encouraged. Outside of a clinical trial, proceeding directly to concurrent systemic RT—high-dose cisplatin preferred—is considered the gold standard by many NCCN Panel Members in several settings.[77-80,282,304] When induction chemotherapy is used, data show 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. However, paclitaxel, cisplatin, and 5-FU is also an option for induction chemotherapy.[271]

Radiation Therapy Fractionation

For the 2104 update, extensive revisions were made to the radiation guidelines (see *Head and Neck Radiation Therapy* in this Discussion). Standard conventional fractionation is preferred when RT 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. Recent data suggest that IMRT may be useful for decreasing toxicity.[305,306]

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 in the NCCN Guidelines for Head and Neck Cancers) depends on a complete H&N examination coupled with appropriate studies.[16] At the time of diagnosis, approximately 60% of patients with cancer of the hypopharynx have locally advanced disease with spread to regional nodes. Furthermore, autopsy series have shown a high rate of distant metastases (60%) involving virtually every organ.[307] For patients with

cancer of the hypopharynx, the prognosis can be quite poor despite aggressive combined modality treatment.

Treatment

Patients with resectable disease are divided into 2 groups based on the indicated surgical options: 1) those with early-stage cancer (most T1, N0; selected T2, N0) amenable to larynx preserving (conservation) surgery; and 2) those with advanced resectable cancer (T1, N+; T2–4a, any N) requiring (amenable to) pharyngectomy with total laryngectomy. The surgery and RT options for the former group represent a consensus among the panel members. For the 2014 update, extensive revisions were made to the radiation guidelines (see *Head and Neck Radiation Therapy* in this Discussion).

Patients with more advanced disease (defined as T1, N+; T2–3, any N)—for whom the indicated surgical option is total laryngectomy and partial (or total) pharyngectomy—may be managed with 3 approaches in addition to enrollment in multimodality clinical trials: 1) induction chemotherapy followed by definitive RT (category 1 for RT) if a complete response was achieved at the primary site[279] or followed by other options depending on the response; 2) surgery with neck dissection and postoperative radiation or chemoradiation as dictated by pathologic risk features; or 3) concurrent systemic therapy/RT. When using concurrent systemic therapy/RT, the preferred systemic agent is high-dose cisplatin (category 1). Fractionation for RT is discussed in the algorithm. Given the functional loss resulting from this surgery and the poor prognosis, participation in multimodality clinical trials is emphasized.

The recommendation of the induction chemotherapy/definitive RT option is based on an EORTC randomized trial.[279] This trial enrolled 194 eligible patients with stage II to IV resectable squamous cell carcinoma of the pyriform sinus (152 patients) and aryepiglottic fold (42 patients), excluding patients with T1 or N2c disease. Patients were randomly assigned either to laryngopharyngectomy and postoperative RT, or to chemotherapy with cisplatin and 5-FU for a maximum of 3 cycles, followed by definitive RT. In contrast to a similar approach used for laryngeal cancer, a complete response to induction chemotherapy was required before proceeding with definitive RT. The published results showed equivalent survival, with median survival duration and a 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.[279] A functioning larynx was preserved in 42% of patients who did not undergo surgery. Local or regional failure rates did not differ between the surgery-treated patients and chemotherapy-treated patients, although the chemotherapy recipients did show a significant reduction in distant metastases as a site of first failure (P=.041).

For induction chemotherapy as part of a larynx preservation strategy, inclusion of only patients with the specified TN stages is recommended. Success on larynx preservation with an induction chemotherapy strategy is best established for patients who had a complete response to induction therapy at the primary site and stable or improved disease in the neck. A randomized trial showed that an alternating regimen of cisplatin/5-FU with RT yielded larynx preservation, progression-free interval, and overall survival rates equivalent to those obtained with induction platinum/5-FU followed by RT.[308] Given available randomized data demonstrating the superiority of TPF compared with PF for induction chemoradiation, the triplet is now recommended as induction for this approach.[149,154,297]

As noted in the algorithm, surgery is recommended if less than a partial response (or a partial response) occurs after induction chemotherapy.

The nature of the operation will depend on the stage and extent of the tumor. Partial laryngeal surgery may still be considered, although most patients will require total laryngectomy. In this situation, or when primary surgery is the selected management path, postoperative chemotherapy/RT 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 RT alone or when considering adding chemotherapy to RT. Severe late toxicity appears to be associated with the amount of RT.[296] Options for patients with T4a, any N disease include surgery plus neck dissection (preferred) followed by adjuvant chemotherapy/RT or RT, multimodality clinical trials, or several 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.[309-312] Regional recurrences are uncommon in this disease, occurring in only 10% to 19% of patients.[312,313] The 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. RT was the standard treatment for all stages of this disease, until the mid-1990s, when trial data showed improved survival for locally advanced tumors treated with concurrent RT and cisplatin.[304] For the 2014 update, extensive revisions were made to the radiation guidelines (see *Head and Neck Radiation Therapy* in this Discussion).

Workup and Staging

The workup of nasopharyngeal cancer includes a complete H&N examination and other studies. These studies are important to determine the full extent of tumor in order to assign stage appropriately and to design radiation ports that will encompass all the disease with appropriate doses. Multidisciplinary consultation is encouraged. The 2010 AJCC staging classification (7th edition) is used as the basis for treatment recommendations (see Table 2 in the NCCN Guidelines for Head and Neck Cancers).[16]

Treatment

Patients with T1, N0, M0 nasopharyngeal tumors may be treated with definitive RT alone. For early-stage cancer in this setting, radiation doses of 66 to 70 Gy given with standard fractions are necessary for control of the primary tumor and involved lymph nodes. 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 RT alone.[314,315]

The combination of RT 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 RT versus external radiation alone, closed early when an interim analysis disclosed a significant survival advantage favoring the combined chemotherapy and radiation group.[304] 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 adding chemotherapy to RT. After combined chemotherapy and radiation,

adjuvant chemotherapy was also given in this trial.[316] In addition, the administration of the cisplatin dose was spread out over several days, and this regimen appeared to reduce toxicity while still providing a beneficial antitumor effect.

Another phase III randomized trial showed that concurrent chemotherapy/RT (using weekly cisplatin) increased survival when compared with RT alone.[317] Five-year overall survival was 70% for the chemotherapy/RT group versus 59% for the RT group. A randomized trial compared chemotherapy/RT using cisplatin versus carboplatin and found that the 3-year overall survival rates were similar (78% vs. 79%).[303] However, the NCCN Guidelines recommend cisplatin for chemotherapy/RT in patients who do not have a contraindication to the drug, because more data from randomized trials support the use of cisplatin in this setting.[304,317] A recent phase III randomized trial compared concurrent chemotherapy/RT with (or without) adjuvant chemotherapy (cisplatin/5-FU).[318] The addition of adjuvant chemotherapy did not lead to a significant improvement in the reported outcomes including overall survival, although long-term survival data are not yet available. Based on this study, the NCCN Panel revised the recommendation to category 2A for concurrent chemoradiotherapy (cisplatin) with adjuvant chemotherapy for nasopharyngeal cancer; previously, the recommendation had been category 1. For the 2014 update, the panel also added a new option of concurrent chemoradiotherapy (cisplatin) without adjuvant chemotherapy with a category 2A recommendation. The NCCN Guidelines recommend 2 options for both T1, N1–3; and for T2–T4, any N lesions: 1) concurrent chemotherapy (cisplatin) plus RT followed by adjuvant cisplatin/5-FU; and 2) concurrent chemotherapy (cisplatin) plus RT alone (ie, without adjuvant chemotherapy).[304,317,318] If using adjuvant chemotherapy, adjuvant carboplatin/5-FU is also an option; however, this recommendation was revised to category 2B for the 2014 update because there is less experience using carboplatin in this setting and because the recent Chen et al study suggests that it is reasonable not to use adjuvant chemotherapy.[318,319] The panel is interested in further follow-up to the Chen et al study to clarify the role of adjuvant chemotherapy in this setting.[318]

Induction chemotherapy (category 3) (followed by chemotherapy/RT) is also recommended for patients with nasopharyngeal cancer with either T1, N1–3 or T2–T4, any N lesions. Panel members had widespread disagreement regarding whether induction chemotherapy is appropriate, which is reflected in the category 3 recommendation (see *The Induction Chemotherapy Controversy* in this Discussion). Several induction/sequential chemotherapy options are recommended in the algorithm for nasopharyngeal cancer.[272,303,317,320] For the 2014 update, docetaxel/cisplatin (category 2B) was added as an option.[321] Although an unusual occurrence, a patient with residual disease in the neck and a complete response at the primary should undergo a neck dissection.

For patients who present with metastatic disease, recommended initial therapy includes either a platinum-based combination chemotherapy regimen or concurrent chemotherapy/RT; treatment depends on whether disease is localized or widespread.[304,317,319] For platinum-based combination chemotherapy, the different options are listed in the algorithm.[303,320]

The management of patients with recurrent or persistent nasopharyngeal cancer is described in the algorithm. Unless otherwise specified, regimens or single agents can be used for either nasopharyngeal or non-nasopharyngeal cancer. Combination therapy options include: 1) cisplatin or carboplatin with docetaxel or paclitaxel;

2) cisplatin/5-FU; or 3) cetuximab/carboplatin.[322] For those who have failed platinum-based therapy, options are listed in the algorithm.[323,324]

Follow-up/Surveillance

Recommendations for surveillance are provided in the algorithm.

Cancer of the Larynx

The larynx is divided into 3 regions: supraglottis, glottis, and subglottis. The distribution of cancers is as follows: 30% to 35% in the supraglottic region, 60% to 65% in the glottic region, and 5% in the subglottic region. The incidence and pattern of metastatic spread to regional nodes vary with the primary region. More than 50% of patients with supraglottic primaries present with spread to regional nodes because of an abundant lymphatic network that crosses the midline. Bilateral adenopathy is not uncommon with early-stage supraglottic primaries. Thus, supraglottic cancer is often locally advanced at diagnosis. In contrast, the lymphatic drainage of the glottis is sparse and early-stage primaries rarely spread to regional nodes. Because hoarseness is an early symptom, most glottic cancer is early stage at diagnosis. Thus, glottic cancer has an excellent cure rate of 80% to 90%. Nodal involvement adversely affects survival rates.

Workup and Staging

The evaluation of the patient to determine tumor stage is similar for glottic and supraglottic primaries. Multidisciplinary consultation is critical for both sites because of the potential for loss of speech and, in some instances, for swallowing dysfunction. 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 in the NCCN Guidelines for Head and Neck Cancers).[16]

Treatment

In the NCCN Guidelines, the treatment of patients with laryngeal cancer is divided into 2 categories: 1) tumors of the glottic larynx; or 2) tumors of the supraglottic larynx. Subglottic cancer is not discussed, because it is so uncommon. For the 2104 update, extensive revisions were made to the radiation guidelines.

For patients with carcinoma in situ of the larynx, recommended treatment options include 1) endoscopic removal (ie, stripping, laser) which is preferred; or 2) RT.[325,326] For early-stage glottic or supraglottic cancer, surgery (partial laryngectomy) or RT have similar effectiveness.[327] 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, NO glottic cancer with either other risk features or positive margins.[79] 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 when 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 and supraglottic primaries are usually managed with a combined modality approach. 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.[278,293] When using systemic therapy/RT, high-dose cisplatin (category 1) is preferred (at 100 mg/m^2 on days 1, 22, and 43).[278] 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 *The Induction Chemotherapy Controversy* in this Discussion).[278] 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 *The Induction Chemotherapy Controversy* in this Discussion).[278] Definitive RT (without chemotherapy) is an option for patients with T3, N0-1 disease who are medically unfit or refuse chemotherapy. Surgery is reserved for managing the neck as indicated, for those patients whose disease persists after chemotherapy/RT or RT, or for those patients who develop a subsequent locoregional recurrence.

The NCCN recommendations for managing locally advanced, resectable glottic and supraglottic cancers (in which total laryngectomy is indicated but laryngeal preservation is desired) with concurrent cisplatin and radiation are based on Intergroup trial R91-11.[278,293] Before 2002, either induction chemotherapy with cisplatin/5-FU followed by RT (based on the VA Laryngeal Cancer Study Group trial[280]) or definitive RT alone (without chemotherapy) were the standard of care options recommended in the NCCN Guidelines for Head and Neck Cancers. However, concurrent RT and systemic therapy (eg, cisplatin 100 mg/m^2 preferred [category 1]) is now the recommended option for achieving laryngeal preservation.[278,293]

R91-11 was a successor trial to the VA trial and compared 3 non-surgical regimens: 1) induction cisplatin/5-FU followed by RT (control arm and identical to that in the VA trial); 2) concurrent RT and high-dose cisplatin 100 mg/m^2 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) to salvage 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 to 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 T3, N0 and T4a, N0 supraglottic cancers and for most T3, any N glottic cancers.[293] 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 when compared with either induction chemotherapy or RT alone.[278] Overall survival was not statistically different for all treatment groups; there was more non-cancer–related mortality among patients treated with concurrent cisplatin/RT.

For patients with glottic and supraglottic T4a tumors, the standard approach is total laryngectomy with thyroidectomy and neck dissection as indicated (depending on node involvement) followed by adjuvant treatment. For patients with glottic T4a larynx 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: 1) considering concurrent chemoradiation; 2) clinical trials; or 3) induction chemotherapy with additional management based on response.[278,293]

Follow-up/Surveillance

Recommendations for surveillance are provided in the algorithm. 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.

Paranasal Tumors (Maxillary and Ethmoid Sinus Tumors)

Tumors of the paranasal sinuses are rare, and patients are often asymptomatic until late in the course of their disease. Tumors of the maxillary sinus are more common than those of the ethmoid sinus or nasal cavity.[16] Note that the workup for patients with suspected paranasal sinus tumors includes a complete H&N CT with contrast and/MRI; dental/prosthetic consultation is recommended if clinically indicated. A new section on *Principles of Dental Evaluation and Management* was added for the 2014 update (see this Discussion).

Although the most common histology for these tumors is squamous cell carcinoma, multiple histologies have been reported including adenocarcinoma, esthesioneuroblastoma (also known as olfactory neuroblastoma), minor salivary gland tumors, and undifferentiated carcinoma (eg, sinonasal undifferentiated carcinoma [SNUC], small cell neuroendocrine).[328-331] Locoregional control and incidence of distant metastasis are dependent on T stage, N stage, and tumor histology.[332] However, T stage remains the most reliable predictor of survival and local regional control (see Table 4 in the NCCN Guidelines for Head and Neck Cancers).[16] Mucosal melanoma (MM) also occurs in the paranasal sinus region, nasal cavity, and oral cavity. Biopsy results may also indicate that patients have sarcoma or lymphoma (see the NCCN Guidelines for Soft Tissue Sarcoma and Non-Hodgkin's Lymphoma).[333,334]

Ethmoid Sinus Tumors

Patients with early-stage ethmoid sinus cancer are typically asymptomatic. These neoplasms are often found after a routine nasal polypectomy or during the course of a nasal endoscopic procedure. For a patient with gross residual disease who has had a nasal endoscopic surgical procedure, the preferred treatment is complete surgical resection of the residual tumor. This procedure often entails an anterior craniofacial resection to remove the cribriform plate and to ensure clear surgical margins. PET/CT may be considered in the workup of patients with clinically apparent stage III or IV disease.

Most patients with ethmoid sinus cancer present after having had an incomplete resection. The patient who is diagnosed after incomplete resection (eg, polypectomy)—and has no documented residual disease on physical examination, imaging, and/or endoscopy—should be treated with surgical resection if feasible. If no adverse pathologic factors are found, this treatment may obviate the need for postoperative RT in T1 patients only (category 2B). However, RT may be used as definitive treatment in patients if pre-biopsy imaging studies and nasal endoscopy show that the superior extent of the disease does not involve the skull base. Note that extensive revisions were made to the radiation guidelines (see *Head and Neck Radiation Therapy* in this Discussion).

Systemic therapy should be part of the overall treatment for patients with SNUC or small cell neuroendocrine histologies.[335-344] Surgery and RT have been used to treat patients with esthesioneuroblastomas; chemotherapy has also been incorporated into the local/regional treatment.[343-350] Long-term follow-up is necessary for esthesioneuroblastomas, because recurrence can even occur after 15 years.[343,351,352]

Maxillary Sinus Tumors

Surgical resection for all T stages (except T4b, any N) followed by postoperative therapy remains a cornerstone of treatment for maxillary sinus tumors.[353-356] However, definitive RT or chemotherapy/RT is recommended for T4b, any N, although this is a category 2B recommendation for patients with T3-4a, N0 disease.[357] Recent studies using IMRT have shown that it reduces the incidence of complications, such as radiation-induced ophthalmologic toxicity; however, the 5-year overall survival rate has not improved.[154,355,358-361] Extensive revisions were made to the radiation guidelines (see *Head and Neck Radiation Therapy* in this Discussion). Participation in clinical trials is recommended for patients with malignant tumors of the paranasal sinuses.

Follow-up

Recommendations for surveillance are provided in the algorithm.

Very Advanced Head and Neck Cancers

Very advanced H&N cancers include: 1) newly diagnosed locally advanced T4b (M0); 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 comments about *unresectable disease* in the section on *Head and Neck Surgery* in this Discussion). 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 *Head and Neck Radiation Therapy* in this Discussion).

Newly Diagnosed Advanced Disease

For patients with a 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).[282] Other category 1 options include: 1) carboplatin/5-FU, or 2) cetuximab.[116,362] Other systemic therapy/RT options are listed in the guidelines. The NCCN Panel had a major disagreement regarding whether induction chemotherapy (eg, TPF) 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 *The Induction Chemotherapy Controversy* in this Discussion).[272,276] Other options for patients with PS 2–3 are described in the algorithm.

Many randomized trials[81,122,123,282-288] and meta-analyses of clinical trials[273,289-292] 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 relatively 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^2.[282]

Bonner et al 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.[363] Locoregional control and median overall survival (49 months vs. 29.3 months, *P* = .03) were significantly improved in patients treated with RT and cetuximab compared to RT alone. RT and cetuximab 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.[116,364,365] 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. 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. For patients with recurrent disease who are 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. Note that the *Principles of Radiation Therapy* were extensively revised for patients with very advanced H&N cancers (see *Head and Neck Radiation Therapy* in this Discussion).

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.[366] Unless otherwise specified, regimens or single agents can be used for either nasopharyngeal or non-nasopharyngeal cancer. Response rates to single agents range from 15% to 35%.[247,367,368] Active and more commonly used single agents include cisplatin, carboplatin, paclitaxel, docetaxel, 5-FU, methotrexate, capecitabine, cetuximab (for non-nasopharyngeal cancer), gemcitabine (for nasopharyngeal cancer), and vinorelbine (for non-nasopharyngeal cancer).[247,324,366,369-385] 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);[386] 2) cisplatin or carboplatin, plus a taxane;[387,388] 3) cisplatin with cetuximab (for non-nasopharyngeal cancer only);[370] or 4) cisplatin with 5-FU.[375,388] These combination regimens, on average, result in a doubling of response rates compared to single agents. Regimens for metastatic nasopharyngeal cancer are described in a previous section (see *Cancer of the Nasopharynx* in this Discussion). Randomized trials assessing a cisplatin-based combination regimen (such as 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.[369,375,388-390] Historically, the median survival with chemotherapy is approximately 6 months, 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.[375] 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.[388] 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 (TKIs) (ie, erlotinib, gefitinib).

Data from phase II studies indicate that in the cisplatin-refractory setting, the single-agent response rate of cetuximab is about 12% to 14%. Burtness et al[370] compared cisplatin plus cetuximab versus cisplatin plus placebo as first-line treatment of recurrent disease; they 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 to the standard chemotherapy doublet (10.1 vs. 7.4 months, $P = .04$).[386] 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 to treatment with methotrexate.[374] Available data for novel agents have not established them as treatment options for recurrent or metastatic H&N cancers outside of a clinical trial.[391,392]

For the 2014 update, the NCCN Panel added 3 new combination regimens for recurrent, unresectable, or metastatic disease: 1) cisplatin/docetaxel/cetuximab (for non-nasopharyngeal cancer);[393] 2) cisplatin/paclitaxel/cetuximab (for non-nasopharyngeal cancer);[247,394] and 3) cisplatin/gemcitabine (for nasopharyngeal cancer).[395] For the cisplatin/docetaxel/cetuximab regimen, the median PFS was 7.1 months and overall survival was 15.3 months; 1-year overall survival was 58.6%. This newer taxane-based regimen has impressive overall survival and is an option for patients with good PS. However, the standard of care for recurrent, unresectable, or metastatic non-nasopharyngeal cancer is considered to be the regimen from the EXTREME trial of cetuximab plus cisplatin/5-FU or carboplatin/5-FU (category 1).[386] A recent trial compared 5 different cisplatin-based regimens for nasopharyngeal cancer and reported that a cisplatin/gemcitabine regimen was effective although not better than either cisplatin/5-FU or cisplatin/paclitaxel.[395]

The standard treatment of patients with incurable, persistent, recurrent, or metastatic H&N cancers should be dictated, in large part, by the patient's PS. Patients should be fully informed about the goals of treatment, cost of combination chemotherapy, and potential for added toxicity.

Occult Primary Cancer

When patients present with metastatic tumor in a neck node and no primary site can be identified after appropriate investigation, the tumor is defined as an *occult* or unknown primary cancer; this is an uncommon disease, accounting for about 5% of patients presenting to referral centers. Although patients with very small tonsil and tongue base cancers frequently present with enlarged neck nodes and are initially classified as an *unknown primary*, most will eventually be diagnosed by directed biopsy and tonsillectomy. H&N cancer of unknown primary site is a highly curable disease. After appropriate

evaluation and treatment, most patients experience low morbidity and many will be cured. The primary tumor becomes apparent on follow-up only in a few cases. Patients and oncologists are often concerned when the primary cancer cannot be found. This concern may lead to intensive, fruitless, and costly diagnostic maneuvers.

Most patients older than 40 years who present with a neck mass prove to have metastatic cancer. The source of the lymphadenopathy is almost always discovered in the course of a complete H&N examination, which should be performed on all patients with neck masses before other studies are initiated. The following should be assessed during office evaluation: 1) risk factors (eg, tobacco or alcohol use); 2) antecedent history of malignancy; and 3) prior resection, destruction, or regression of cutaneous lesions.

Workup

Patients with a neck mass should have a complete H&N examination. FNA is preferred (over open biopsy), which generally guides management and treatment planning. Unless FNA is inconclusive, core or open biopsy should be avoided because it may alter or interfere with subsequent treatment. Open biopsy should not be performed unless the patient is prepared for definitive surgical management of the malignancy as indicated, if documented in the operating room. This management may entail a formal neck dissection. Therefore, an open biopsy of an undiagnosed neck mass should not be undertaken lightly, and patients should be apprised of treatment decisions and related sequelae.

When a needle biopsy shows squamous cell carcinoma, adenocarcinoma, or anaplastic/undifferentiated epithelial cancer and no primary site has been found, additional studies are needed. A PET/CT scan should only be done (before biopsy) if other tests do not reveal a primary. HPV-16 and Epstein Barr Virus (EBV) testing are suggested for squamous cell or undifferentiated histology.[324,396-399] HPV testing can be useful in workup and management of cancers of the neck of unknown primary. An HPV-positive test strongly suggests an occult primary is located in the tonsil or base of tongue regions, permitting one to customize radiation targets to these mucosal regions.[265]

When the imaging studies and a complete H&N examination do not reveal a primary tumor, then an examination under anesthesia should be performed. Mucosal sites should be inspected and examined. Appropriate endoscopies with directed biopsies of likely primary sites are recommended, but they seldom disclose a primary cancer. Many primary cancers are identified after tonsillectomy. However, the therapeutic benefit of this surgery is uncertain, because when patients have been treated without tonsillectomy, only a few develop a clinically significant primary tumor.

Treatment

Neck dissection is recommended for all patients with thyroglobulin-negative and calcitonin-negative adenocarcinoma. If the metastatic adenocarcinoma presents high in the neck, parotidectomy may be included with the neck dissection. After neck dissection, management depends on the findings (ie, N1 without extracapsular spread, N2 or N3 without extracapsular spread, or extracapsular spread).

Among NCCN Member Institutions, significant variation exists regarding the management of squamous cell carcinoma, poorly differentiated or nonkeratinizing squamous cell carcinoma, anaplastic cancer (not thyroid) of unknown primary site, or other uncommon histologies. Most panel members believe such patients should be managed with surgery (which is preferred for <N2 disease) and neck dissection (levels I–V) followed by RT or chemotherapy/RT. The following options are also

recommended: 1) chemoradiation for those with N2 or greater disease (category 2B); 2) primary RT for those with less than N2 disease (category 2B); or 3) induction chemotherapy (category 3) followed by chemoradiation or RT. A neck dissection may be recommended after treatment, depending on the clinical response.

After a neck dissection, recommendations vary depending on the amount of nodal disease and the presence or absence of extracapsular spread. For N1 disease without extracapsular spread, NCCN Member Institutions recommend either: 1) radiation that encompasses the target volume; or 2) careful observation with regular H&N examinations. Postoperative radiation or considering concurrent chemoradiation (category 2B for chemoradiation) is recommended for N2 or N3 disease without extracapsular spread. For extracapsular spread, concurrent chemoradiation is a category 1 recommendation; RT alone is an option.[77,78] Note that the *Principles of Radiation Therapy* were extensively revised for this site (see *Head and Neck Radiation Therapy* in this Discussion).

Salivary Gland Tumors

Salivary gland tumors can arise in the major salivary glands (ie, parotid, submandibular, sublingual) or in one of the minor salivary glands, which are widely spread throughout the aerodigestive tract.[400] Many minor salivary gland tumors are located on the hard palate. Approximately 20% of the parotid gland tumors are malignant; the incidence of malignancy in submandibular and minor salivary gland tumors is approximately 50% and 80%, respectively. These malignant tumors constitute a broad spectrum of histologic types, including mucoepidermoid, acinic, adenocarcinoma, adenoid cystic carcinoma, malignant myoepithelial tumors, and squamous carcinoma. The primary diagnosis of squamous carcinoma of the parotid gland is rare; however, the parotid is a frequent site of metastasis from skin cancer.[401] Prognosis and tendency to metastasize vary among these histologic types. Major prognostic factors are histologic grade, tumor size, and local invasion. Staging is done using the AJCC Cancer Staging Manual (7th edition) (see Table 5 in the NCCN Guidelines for Head and Neck Cancers).[16]

Treatment

The major therapeutic approach for salivary gland tumors is adequate and appropriate surgical resection.[402-405] Surgical intervention requires careful planning and execution, particularly in parotid tumor surgery because the facial nerve is in the gland, which should be preserved if the nerve is not directly involved by the tumor. Most parotid gland tumors are located in the superficial lobe, and if the facial nerve is functioning preoperatively, the nerve can be preserved in most patients.[406] The facial nerve should be sacrificed if there is preoperative facial nerve involvement with facial palsy or if there is direct invasion of the tumor into the nerve where the tumor cannot be separated from the nerve. Malignant deep lobe parotid tumors are quite rare; however, they are generally a challenge for the surgeon because the patient may require superficial parotidectomy and identification and retraction of the facial nerve to remove the deep lobe parotid tumor.

Most malignant deep lobe parotid tumors will require postoperative RT because of adverse features such as the limitations of surgical margins in the resection of these tumors.[402,404,407] RT is also used in an adjuvant setting for tumors with other adverse features (eg, intermediate, high grade);[403] chemotherapy/RT (category 2B) can also be considered.[408] Efficacy data for chemotherapy/RT in this setting are limited. Extensive safety data are available from the management of squamous cell H&N cancers. With regard to unresectable salivary gland tumors, the NCCN

Panel had less consensus about chemoradiation (which is reflected in the category 2B recommendations), because there are few published trials. However, data support the use of neutron therapy.[409] Chemotherapy may be used for palliation in advanced disease. Various agents alone or in combination (eg, cisplatin, cyclophosphamide, doxorubicin; epirubicin; mitoxantrone; carboplatin and vinorelbine) have been shown in small series to be active for some salivary gland malignant histologies.[410-417] Although targeted therapy is associated with stable disease, it is minimally active and not recommended outside of clinical trials.[414,418]

Follow-up

Recommendations for surveillance are in the algorithm.

Mucosal Melanoma of the Head and Neck

MM is a rare but highly aggressive neoplasm with a poor prognosis.[419,420] It mainly occurs throughout the upper aerodigestive tract.[421] Most MM (70%–80%) occurs in the nasal cavity or paranasal sinus region, and most of the remainder develops in the oral cavity.[422] The incidence of nasal cavity MM appears to be increasing.[419] Sinonasal MM is typically confined to the primary site at presentation.[423] Oral cavity MM more frequently presents with clinically apparent lymph node metastasis.[424] No etiologic risk factors are yet apparent.

Workup and Staging

Workup for MM should include clinical examination and CT and/or MRI for paranasal sinus disease and appropriate imaging for other mucosal sites. PET-CT scanning may be considered to define distant disease in more advanced situations. The AJCC Cancer Staging Manual (7th edition) includes a staging system for MM (see Table 6 in the NCCN Guidelines for Head and Neck Cancers).[16] The AJCC staging recognizes 2 key factors specific to MM: 1) the poor prognosis of MM even with a limited primary burden of disease; and 2) there is still some gradation of survival based on the burden of disease as reflected in local, regional, and distant extent. Thus, the AJCC staging system for MM begins with stage III disease as the most limited form of disease (similar to anaplastic thyroid carcinoma), and the stages reflect the local burden of disease, as well as regional and distant extent. In addition, the AJCC staging system reflects the fact that MM occurs at all mucosal sites in the H&N. Therefore, rules for classifying, staging, and surgical principles should be based on the appropriate anatomic site of origin.

Treatment

Although limited data exist on treatment options, primary treatment should be surgical for stage III to IVA disease; however, surgery is not recommended for stage IVB to C disease.[425] Adjuvant radiation appears effective in improving local control and survival in most case series.[426-428] Postoperative radiation is clearly indicated in more advanced cases.[429] The role of radiation in stage III disease is not clear, but it can be considered on an individual basis by the treating clinicians. NCCN strongly encourages clinical trials for all patients with MM to better define treatment choices at all stages of the disease.

Neck dissection and postoperative radiation are recommended for clinical nodal disease.[430,431] The role of elective neck treatment is unclear. The extension of elective treatment to the neck seems unwarranted in most cases of N0 paranasal sinus MM. However, for oral cavity disease, the likelihood of positive disease is significantly higher and the treatment can be better localized to the ipsilateral neck with both surgery and radiation. Therefore, elective treatment to the neck for oral cavity MM appears justifiable.

Radiation Therapy

The role of RT in MM has not been evaluated in prospective trials. However, recently reported results of a randomized trial in cutaneous melanoma are considered relevant to MM in the postoperative setting after neck dissection (see third paragraph in this section).[432] Retrospective studies in MM have shown local recurrence to be common after surgery alone.[433] After using postoperative radiation, lower rates of local and neck recurrence have been seen in historical comparison series.[428,434-437] Reasonable local control outcomes using RT alone in unresectable or medically inoperable cases have been reported in small cohort series of MMs.[438-440]

For the 2014 update, the RT recommendations for Mucosal Melanoma were extensively revised by using the same terminology as the other sites for H&N cancer. RT is often recommended in the postoperative management of MMs. Primary size or thickness is not used as a risk factor when considering RT to the primary site; all invasive primaries are considered at high risk for local recurrence. For sinonasal primary sites, target volumes may include the primary site without elective treatment of the neck. Because oral cavity primary sites are felt to be at a higher risk for failure in the neck, elective management with neck dissection and RT may be applied.

Indications for postoperative radiation to the neck are generally extrapolated from cutaneous melanoma. Recently, an Australian-New Zealand consortium reported on a randomized trial (250 patients) of postoperative RT versus observation in patients with palpable adenopathy from cutaneous primaries. Postoperative RT was associated with a significant reduction in relapse in the nodal basin (19% vs. 31%) and a significant improvement in lymph node field control.[432] Only 20 patients relapsed who received RT, whereas 34 patients relapsed who received observation only (P = .04). However, no significant differences in overall survival were reported.

Considering this trial and retrospective studies in MM, the NCCN Panel recommends postoperative RT for the following high-risk features: extracapsular disease, involvement of 2 or more neck or intraparotid nodes, any node 3 cm or greater, neck dissection (alone) with no further basin dissection, or recurrence in the neck or soft tissue after initial surgical resection.[441,442] Conventional fractionation is recommended (at 2 Gy per fraction to a total postoperative dose of 60–66 Gy). The Australian-New Zealand randomized trial used 48 Gy in 20 fractions (240 cGy/fraction) to the neck, axilla, or groin.[432] However, the NCCN Panel prefers conventional fractionation to somewhat higher total doses (60–66 Gy) in the neck because of concerns about late effects from larger dose per fraction, which may not be fully expressed for many years after treatment. For recurrences in the nodal basin after surgery, the following schedules are recommended: 1) 48-50 Gy (2.4-3 Gy/fraction); or 2) 30 Gy (6 Gy/fraction).[432,442]

IMRT may be very useful in helping to achieve homogenous dose distributions and to spare critical organs, especially in paranasal sinus sites.[154,359,443] Reports suggest that the use of hypofractionation in cutaneous melanomas (which is convenient) is associated with good outcomes but no clear advantage in cancer control. Little experience is available using large dose per fraction in mucosal sites. Because of the close proximity of neural structures and risk of late effects, hypofractionation (if used) must be carefully planned and delivered.[443]

Systemic Therapy

Systemic therapy used for cutaneous melanoma (eg, interleukin-2) is recommended for MM (see *Systemic Therapy for Advanced or Metastatic Melanoma* in the NCCN Guidelines for [cutaneous]

Melanoma).[423,444] Interferon and interleukin have been used to treat MM.[444,445] Data suggest that *c-KIT* inhibitors (eg, imatinib) may be useful in selected patients with metastatic MM and specific mutations.[446-449] Therefore, *c-KIT* inhibitors are reasonable to use in patients with MM who have *c-KIT* mutations (ie, exon 11 or 13 mutations).[444,450,451] Although vemurafenib is recommended for patients with cutaneous melanoma who have the V600E mutation of the *BRAF* gene, patients with MM rarely have this mutation.[444,451,452]

Follow-up

Recommendations for surveillance are provided in the algorithm. Note that physical examination for MM should include endoscopic inspection for paranasal sinus disease.

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